CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 206497

Name: Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr

Sponsor: Mylan Technologies Inc.

Approval Date: March 14, 2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

APPROVAL LETTER

ANDA 206497

ANDA APPROVAL

Mylan Technologies Inc.
3711 Collins Ferry Road
Morgantown, WV 26505
Attention: Bradley Davis
Head of Regulatory Science, Dermals

Dear Bradley Davis:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 13, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts.

Reference is also made to the complete response letter issued by this office on September 29, 2021, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Daytrana Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, of Noven Pharmaceuticals, Inc. (Noven).

The RLD upon which you have based your ANDA, Noven's Daytrana Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
8,632,802 (the '802 patent)	October 7, 2025
9,034,370 (the '370 patent)	October 7, 2025

9,668,981 (the '981 patent) October 7, 2025

Your ANDA contains paragraph IV certifications to each of the patents[1], under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, under this ANDA. You have notified the Agency Mylan Technologies Inc. (Mylan) complied with the requirements of section 505(j)(2)(B) of the FD&C Act.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts; therefore, we remind you that you must comply with the postmarketing safety reporting requirements for an approved combination product (21 CFR Part 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: https://www.fda.gov/media/128163/download).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at: https://www.fda.gov/media/73013/download. Information and Instructions for completing the form can be found at: https://www.fda.gov/media/132152/download. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[2] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and

any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at: https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your RLD's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled "Changes to an Approved NDA or ANDA" at: https://www.fda.gov/media/71846/download.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] The Agency notes that the '802, '370, and '981 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Catherine Poole

Digitally signed by Catherine Poole
Date: 3/14/2022 08:47:39AM
GUID: 5407887a000a1c0c26055eafb8e3258a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

OTHER ACTION LETTERS

ANDA 206497

COMPLETE RESPONSE

Mylan Technologies Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Bradley Davis
Head of Regulatory Science - Dermals

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 13, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr.

We acknowledge receipt of the February 25, 2021 submission, which constituted a complete response to our February 26, 2018 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. We acknowledge your submitted release specification for the final transdermal system. Please address the following.

   a. (b) (4)

   b.

(b) (4)

2. (b) (4)

3.

BIOEQUIVALENCE

Based upon your manufacturing process changes and the complex nature of the proposed test drug product, your original test batches are considered inadequate to support the bio-waiver request. Therefore, please provide comparative in vitro release test (IVRT) data for your new test product, Methylphenidate Transdermal System, 10 mg/9 hr and 30 mg/9 hr, (b) (4) comparing to the respective reference product strengths with adequate sampling time points (e.g., such as the IVRT sampling times used in your original submission, 0.5, 1.5, 2, 3, 4 and 6 hours) using the FDA recommended dissolution method per the Draft Product Specific Guidance on Methylphenidate Transdermal Film (revised November 2019).

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

DISSOLUTION / CLINICAL BIOEQUIVALENCE / LABELING / FACILITY INSPECTIONS/EVALUATIONS

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be reevaluated upon resubmission.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the *United States Pharmacopeia - National Formulary* (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure that your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY / BIOEQUIVALENCE

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial

response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Megan Tychinski, Regulatory Project Manager, Division of Project Management, at (240) 402 - 2717.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Aaron Sigler

Digitally signed by Aaron Sigler
Date: 9/29/2021 09:42:07AM
GUID: 508da6fa0002827f1a9f2526d1b2cc69

ANDA 206497

COMPLETE RESPONSE

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504
Attention: Bradley Davis
Head of Regulatory Science

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 13, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

We acknowledge receipt of the July 27, 2017 submission, which constituted a complete response to our July 27, 2016 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. (b) (4)
2.
3.
4.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

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LABELING

1. GENERAL COMMENT

   Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-028 approved November 6, 2017.

2. FULL PRESCRIBING INFORMATION: CONTENTS* and FULL PRESCRIBING INFORMATION:

   Revise the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of Fertility".

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

BIOEQUIVALENCE / DISSOLUTION / CLINICAL BIOEQUIVALENCE / FACILITY INSPECTIONS / EVALUATIONS

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be reevaluated upon resubmission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY / LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, call Megan Tychinski, Regulatory Project Manager, Division of Project Management, at (240) 402-2717.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Aaron Sigler

Digitally signed by Aaron Sigler
Date: 2/26/2018 01:15:40PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

COMPLETE RESPONSE

Mylan Technologies, Inc.
110 Lake Street
St. Albans, VT 05478
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

We acknowledge receipt of your amendments dated June 19, 2014; November 17, and November 18, 2015; and February 2, February 18, and February 24, 2016.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. (b) (4)

2.

3.

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

19. (b) (4)

20.

DISSOLUTION

The dissolution testing on your test product, Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, using the FDA recommended dissolution method is incomplete. Your proposed specifications of (b) (4) , are not acceptable. Based on the data submitted, the Office of Bioequivalence recommends following method and specifications.

Medium	0.01 N HCl
Volume	900 mL
Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications*	(b) (4) in 0.5 hr in 1.5 hr in 4 hr

*percent of labeled content

With your response, please indicate if you accept the above FDA recommended method and specifications.

For your future applications, please provide specifications in percent of labeled content expressed in ranges per the USP General Chapter <724> Transdermal Delivery Systems – General Drug Release Standards, and its Acceptance Table.

CLINICAL BIOEQUIVALENCE

The sensitization data in Study MPTP 12130 is not adequate to ensure that the sensitization potential of the proposed generic methylphenidate transdermal system (Test) is no worse than that of the reference listed drug product (RLD) as follows.

We do not agree with your numbers of subjects sensitized or potentially sensitized to each product. When we applied the four criteria described in the FDA product-specific bioequivalence guidance to your data,[1] of 66 subjects who entered the challenge phase, 18

(27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the RLD, respectively, with 100% more test sites than reference sites showing potential sensitization.

We note that you interpreted the term *generally higher* in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we reevaluated your data using your interpretation. Using your interpretation of *generally higher*, 33 test versus 27 RLD skin sites showed potential sensitization. The proportions are 50% for test versus 40.9% for RLD, with 22% more test sites than RLD sites showing sensitization.

The point estimate for the proportion of skin sites showing potential sensitization was higher for the test product compared with the RLD regardless of which interpretation of *generally higher* we used.

We note that there are several formulation differences between your product and the RLD, which makes a difference in potential sensitization biologically plausible.

To address these deficiencies, we recommend one of the following.

1. Provide adequate justification and evidence that potential sensitization of your proposed methylphenidate transdermal system is no worse than that of the reference listed drug.

2. Conduct new sensitization study with the to-be-marketed product. Please refer to the Product-Specific Recommendation for Methylphenidate Film, Extended Release/Transdermal recommended in July 2010 on FDA's guidance page: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm220196.pdf

LABELING

1. GENERAL COMMENTS

   a. Revise your Prescribing Information and Medication Guide to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-023 approved August 14, 2015.

   b. Explain how the container closure system for your pouch label and carton labeling meet the tamper evident requirements of 21 CFR 1302.06.

[1] Draft Guidance on Methylphenidate Film, Extended Release/Transdermal *Recommended Jul 2010* http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm220196.pdf

2. PATCH LABEL

   Space permitting, revise the established name to read "Methylphenidate Transdermal System".

3. POUCH LABEL

   a. Similar to the carton labeling, we recommend adding a usual dosage statement "**Dosage and Administration:** See package insert.". This statement can appear on the back of the pouch.

   b. The proposed expressions of strength on the pouch label/carton labeling lack adequate differentiation and may lead to medication errors. We recommend using a method(s) (e.g., use of different color, bolding, highlighting and etc.) to help differentiate the expressions of strength. Ensure any colors selected to display the expression of strength are sufficiently differentiated between the pouch labels/carton labeling.

   c. Be sure to include a place holder for the lot number and the expiration date.

4. CARTON LABELING

   a. See comments 3.b. and 3.c. above.

   b. To help further differentiate your drug product strengths, we recommend increasing the middle digits of the NDC number by increasing their size in comparison to the remaining digits in the NDC number (similar to your pouch label). For example: xxxxx-XXXX-xx.

   c. We recommend relocating the pharmacist instructions for the Medication Guide to the principal display panel (PDP). In order to accommodate this information on the PDP, the "**Dosage and Administration:** See package insert." statement can appear on the back panel.

5. PRESCRIBING INFORMATION (PI)

   a. GENERAL COMMENTS

      i. We recommend (b) (4) "transdermal system". For example, HIGHLIGHTS OF PI, **DOSAGE FORMS AND STRENGTHS**, (b) (4) to read "Transdermal System".

      ii. When stating strengths and dosages, we recommend placing a space between the number and its associated unit of measurement. For example, HIGHLIGHTS OF PI, **DOSAGE FORMS AND STRENGTHS**, we recommend revising "10mg/9 hours

(1.1 mg/hr), …" to read "10 mg/9 hours (1.1 mg/hr), …" [added space between "10" and "mg"].

iii. When stating strengths and dosages, we recommend having a unit of measurement after every number. For example, FULL PI, **14 CLINICAL STUDIES**, second paragraph, third sentence, we recommend revising "… 10, 15, 20, and 30 mg / 9 hours…" to read "… 10 mg/9 hours, 15 mg/9 hours, 20 mg/9 hours, and 30 mg/9 hours…" [please also note that the spaces were deleted before and after the "/"].

iv. When stating strengths and dosages, we recommend keeping the number and its associated unit of measurement in the same line of text. For example, FULL PI, **14 CLINICAL STUDIES**, third paragraph, last sentence, we recommend placing "20" and "mg/9 hours" hours in the same line of text vs. two separate lines of text.

b. HIGHLIGHTS OF PI

i. Revise the first paragraph to read "**These highlights do not include all the information needed to use METHYLPHENIDATE TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for METHYLPHENIDATE TRANSDERMAL SYSTEM.**"

ii. Revise the title to read "**METHYLPHENIDATE transdermal system, CII**"

iii. Extend the solid line that separates the HIGHLIGHTS OF PI and FULL PI: CONTENTS***** to appear across both columns (vs. just the right column).

iv. (b) (4)

v. Revise the subsection title to read: "**DOSAGE FORMS AND STRENGTHS**".

c. FULL PI: CONTENTS*

i. Revise the section title for "3" to read "**DOSAGE FORMS AND STRENGTHS**".

ii. Revise the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of Fertility".

d. FULL PI

i. Revise the section title for "3" to read "**DOSAGE FORMS AND STRENGTHS**".

ii. Revise the subsection title for "13.1" to read: "**Carcinogenesis, Mutagenesis, Impairment of Fertility**".

iii. Revise the spelling of "*vaculopathy*" in subsection 17.1 "**Information for Patients**" to read "*vasculopathy*".

6. MEDICATION GUIDE

   a. **Before you start using methylphenidate transdermal system, tell your doctor if you** (b) (4)

   b.

7. STRUCTURED PRODUCT LABELING (SPL), Data Elements: (b) (4) (b) (4) to read "methylphenidate transdermal system".

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address – http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

BIOEQUIVALENCE, FACILITY INSPECTIONS/EVALUATIONS

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally the compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

Your resubmission in response to this complete response letter will be considered a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY/DISSOLUTION/CLINICAL BIOEQUIVALENCE/ LABELING

Upon review of your amendment, FDA may identify information in the amendment that requires a change in classification.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Megan Tychinski, Regulatory Project Manager, Division of Project Management, at (240) 402-2717.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 7/27/2016 01:34:55PM
GUID: 5277df670008860f7e1231f730a8684c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

LABELING

6.1113DPLATE:R1SL

Methylphenidate Transdermal System 1.1 mg/hr

6.1114DPLATE:R1SL

Methylphenidate Transdermal System 1.6 mg/hr

6.1115DPLATE:R1SL

Methylphenidate Transdermal System 2.2 mg/hr

6.1112DPLATE:R1SL

Methylphenidate Transdermal System 3.3 mg/hr

Contains: 1 Transdermal System

NDC 0378-8260-16 Rx only

Methylphenidate

Transdermal System

CII

8260:1

This pouch is Child Resistant. Cut Here.

11 mg/hr

Delivers 10 mg over 9 hours (1.1 mg/hr)

Transdermal system should be worn for approximately 9 hours.
Each transdermal system contains 10.4 mg of methylphenidate.

Active ingredient release is limited; please see recommended dosing in patient instructions.

For transdermal use only (applied only to skin).

Important: Keep out of the reach of children.
It is important that this product is disposed of properly.
See patient instructions for disposal information.

Mylan®

Inactive components: polyisobutylene adhesive, mineral oil, hydrophobic colloidal silica, polyester/ethylene vinyl acetate laminate backing film, and polyester release liner.

Keep all transdermal systems within provided containers and dispense one transdermal system daily. Apply immediately upon removal from pouch.

Do not store unpouched. Do not store transdermal systems in refrigerators or freezers.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dosage and Administration: See package insert.

8260:1

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan®
Mylan.com

N 3 0378-8260-16 2

844

Contains: 1 Transdermal System

NDC 0378-8261-16 Rx only

Methylphenidate CII

Transdermal System

8261:1

16 mg/hr

Delivers 15 mg over 9 hours (1.6 mg/hr)

Transdermal system should be worn for approximately 9 hours.
Each transdermal system contains 15.6 mg of methylphenidate.

Active ingredient release is limited; please see recommended dosing in patient instructions.

For transdermal use only (applied only to skin).

Important: Keep out of the reach of children.
It is important that this product is disposed of properly.
See patient instructions for disposal information.

Mylan®

This pouch is Child Resistant. Cut Here.

Inactive components: polyisobutylene adhesive, mineral oil, hydrophobic colloidal silica, polyester/ethylene vinyl acetate laminate backing film, and polyester release liner.

Keep all transdermal systems within provided containers and dispense one transdermal system daily. Apply immediately upon removal from pouch. Do not store unpouched. Do not store transdermal systems in refrigerators or freezers.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dosage and Administration: See package insert.

8261:1

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan®
Mylan.com

N 3 0378-8261-16 9

Contains: 1 Transdermal System

NDC 0378-8262-16 Rx only

Methylphenidate CII

8262:1

Transdermal System

22 mg/hr

Delivers 20 mg over 9 hours (2.2 mg/hr)

Transdermal system should be worn for approximately 9 hours.
Each transdermal system contains 20.7 mg of methylphenidate.

Active ingredient release is limited; please see recommended dosing in patient instructions.

For transdermal use only (applied only to skin).

Important: Keep out of the reach of children.
It is important that this product is disposed of properly.
See patient instructions for disposal information.

Mylan®

This pouch is Child Resistant. Cut Here.

845

Inactive components: polyisobutylene adhesive, mineral oil, hydrophobic colloidal silica, polyester/ethylene vinyl acetate laminate backing film, and polyester release liner.

Keep all transdermal systems within provided containers and dispense one transdermal system daily. Apply immediately upon removal from pouch. Do not store unpouched. Do not store transdermal systems in refrigerators or freezers.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dosage and Administration: See package insert.

8262:1

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan®
Mylan.com

N 3 0378-8262-16 6

Contains: 1 Transdermal System

NDC 0378-8263-16 Rx only

Methylphenidate CII

8263:1

Transdermal System

3.3 mg/hr

Delivers 30 mg over 9 hours (3.3 mg/hr)
Transdermal system should be worn for approximately 9 hours.
Each transdermal system contains 31.1 mg of methylphenidate.

Active ingredient release is limited; please see recommended dosing in patient instructions.

For transdermal use only (applied only to skin).

Important: Keep out of the reach of children.
It is important that this product is disposed of properly.
See patient instructions for disposal information.

Mylan®

This pouch is Child Resistant. Cut Here.

846

Inactive components: polyisobutylene adhesive, mineral oil, hydrophobic colloidal silica, polyester/ethylene vinyl acetate laminate backing film, and polyester release liner.
Keep all transdermal systems within provided containers and dispense one transdermal system daily. Apply immediately upon removal from pouch.
Do not store unpouched. Do not store transdermal systems in refrigerators or freezers.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Dosage and Administration: See package insert.

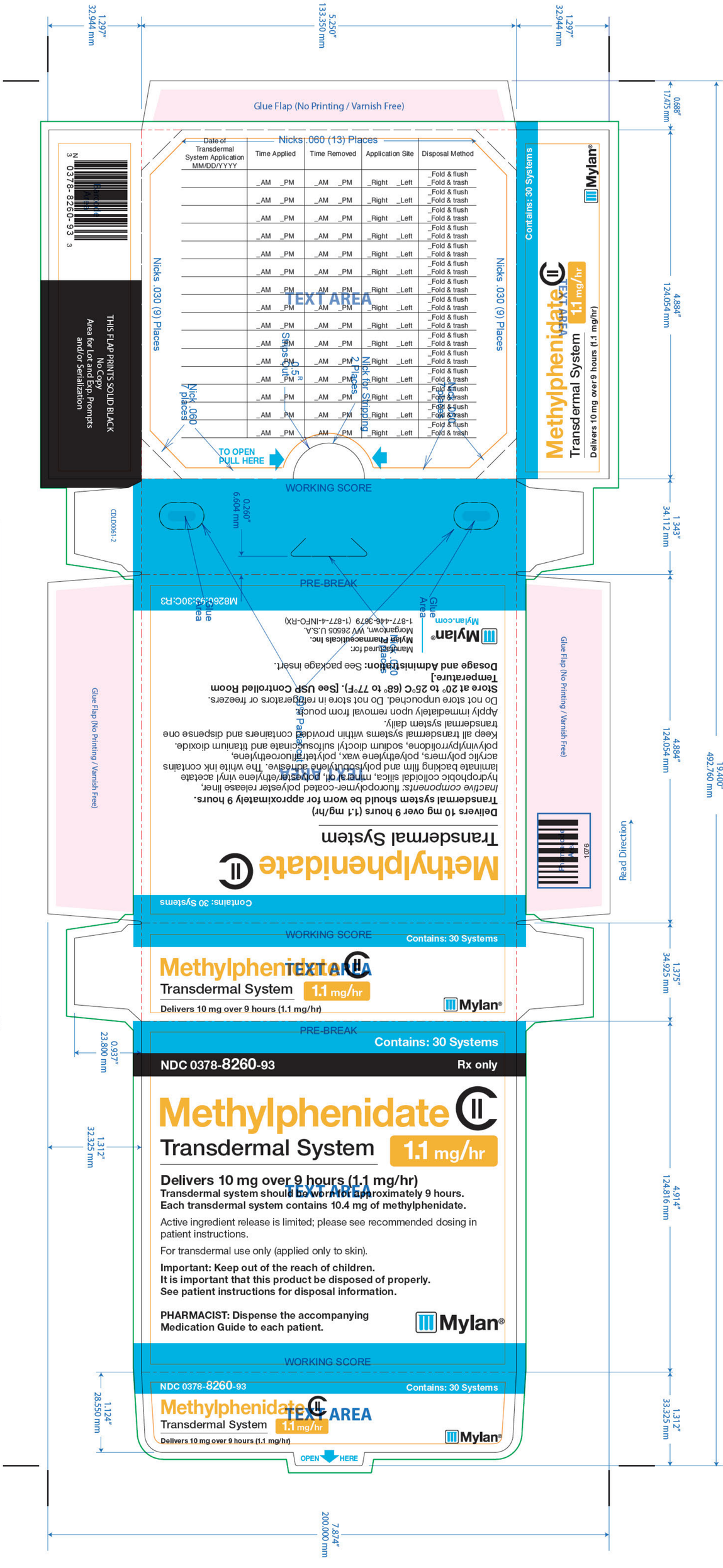
8263:1

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan®
Mylan.com

N3 0378-8263-16 3

TABLE OF CONTENTS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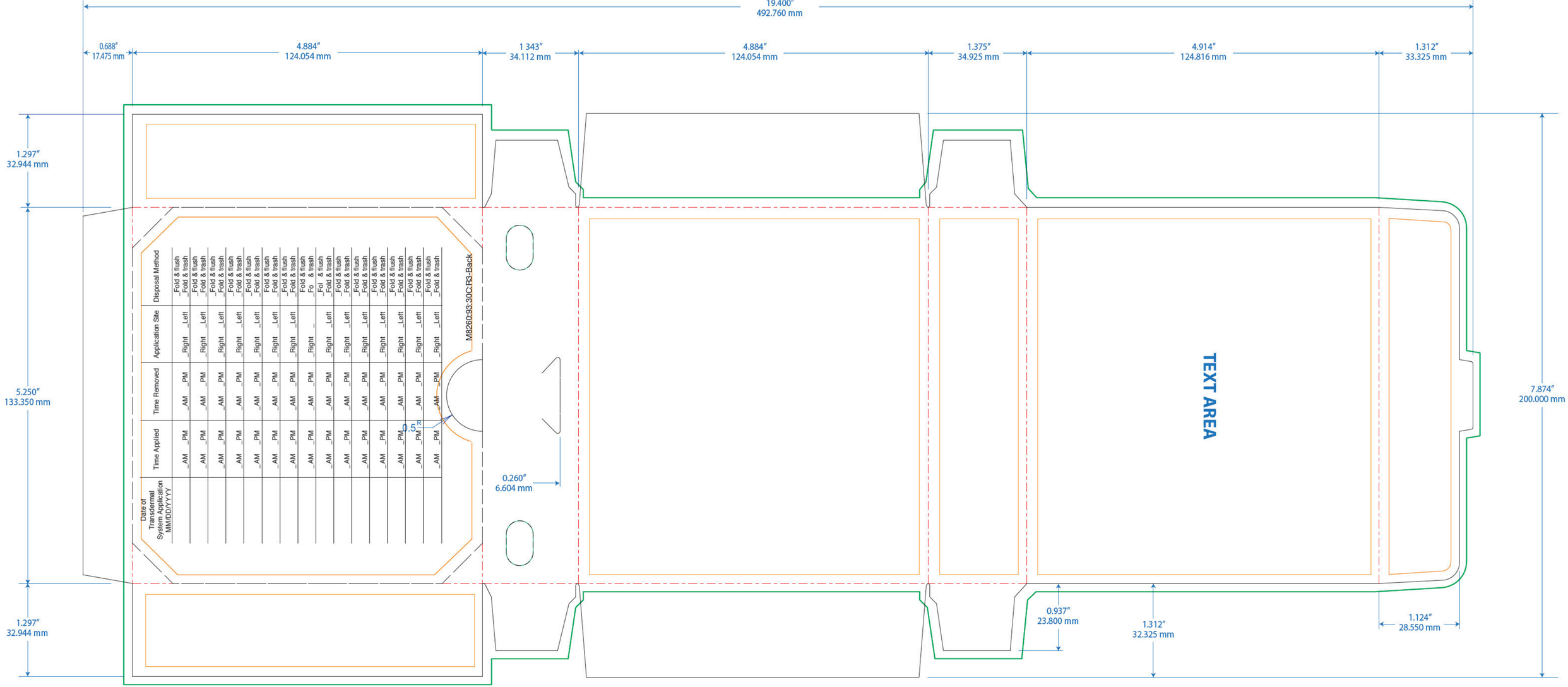
Nicks .060 (13) Places
Date of Transdermal System Application MM/DD/YYYY
Time Applied
Time Removed
Application Site
Disposal Method
_AM _PM
_Right _Left
_Fold & flush
_Fold & trash
Nicks .030 (9) Places
TEXT AREA
TO OPEN PULL HERE
Contains: 30 Systems
Mylan®
Methylphenidate
Transdermal System
1.1 mg/hr
Delivers 10 mg over 9 hours (1.1 mg/hr)
N 3 0378-8260-93 3
THIS FLAP PRINTS SOLID BLACK
No Copy
Area for Lot and Exp. Prompts and/or Serialization
WORKING SCORE
PRE-BREAK
Glue Area
Mylan.com
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
1-877-446-3679 (1-877-4-INFO-RX)
Dosage and Administration: See package insert.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Delivers 10 mg over 9 hours (1.1 mg/hr)
Transdermal system should be worn for approximately 9 hours.
Inactive components: fluoropolymer-coated polyester release liner, hydrophobic colloidal silica, mineral oil, polyester/ethylene vinyl acetate laminate backing film and polyisobutylene adhesive. The white ink contains acrylic polymers, polyethylene wax, polytetrafluoroethylene, polyvinylpyrrolidone, sodium dioctyl sulfosuccinate and titanium dioxide.
Keep all transdermal systems within provided containers and dispense one transdermal system daily.
Apply immediately upon removal from pouch.
Do not store unpouched. Do not store in refrigerators or freezers.
Contains: 30 Systems
NDC 0378-8260-93
Rx only
Methylphenidate
Transdermal System
1.1 mg/hr
Delivers 10 mg over 9 hours (1.1 mg/hr)
Transdermal system should be worn for approximately 9 hours.
Each transdermal system contains 10.4 mg of methylphenidate.
Active ingredient release is limited; please see recommended dosing in patient instructions.
For transdermal use only (applied only to skin).
Important: Keep out of the reach of children.
It is important that this product be disposed of properly.
See patient instructions for disposal information.
PHARMACIST: Dispense the accompanying Medication Guide to each patient.
TEXT AREA
OPEN HERE
Read Direction
CDL00061-2
(b) (4)
1.297" 32.944 mm
5.250" 133.350 mm
0.688" 17.475 mm
4.884" 124.054 mm
1.343" 34.112 mm
1.375" 34.925 mm
0.937" 23.800 mm
1.312" 32.325 mm
1.124" 28.550 mm
19.400" 492.760 mm
7.874" 200.000 mm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32.944 mm
5.250″
133.350 mm
1.297″
32.944 mm
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200.000 mm
Date of Transdermal System Application MM/DD/YYYY
Time Applied
Time Removed
Application Site
Disposal Method
M8260:93:30C:R3:Back
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28.550 mm

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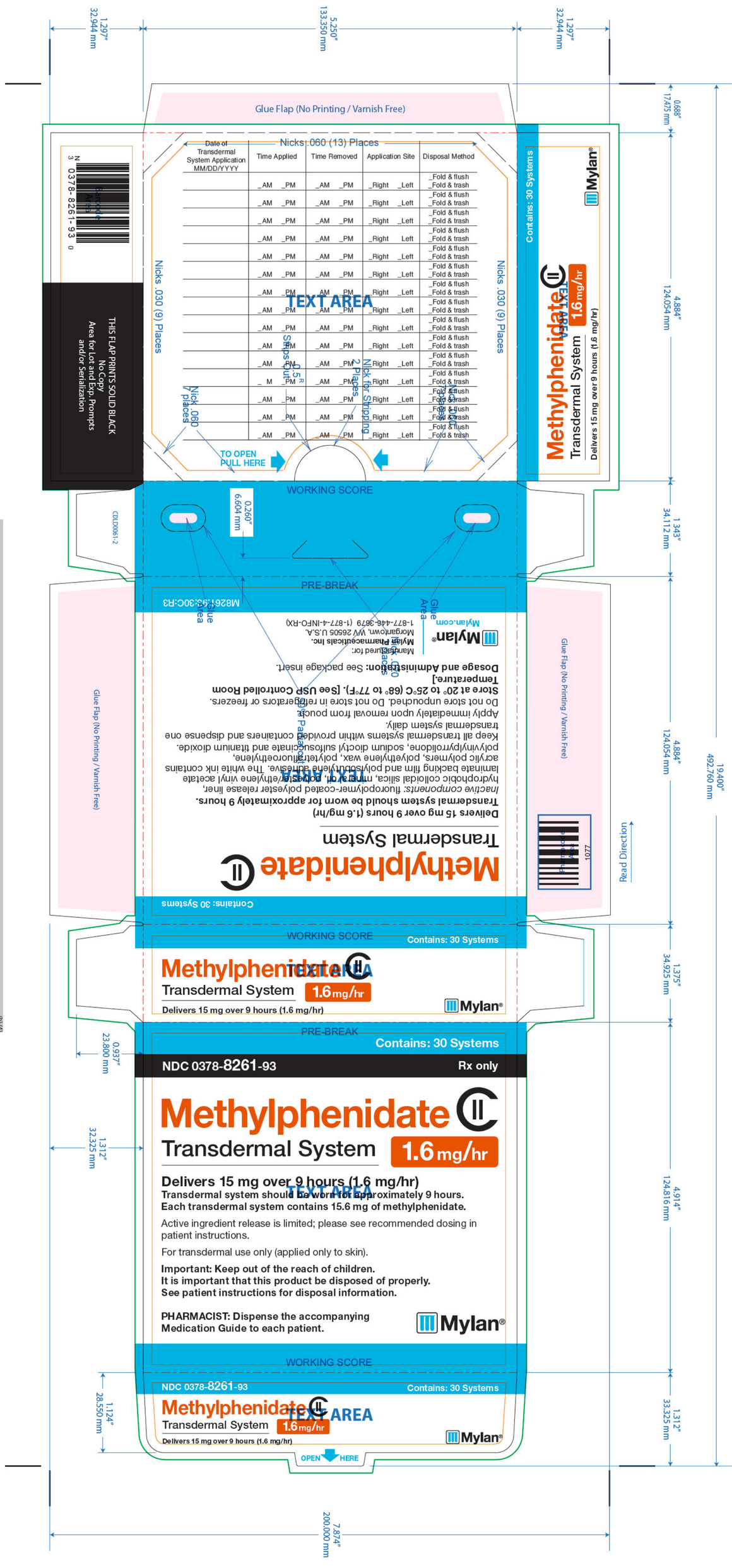
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Nicks .060 (13) Places
Date of Transdermal System Application MM/DD/YYYY
Time Applied
Time Removed
Application Site
Disposal Method
_AM _PM
_Right _Left
_Fold & flush
_Fold & trash
TEXT AREA
Nicks .030 (9) Places
Contains: 30 Systems
Mylan®
Methylphenidate
Transdermal System
1.6 mg/hr
Delivers 15 mg over 9 hours (1.6 mg/hr)
THIS FLAP PRINTS SOLID BLACK
No Copy
Area for Lot and Exp. Prompts and/or Serialization
Nick .060 7 places
Nicks .030 2 Places
Nick for Stripping
Snips Out
TO OPEN PULL HERE
WORKING SCORE
0.260" 6.604 mm
PRE-BREAK
Glue Area
Mylan.com
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
1-877-446-3679 (1-877-4-INFO-RX)
Dosage and Administration: See package insert.
Temperature.]
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room
Do not store unpouched. Do not store in refrigerators or freezers.
Apply immediately upon removal from pouch.
transdermal system daily.
Keep all transdermal systems within provided containers and dispense one
polyvinylpyrrolidone, sodium dioctyl sulfosuccinate and titanium dioxide.
acrylic polymers, polyethylene wax, polytetrafluoroethylene,
laminate backing film and polyisobutylene adhesive. The white ink contains
hydrophobic colloidal silica, methacrylic acid/ethylene vinyl acetate
Inactive components: fluoropolymer-coated polyester release liner,
Transdermal system should be worn for approximately 9 hours.
Delivers 15 mg over 9 hours (1.6 mg/hr)
Contains: 30 Systems
Read Direction
Contains: 30 Systems
NDC 0378-8261-93
Rx only
Methylphenidate
Transdermal System
1.6 mg/hr
Delivers 15 mg over 9 hours (1.6 mg/hr)
Transdermal system should be worn for approximately 9 hours.
Each transdermal system contains 15.6 mg of methylphenidate.
Active ingredient release is limited; please see recommended dosing in patient instructions.
For transdermal use only (applied only to skin).
Important: Keep out of the reach of children.
It is important that this product be disposed of properly.
See patient instructions for disposal information.
PHARMACIST: Dispense the accompanying Medication Guide to each patient.
OPEN HERE
CDLD0061-2
(0) (4)
1.297" 32.944 mm
5.250" 133.350 mm
1.297" 32.944 mm
0.688" 17.475 mm
4.884" 124.054 mm
1.343" 34.112 mm
4.884" 124.054 mm
1.375" 34.925 mm
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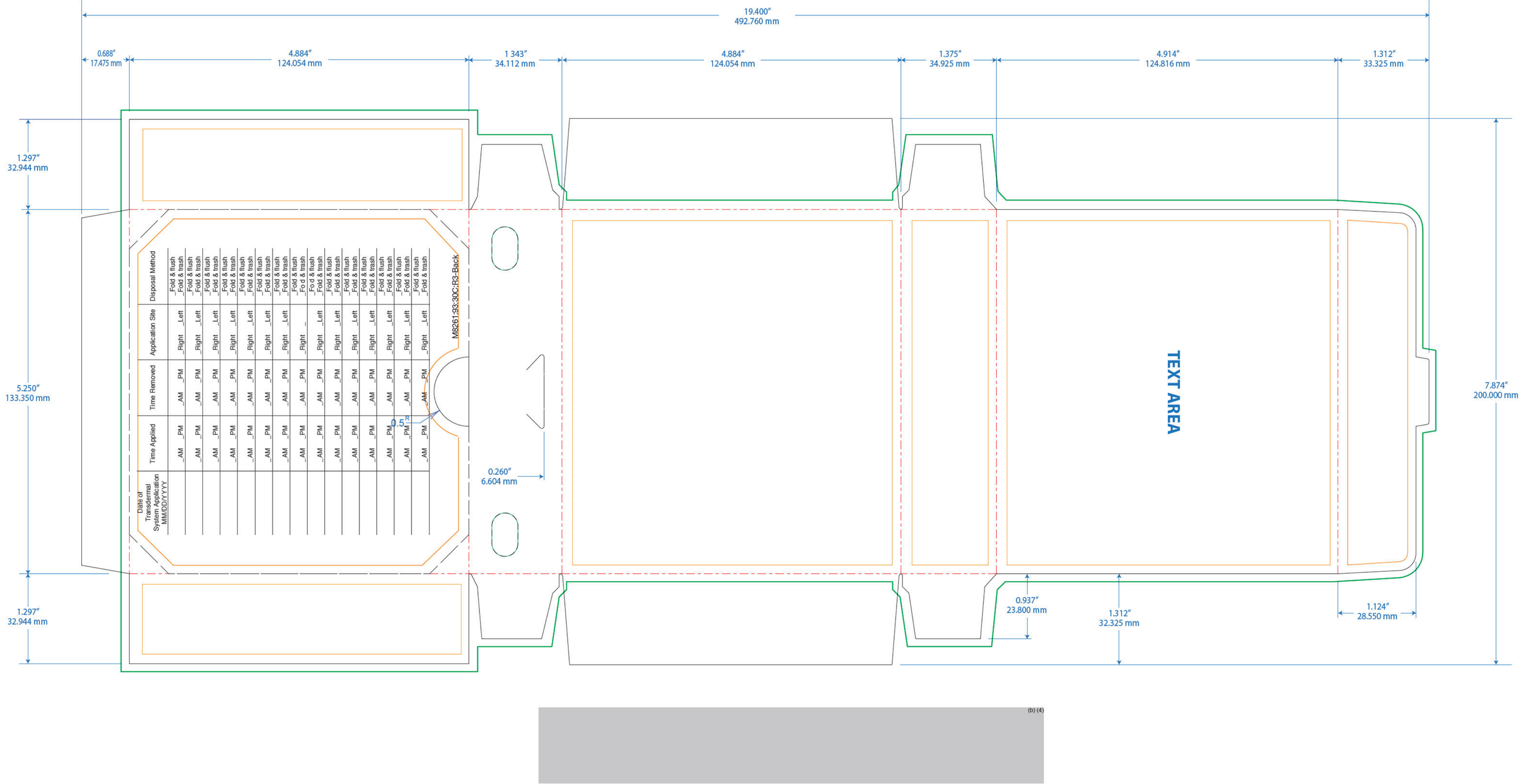
4.914" 124.816 mm
1.124" 28.550 mm
1.312" 33.325 mm
19.400" 492.760 mm
7.874" 200.000 mm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133.350 mm
1.297″
32.944 mm
7.874″
200.000 mm
Date of Transdermal System Application MM/DD/YYYY
Time Applied
Time Removed
Application Site
Disposal Method
_AM _PM
_Right _Left
_Fold & flush
_Fold & trash
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0.260″
6.604 mm
TEXT AREA
0.937″
23.800 mm
1.312″
32.325 mm
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28.550 mm

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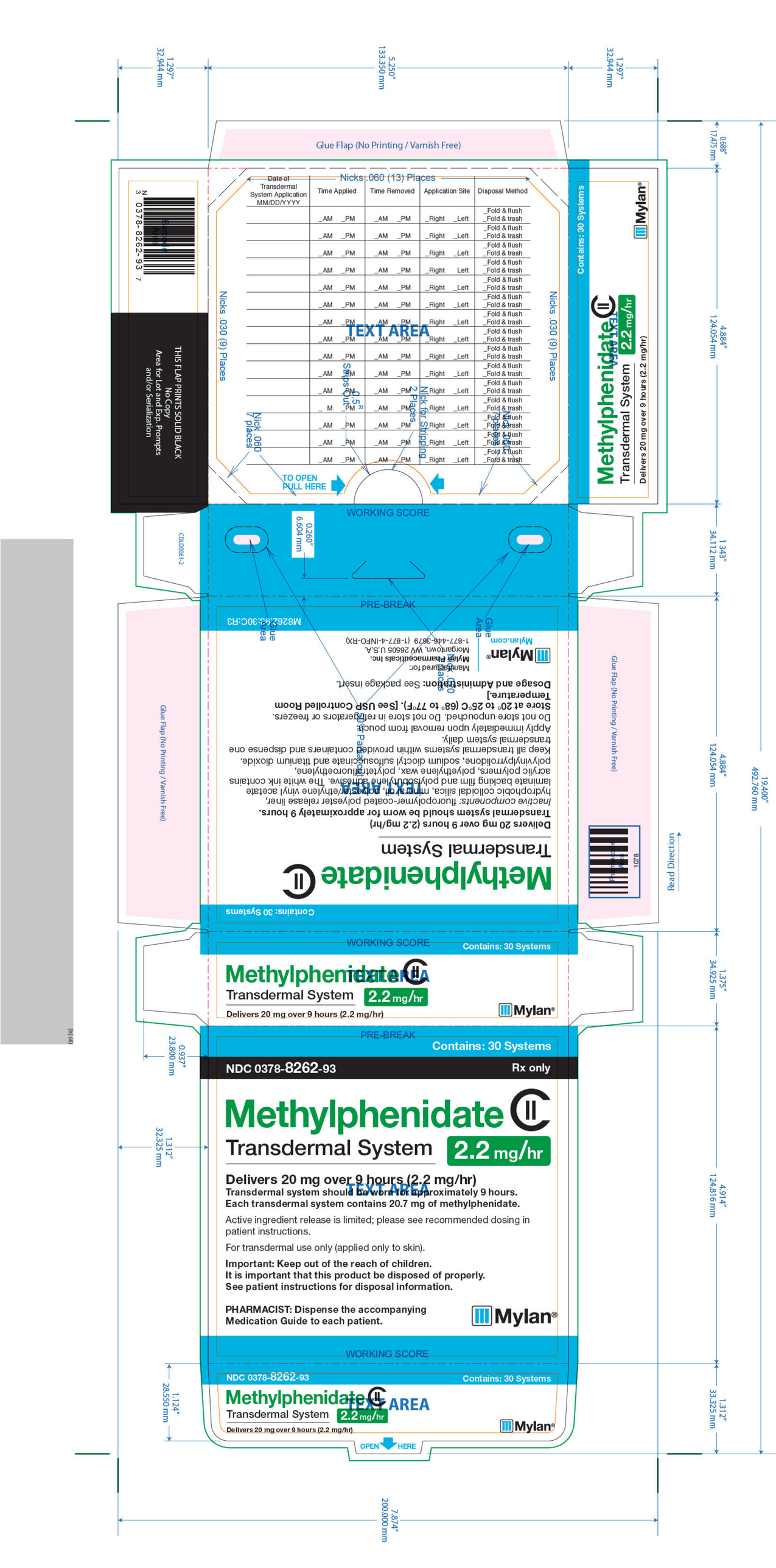
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Time Applied
Time Removed
Application Site
Disposal Method
_AM _PM
_Right _Left
_Fold & flush
_Fold & trash
TEXT AREA
Nicks .030 (9) Places
Nicks .030 (9) Places
Contains: 30 Systems
Mylan®
Methylphenidate
Transdermal System
2.2 mg/hr
Delivers 20 mg over 9 hours (2.2 mg/hr)
N 3 0378-8262-93 7
Remove Liner
THIS FLAP PRINTS SOLID BLACK
No Copy
Area for Lot and Exp. Prompts and/or Serialization
Nick .060 7 places
Steps Cut
Nick for Stripping
2 Places
TO OPEN PULL HERE
WORKING SCORE
0.260" 6.604 mm
CDLD0061-2
PRE-BREAK
M8262;93;30C;R3
Glue Area
Mylan.com
Mylan®
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
1-877-446-3679 (1-877-4-INFO-RX)
Dosage and Administration: See package insert.
Temperature.]
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room
Do not store unpouched. Do not store in refrigerators or freezers.
Apply immediately upon removal from pouch.
transdermal system daily.
Keep all transdermal systems within provided containers and dispense one
polyvinylpyrrolidone, sodium dioctyl sulfosuccinate and titanium dioxide.
acrylic polymers, polyethylene wax, polytetrafluoroethylene,
laminate backing film and polyisobutylene adhesive. The white ink contains
hydrophobic colloidal silica, microcrystalline, polyester/ethylene vinyl acetate
Inactive components: fluoropolymer-coated polyester release liner,
Transdermal system should be worn for approximately 9 hours.
Delivers 20 mg over 9 hours (2.2 mg/hr)
TEXT AREA
Methylphenidate
Transdermal System
Contains: 30 Systems
Glue Area
Glue Flap (No Printing / Varnish Free)
Glue Flap (No Printing / Varnish Free)
Read Direction
WORKING SCORE
Contains: 30 Systems
Methylphenidate
Transdermal System
2.2 mg/hr
Delivers 20 mg over 9 hours (2.2 mg/hr)
Mylan®
PRE-BREAK
Contains: 30 Systems
NDC 0378-8262-93
Rx only
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Important: Keep out of the reach of children.
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NDC 0378-8262-93
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1.297" 32.944 mm
5.250" 133.350 mm
1.297" 32.944 mm
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4.884" 124.054 mm
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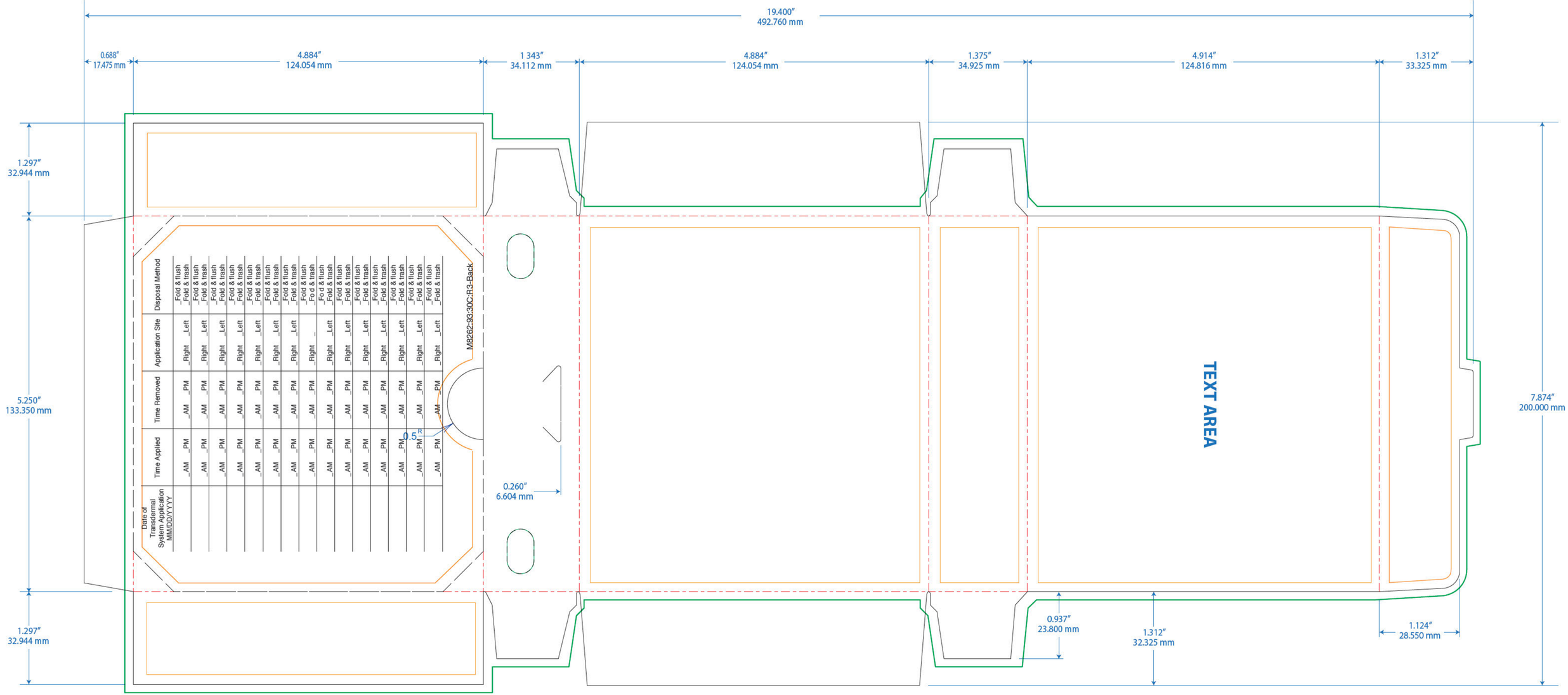
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33.325 mm
1.297″
32.944 mm
5.250″
133.350 mm
1.297″
32.944 mm
7.874″
200.000 mm
Disposal Method
Application Site
Time Removed
Time Applied
Date of Transdermal System Application MM/DD/YYYY
Fold & flush
Fold & trash
Left
Right
AM
PM
M8262:93:30C:R3:Back
0.5
0.260″
6.604 mm
TEXT AREA
0.937″
23.800 mm
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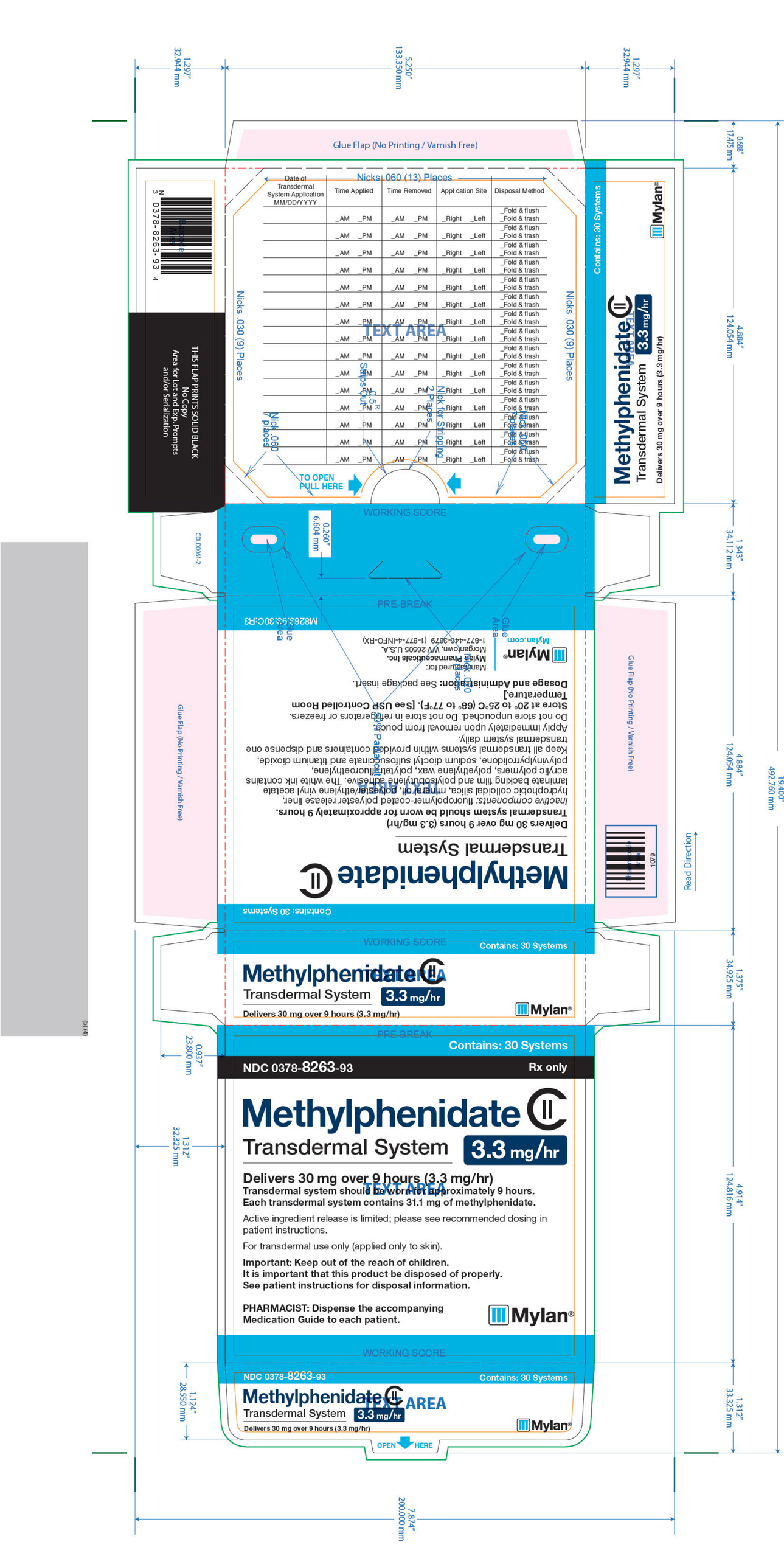
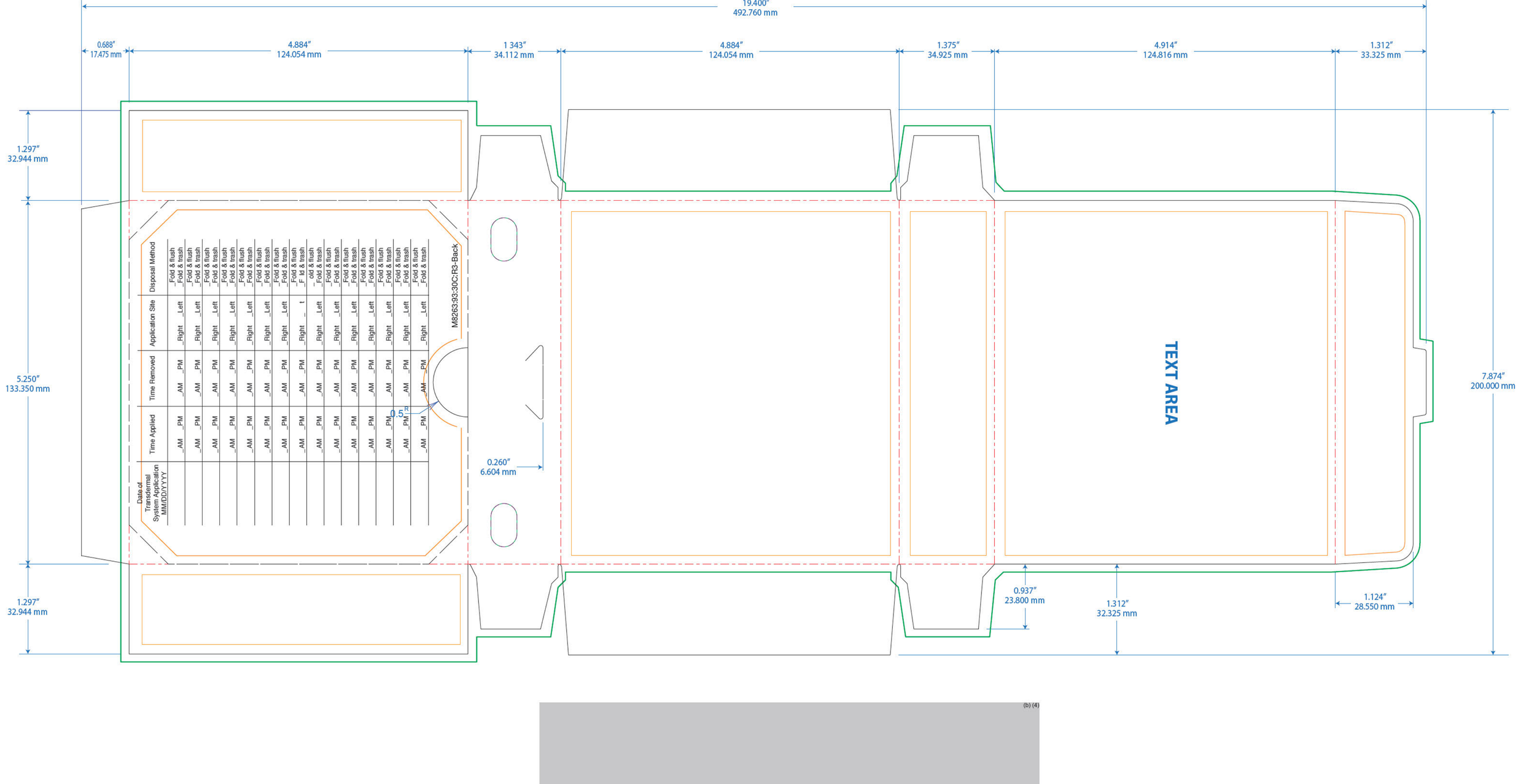
1.124″
28.550 mm

(b) (4)


Glue Flap (No Printing / Varnish Free)
Nicks .060 (13) Places
Date of Transdermal System Application MM/DD/YYYY
Time Applied
Time Removed
Appl cation Site
Disposal Method
_AM _PM
_Right _Left
_Fold & flush
_Fold & trash
Nicks .030 (9) Places
Contains: 30 Systems
Mylan®
Methylphenidate
Transdermal System 3.3 mg/hr
Delivers 30 mg over 9 hours (3.3 mg/hr)
TEXT AREA
THIS FLAP PRINTS SOLID BLACK
No Copy
Area for Lot and Exp. Prompts
and/or Serialization
Nick .060 7 places
Nick .060 2 Places
Nick for Stripping
Steps Cut 1.5R
TO OPEN PULL HERE
WORKING SCORE
0.260" 6.604 mm
CDLD0061-2
PRE-BREAK
M8263:93:30C:R3
Glue Area
Mylan®
Mylan.com
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
1-877-446-3679 (1-877-4-INFO-RX)
Dosage and Administration: See package insert.
Temperature.]
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room
Do not store unpouched. Do not store in refrigerators or freezers.
Apply immediately upon removal from pouch.
transdermal system daily.
Keep all transdermal systems within provided containers and dispense one
polyvinylpyrrolidone, sodium dioctyl sulfosuccinate and titanium dioxide.
acrylic polymers, polyethylene wax, polytetrafluoroethylene,
laminate backing film and polyisobutylene adhesive. The white ink contains
hydrophobic colloidal silica, mineral oil, polyester/ethylene vinyl acetate
Inactive components: fluoropolymer-coated polyester release liner,
Transdermal system should be worn for approximately 9 hours.
Delivers 30 mg over 9 hours (3.3 mg/hr)
Contains: 30 Systems
Methylphenidate
Transdermal System
Read Direction
Glue Flap (No Printing / Varnish Free)
Contains: 30 Systems
NDC 0378-8263-93
Rx only
Methylphenidate
Transdermal System 3.3 mg/hr
Delivers 30 mg over 9 hours (3.3 mg/hr)
Transdermal system should be worn for approximately 9 hours.
Each transdermal system contains 31.1 mg of methylphenidate.
Active ingredient release is limited; please see recommended dosing in patient instructions.
For transdermal use only (applied only to skin).
Important: Keep out of the reach of children.
It is important that this product be disposed of properly.
See patient instructions for disposal information.
PHARMACIST: Dispense the accompanying Medication Guide to each patient.
Mylan®
WORKING SCORE
NDC 0378-8263-93
Contains: 30 Systems
Methylphenidate
Transdermal System 3.3 mg/hr
Delivers 30 mg over 9 hours (3.3 mg/hr)
Mylan®
OPEN HERE
1.297" 32.944 mm
5.250" 133.350 mm
1.297" 32.944 mm
0.688" 17.475 mm
4.884" 124.054 mm
1.343" 34.112 mm
4.884" 124.054 mm
1.375" 34.925 mm
0.937" 23.800 mm
1.312" 32.325 mm
4.914" 124.816 mm
1.124" 28.550 mm
1.312" 33.325 mm
19.400" 492.760 mm
7.874" 200.000 mm


19.400″
492.760 mm
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34.112 mm
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124.054 mm
1.375″
34.925 mm
4.914″
124.816 mm
1.312″
33.325 mm
1.297″
32.944 mm
5.250″
133.350 mm
1.297″
32.944 mm
7.874″
200.000 mm
Date of Transdermal System Application MM/DD/YYYY
Time Applied
Time Removed
Application Site
Disposal Method
M8263:93:30C:R3-Back
0.5
0.260″
6.604 mm
TEXT AREA
0.937″
23.800 mm
1.312″
32.325 mm
1.124″
28.550 mm

(b) (4)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METHYLPHENIDATE TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for METHYLPHENIDATE TRANSDERMAL SYSTEM.

METHYLPHENIDATE transdermal system Ⓒ
Initial U.S. Approval: 2006

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning

Methylphenidate transdermal system should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior.

----------INDICATIONS AND USAGE----------

- Methylphenidate transdermal system is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). (1)
- Children (ages 6-12): the efficacy of methylphenidate transdermal system in ADHD was established in two 7-week controlled trials in children (1)
- Adolescents (ages 13-17): the efficacy of methylphenidate transdermal system in ADHD was established in one 7-week, controlled study in adolescents (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dose for patients new to or converting from another formulation of methylphenidate is 10 mg. (2)
- Methylphenidate transdermal system should be applied to the hip area (using alternating sites) 2 hours before an effect is needed and should be removed 9 hours after application. Methylphenidate transdermal system may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. (2)
- Dosage should be titrated to effect. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient. (2)
- **Patients should be advised to follow the full instructions for transdermal system use provided in the Medication Guide.** (17)

----------DOSAGE FORMS AND STRENGTHS----------

- Transdermal System: 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), 30 mg/9 hours (3.3 mg/hr)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to methylphenidate (4.1)
- Marked anxiety, tension, or agitation (4.2)
- Glaucoma (4.3)
- Tics or a family history or diagnosis of Tourette's syndrome (4.4)
- Patients currently using or within 2 weeks of using an MAO inhibitor (4.5)

----------WARNINGS AND PRECAUTIONS----------

- Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (5.1)
- Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. (5.1)
- Psychiatric Adverse Events: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior. (5.2)
- Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. (5.3)
- Priapism: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed (5.4)
- Peripheral Vasculopathy, including Raynaud's phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.5)
- Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients. (5.6)
- Chemical Leukoderma: Methylphenidate transdermal system use may result in a persistent loss of skin pigmentation at and around the application site. Loss of pigmentation, in some cases, has been reported at other sites distant from the application site. Monitor for signs of skin depigmentation. Discontinue methylphenidate transdermal system if it occurs. (5.7)
- Contact Sensitization: Use of methylphenidate transdermal system may lead to contact sensitization. Treatment should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of methylphenidate transdermal system and is not by itself an indication of sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the transdermal system site. (5.8)
- Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (5.9)
- External Heat: Patients should be advised to avoid exposing the methylphenidate transdermal system application site to direct external heat sources. When heat is applied to methylphenidate transdermal system after transdermal system application, both the rate and extent of absorption are significantly increased. (5.10)
- Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy. (5.11)

----------ADVERSE REACTIONS----------

- Children (ages 6-12): The most commonly (≥ 5% and twice the rate of placebo) reported adverse reactions in a placebo-controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affect lability, and anorexia (6.1).
- Adolescents (ages 13-17): The most commonly (≥ 5% and twice the rate of placebo) reported adverse reactions in a placebo-controlled trial in adolescents aged 13-17 included appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain, and anorexia. The majority of subjects in these trials had erythema at the application site (6.1).
- The most common (≥ 2% of subjects) adverse reaction associated with discontinuations in controlled clinical trials in children or adolescents was application site reactions (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Methylphenidate transdermal system may increase blood pressure; use cautiously with vasopressors. (7.2)
- Antihypertensive drugs: Monitor blood pressure. Adjust dosage of antihypertensive drug as needed. (7 3)
- Methylphenidate may inhibit metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric Use: has not been studied in children under 6 years of age. (8.4)
- Geriatric Use: has not been studied in geriatric patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DRUG DEPENDENCE

Methylphenidate transdermal system should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 INDICATIONS AND USAGE

Methylphenidate transdermal system is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of methylphenidate transdermal system in patients diagnosed with ADHD was established in two 7-week controlled clinical trials in children (ages 6-12) and one 7-week, controlled clinical trial in adolescents (ages 13-17).

A diagnosis of ADHD (DSM-IV-TR®) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

1.1 Special Diagnostic Considerations

The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV-TR® characteristics.

1.2 Need for Comprehensive Treatment Program

Methylphenidate transdermal system is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis.

Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

2 DOSAGE AND ADMINISTRATION

It is recommended that methylphenidate transdermal system be applied to the hip area 2 hours before an effect is needed and should be removed 9 hours after application. Dosage should be titrated to effect. The recommended dose titration schedule is shown in the table below. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient.

Table 1 Methylphenidate Transdermal System - Recommended Titration Schedule (Patients New to Methylphenidate)

Upward Titration, if Response is Not Maximized				
	Week 1	Week 2	Week 3	Week 4
Transdermal System Size	9.6 cm^2	14.4 cm^2	19.2 cm^2	28.8 cm^2
Nominal Delivered Dose* (mg/9 hours)	10 mg	15 mg	20 mg	30 mg
Delivery Rate*	(1.1 mg/hr)*	(1.6 mg/hr)*	(2.2 mg/hr)*	(3.3 mg/hr)*

*Nominal *in vivo* delivery rate in children and adolescents when applied to the hip, based on a 9-hour wear period.

Patients converting from another formulation of methylphenidate should follow the above titration schedule due to differences in bioavailability of methylphenidate transdermal system compared to other products.

2.1 Application

The parent or caregiver should be encouraged to use the administration chart included with each carton of methylphenidate transdermal system to monitor application and removal time, and method of disposal. It is recommended that parents or caregivers apply and remove the transdermal system for children; responsible adolescents may apply or remove the transdermal system themselves if appropriate. The Medication Guide included at the end of this insert also includes a timetable to calculate when to remove methylphenidate transdermal system, based on the 9-hour application time.

The adhesive side of methylphenidate transdermal system should be placed on a clean, dry area of the hip. The area selected should not be oily, damaged, or irritated. Apply the transdermal system to the hip area avoiding the waistline, since clothing may cause the transdermal system to rub off. When applying the transdermal system the next morning, place on the opposite hip at a new site if possible.

If patients or caregivers experience difficulty separating the transdermal system from the release liner or observe transfer of adhesive to the liner, tearing and/or other damage to the transdermal system during removal from the liner, the transdermal system should be discarded according to

the directions provided below, and a new transdermal system should be applied. Patients or caregivers should inspect the release liner to ensure that no adhesive containing medication has transferred to the liner. If adhesive transfer has occurred, the transdermal system should be discarded.

Methylphenidate transdermal system should be applied immediately after opening the individual pouch and removing the protective liner. Do not use if the individual pouch seal is broken or if the transdermal system appears to be damaged. Do not cut transdermal systems. Only intact transdermal systems should be applied. The transdermal system should then be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure that there is good contact of the transdermal system with the skin, especially around the edges. Exposure to water during bathing, swimming, or showering can affect transdermal system adherence. Transdermal systems should not be applied or re-applied with dressings, tape, or other common adhesives. In the event that a transdermal system does not fully adhere to the skin upon application, or becomes partially or fully detached during wear time, the transdermal system should be discarded according to the directions provided in this label *[see Dosage and Administration (2.3)]* and a new transdermal system may be applied at a different site. The total recommended wear time for that day should remain 9 hours regardless of the number of transdermal systems used *[see Patient Counseling Information (17)]*.

All patients should be advised to avoid exposing the methylphenidate transdermal system application site to direct external heat sources, such as hair dryers, heating pads, electric blankets, heated water beds, etc., while wearing the transdermal system *[see Warnings and Precautions (5.10)]*. When heat is applied to methylphenidate transdermal system after transdermal system application, both the rate and the extent of absorption are significantly increased. The temperature-dependent increase in methylphenidate absorption can be greater than 2-fold *[see Clinical Pharmacology (12.3)]*. This increased absorption can be clinically significant and result in overdose of methylphenidate *[see Overdosage (10)]*.

Transdermal systems should not be stored in refrigerators or freezers.

2.2 Removal of Methylphenidate Transdermal System

Methylphenidate transdermal systems should be peeled off slowly. If necessary, transdermal system removal may be facilitated by gently applying an oil-based product (i.e., petroleum jelly, olive oil, or mineral oil) to the transdermal system edges, gently working the oil underneath the transdermal system edges. If any adhesive remains on the skin following transdermal system removal, an oil-based product may be applied to transdermal system sites in an effort to gently loosen and remove any residual adhesive that remains following transdermal system removal.

In the unlikely event that a transdermal system remains tightly adhered despite these measures, the patient or caregiver should contact the physician or pharmacist. Nonmedical adhesive removers and acetone-based products (i.e., nail polish remover) should not be used to remove methylphenidate transdermal systems or adhesive.

2.3 Disposal of Methylphenidate Transdermal System

Upon removal of methylphenidate transdermal system, used transdermal systems should be folded so that the adhesive side of the transdermal system adheres to itself and should be flushed down the toilet or disposed of in an appropriate lidded container. If the patient stops using the prescription, each unused transdermal system should be removed from its individual pouch, separated from the protective liner, folded onto itself, and disposed of in the same manner as used transdermal systems.

The parent or caregiver should be encouraged to record on the administration chart included with each carton the time that each transdermal system was applied and removed. If a transdermal system was removed without the parent or caregiver's knowledge, or if a transdermal system is missing from the carton or pouch, the parent or caregiver should be encouraged to ask the child when and how the transdermal system was removed.

2.4 Maintenance/Extended Treatment

There is no body of evidence available from controlled clinical trials to indicate how long the patient with ADHD should be treated with methylphenidate transdermal system. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. The effectiveness of methylphenidate transdermal system for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use methylphenidate transdermal system for extended periods should periodically re-evaluate the long-term usefulness of methylphenidate transdermal system for the individual patient with periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

2.5 Dose/Wear Time Reduction and Discontinuation

Methylphenidate transdermal system may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. Plasma concentrations of *d*-methylphenidate generally begin declining when the transdermal system is removed, although absorption may continue for several hours. Individualization of wear time may help manage some of the side effects caused by methylphenidate. If aggravation of symptoms or other adverse events occur, the dosage or wear time should be reduced, or, if necessary, the drug should be discontinued. Residual methylphenidate remains in used transdermal systems when worn as recommended.

3 DOSAGE FORMS AND STRENGTHS

Four dosage strengths of Methylphenidate Transdermal System are available as 10 mg/9 hrs (1.1 mg/hr), 15 mg/9 hrs (1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) or 30 mg/9 hrs (3.3 mg/hr) of methylphenidate.

- Each dosage form is a translucent rectangular transdermal system with rounded corners consisting of a matte backing film randomly printed with "Methylphenidate Transdermal System" and the "mg/hr" strength in white ink, an adhesive layer and a clear to slightly hazy oversized release liner that is slit. Each transdermal system is overlaid with an additional clear to slightly hazy oversized release liner and is contained in a square, flat pouch that is imprinted with lot number and expiration date.

Nominal Dose Delivered (mg) Over 9 Hours*	Dosage Rate* (mg/hr)	Transdermal System Size (cm^2)	Methylphenidate Content per Transdermal System (mg)
10	1.1	9.6	10.4
15	1.6	14.4	15.6
20	2.2	19.2	20.7
30	3.3	28.8	31.1

*Nominal *in vivo* delivery rate in children and adolescents when applied to the hip, based on a 9-hour wear period.

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate

Methylphenidate transdermal system is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product (fluoropolymer-coated polyester, hydrophobic colloidal silica, mineral oil, polyester/ethylene vinyl acetate laminate film backing, polyisobutylene adhesive and white ink). The white ink contains acrylic polymers, polyethylene wax, polytetrafluoroethylene, polyvinylpyrrolidone, sodium dioctyl sulfosuccinate and titanium dioxide *[see Description (11.1)]*.

4.2 Agitation

Methylphenidate transdermal system is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

4.3 Glaucoma

Methylphenidate transdermal system is contraindicated in patients with glaucoma.

4.4 Tics

Methylphenidate transdermal system is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome *[see Adverse Reactions (6.1)]*.

4.5 Monoamine Oxidase Inhibitors

Methylphenidate transdermal system is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

5 WARNINGS AND PRECAUTIONS

5.1 Serious Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems: *Children and Adolescents:* Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry

an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults: Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions: Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia *[see Adverse Reactions (6.1)]*.

Assessing Cardiovascular Status in Patients Being Treated With Stimulant Medications: Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

5.2 Psychiatric Adverse Events

Pre-existing Psychosis: Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness: Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms: Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short term,

placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to none in placebo-treated patients.

Aggression: Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

5.3 Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

5.4 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.5 Peripheral Vasculopathy, including Raynaud's phenomenon

Stimulant medications, including methylphenidate transdermal system, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.6 Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well.

Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.7 Chemical Leukoderma

Methylphenidate transdermal system use may result in a persistent loss of skin pigmentation at and around the application site. Loss of pigmentation, in some cases, has been reported at other sites distant from the application site. Chemical leukoderma can mimic the appearance of vitiligo, particularly when the loss of skin pigmentation involves areas distant from the application site. Individuals with a history of vitiligo and/or a family history of vitiligo may be more at risk. Skin depigmentation may persist even after methylphenidate transdermal system use is discontinued. Monitor for signs of skin depigmentation, and advise patients to immediately inform their healthcare provider if changes in skin pigmentation occur. Discontinue use of the methylphenidate transdermal system in patients with chemical leukoderma.

5.8 Contact Sensitization

In an open-label study of 305 subjects conducted to characterize dermal reactions in children with ADHD treated with methylphenidate transdermal system using a 9-hour wear time, one subject (0.3%) was confirmed by transdermal system testing to be sensitized to methylphenidate (allergic contact dermatitis). This subject experienced erythema and edema at methylphenidate transdermal system application sites with concurrent urticarial lesions on the abdomen and legs resulting in treatment discontinuation. This subject was not transitioned to oral methylphenidate.

Use of methylphenidate transdermal system may lead to contact sensitization. Methylphenidate transdermal system should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of methylphenidate transdermal system and is not by itself an indication of sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the transdermal system site. Confirmation of a diagnosis of contact sensitization (allergic contact dermatitis) may require further diagnostic testing.

Patients sensitized from use of methylphenidate transdermal system, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, e.g., orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive transdermal system-test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting. No cases of systemic sensitization have been observed in clinical trials of methylphenidate transdermal system.

Patients who develop contact sensitization to methylphenidate transdermal system and require oral treatment with methylphenidate should be initiated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate by exposure to methylphenidate transdermal system may not be able to take methylphenidate in any form.

5.9 Visual Disturbance
Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

5.10 Patients Using External Heat
Patients should be advised to avoid exposing the methylphenidate transdermal system application site to direct external heat sources, such as hair dryers, heating pads, electric blankets, heated water beds, etc., while wearing the transdermal system. When heat is applied to methylphenidate transdermal system after transdermal system application, both the rate and extent of absorption are significantly increased. The temperature-dependent increase in methylphenidate absorption can be greater than 2-fold *[see Clinical Pharmacology (12.3)]*. This increased absorption can be clinically significant and can result in overdose of methylphenidate *[see Overdosage (10)]*.

5.11 Hematologic Monitoring
Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

6 ADVERSE REACTIONS
Detailed information on serious and adverse reactions of particular importance is provided in the *Boxed Warning* and *Warnings and Precautions (5)* sections:

- Drug dependence *[see Boxed Warning]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4.1)]*
- Marked anxiety, tension, or agitation *[see Contraindications (4.2)]*
- Glaucoma *[see Contraindications (4.3)]*
- Tics or a family history of Tourette's syndrome *[see Contraindications (4.4)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4.5) and Drug Interactions (7.1)]*
- Serious Cardiovascular Events *[see Warnings and Precautions (5.1)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.1)]*
- Psychiatric Adverse Events *[see Warnings and Precautions (5.2)]*
- Seizures *[see Warnings and Precautions (5.3)]*
- Priapism *[see Warnings and Precautions (5.4)]*
- Peripheral Vasculopathy *[see Warnings and Precautions (5.5)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.6)]*
- Chemical Leukoderma *[see Warnings and Precautions (5.7)]*
- Contact Sensitization *[see Warnings and Precautions (5.8)]*
- Visual Disturbance *[see Warnings and Precautions (5.9)]*
- External Heat *[see Warnings and Precautions (5.10)]*
- Hematologic Monitoring *[see Warnings and Precautions (5.11)]*

The most commonly reported (frequency ≥ 5% and twice the rate of placebo) adverse reactions in a controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affect lability, and anorexia. The most commonly reported (frequency ≥ 5% and twice the rate of placebo) adverse reactions in a controlled trial in adolescents aged 13-17 were appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain, and anorexia *[see Adverse Reactions (6.1)]*.

The most common (≥ 2% of subjects) adverse reaction associated with discontinuations in double-blind clinical trials in children or adolescents was application site reactions *[see Adverse Reactions (6.1)]*.

The overall methylphenidate transdermal system development program included exposure to methylphenidate transdermal system in a total of 2,152 participants in clinical trials, including 1,529 children aged 6-12, 223 adolescents aged 13-17, and 400 adults. The 1,752 child and adolescent subjects aged 6-17 years were evaluated in 10 controlled clinical studies, 7 open-label clinical studies, and 5 clinical pharmacology studies. In a combined studies pool of children using methylphenidate transdermal system with a wear time of 9 hours, 212 subjects were exposed for ≥ 6 months and 115 were exposed for ≥ 1 year; 85 adolescents have been exposed for ≥ 6 months. Most patients studied were exposed to methylphenidate transdermal system sizes of 12.5 cm^2, 18.75 cm^2, 25 cm^2, or 37.5 cm^2, with a wear time of 9 hours.

In the data presented below, the adverse reactions reported during exposure were obtained primarily by general inquiry at each visit, and were recorded by the clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of events into a smaller number of standardized event categories.

Throughout this section adverse reactions reported are events that were considered to be reasonably associated with the use of methylphenidate transdermal system based on comprehensive assessment of the available adverse event information. A causal association for methylphenidate transdermal system often cannot be reliably established in individual cases. Further, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions Associated With Discontinuation of Treatment: In a 7-week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with methylphenidate transdermal system discontinued due to adverse events compared with 1.2% (1/85) receiving placebo. The most commonly reported (≥ 1% and twice the rate of placebo) adverse reactions leading to discontinuation in the methylphenidate transdermal system group were application site reaction (2%), tics (1%), headache (1%), and irritability (1%).

In a 7-week double-blind, parallel-group, placebo-controlled study in adolescents with ADHD conducted in the outpatient setting, 5.5% (8/145) of patients treated with methylphenidate transdermal system discontinued due to adverse reactions compared with 2.8% (2/72) receiving placebo. The most commonly reported adverse reactions leading to discontinuation in the

methylphenidate transdermal system group were application site reaction (2%) and decreased appetite/anorexia (1.4%).

Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Trials: *Skin Irritation and Application Site Reactions:* Methylphenidate transdermal system is a dermal irritant. In addition to the most commonly reported adverse reactions presented in Table 2, the majority of subjects in those studies had minimal to definite skin erythema at the transdermal system application site. This erythema generally caused no or minimal discomfort and did not usually interfere with therapy or result in discontinuation from treatment. Erythema is not by itself a manifestation of contact sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the transdermal system site *[see Warnings and Precautions (5.8)]*.

Most Commonly Reported Adverse Reactions: Table 2 lists treatment-emergent adverse reactions reported in ≥ 1% methylphenidate transdermal system-treated children or adolescents with ADHD in two 7 week double-blind, parallel-group, placebo-controlled studies conducted in the outpatient setting. Overall, in these studies, 75.5% of children and 78.6% of adolescents experienced at least 1 adverse event.

Table 2 Number (%) of Subjects with Commonly Reported Adverse Reactions (≥ 1% in the Methylphenidate Transdermal System Group) in 7-Week Placebo-Controlled Studies in Either Children or Adolescents - Safety Population

	Adolescents		Children	
System Organ Class Preferred term	Placebo N = 72	Methylphenidate Transdermal System N = 145	Placebo N = 85	Methylphenidate Transdermal System N = 98
Cardiac Disorders				
Tachycardia	0 (0)	1 (0.7)	0 (0)	1 (1.0)
Gastrointestinal disorders				
Abdominal pain	0 (0)	7 (4.8)	5 (5.9)	7 (7.1)
Nausea	2 (2.8)	14 (9.7)	2 (2.4)	12 (12.2)
Vomiting	1 (1.4)	5 (3.4)	4 (4.7)	10 (10.2)
Investigations				
Weight decreased	1 (1.4)	8 (5.5)	0 (0)	9 (9.2)

Metabolism and nutrition disorders				
Anorexia	1 (1.4)	7 (4.8)	1 (1.2)	5 (5.1)
Decreased appetite	1 (1.4)	37 (25.5)	4 (4.7)	25 (25.5)
Nervous system disorders				
Dizziness	1 (1.4)	8 (5.5)	1 (1.2)	0 (0)
Headache	9 (12.5)	18 (12.4)	10 (11.8)	15 (15.3)
Psychiatric disorders				
Affect lability	1 (1.4)	0 (0)	0 (0)	6 (6.1)*
Insomnia	2 (2.8)	9 (6.2)	4 (4.7)	13 (13.3)
Irritability	5 (6.9)	16 (11)	4 (4.7)	7 (7.1)
Tic	0 (0)	0 (0)	0 (0)	7 (7.1)

*Six subjects had affect lability, all judged as mild and described as increased emotionally sensitive, emotionality, emotional instability, emotional lability, and intermittent emotional

Adverse Reactions With the Long-Term Use of Methylphenidate Transdermal System: In a long-term open-label study of up to 12 months duration in 326 children wearing methylphenidate transdermal system 9 hours daily, the most common (≥ 10%) adverse reactions were decreased appetite, headache, and weight decreased. A total of 30 subjects (9.2%) were withdrawn from the study due to adverse events and 22 additional subjects (6.7%) discontinued treatment as the result of an application site reaction. Other than application site reactions, affect lability (5 subjects, 1.5%) was the only additional adverse reaction leading to discontinuation reported with a frequency of greater than 1%.

In a long-term open-label study of up to 6 months duration in 162 adolescents wearing methylphenidate transdermal system 9 hours daily, the most common (≥ 10%) adverse reactions were decreased appetite and headache. A total of 9 subjects (5.5%) were withdrawn from the study due to adverse events and 3 additional subjects (1.9%) discontinued treatment as the result of an application site reaction. Other adverse reactions leading to discontinuation that occurred with a frequency of greater than 1% included affect lability and irritability (2 subjects each, 1.2%).

6.2 Postmarketing Experience

In addition, the following adverse reactions have been identified during the postapproval use of methylphenidate transdermal system. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to methylphenidate transdermal system exposure.

Cardiac Disorders: palpitations

Eye Disorders: visual disturbances, blurred vision, mydriasis, accommodation disorder

General Disorders and Administration Site Disorders: fatigue, application site reactions such as bleeding, bruising, burn, burning, dermatitis, discharge, discoloration, discomfort, dryness, eczema, edema, erosion, erythema, excoriation, exfoliation, fissure, hyperpigmentation, hypopigmentation, induration, infection, inflammation, irritation, pain, papules, paresthesia, pruritus, rash, scab, swelling, ulcer, urticaria, vesicles, and warmth.

Immune System Disorders: hypersensitivity reactions including generalized erythematous and urticarial rashes, allergic contact dermatitis, angioedema, and anaphylaxis

Investigations: blood pressure increased

Nervous System Disorders: convulsion, dyskinesia, lethargy, somnolence, serotonin syndrome in combination with serotonergic drugs, and extrapyramidal disorder

Psychiatric Disorders: depression, hallucination, nervousness, and libido changes

Skin and Subcutaneous Tissue Disorders: alopecia

6.3 Adverse Reactions With Oral Methylphenidate Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac Disorders: angina, arrhythmia, and pulse increased or decreased

Immune System Disorders: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura

Metabolism and Nutrition Disorders: anorexia and weight loss during prolonged therapy

Nervous System Disorders: drowsiness, rare reports of Tourette's syndrome and toxic psychosis.

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is

uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

Vascular Disorders: blood pressure increased or decreased and cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic System Disorders: leukopenia and/or anemia

Hepatobiliary Disorders: abnormal liver function, ranging from transaminase elevation to severe hepatic injury

Psychiatric Disorders: transient depressed mood

Skin and Subcutaneous Tissue Disorders: scalp hair loss

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors (MAOI)

Concomitant use of MAOIs and CNS stimulants, including methylphenidate transdermal system, can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure *[see Contraindications (4.5)]*. Concomitant use of methylphenidate transdermal system with MAOIs or within 14 days after discontinuing MAOI treatment is contraindicated.

7.2 Vasopressor Agents

Because of a possible effect on blood pressure, methylphenidate transdermal system should be used cautiously with pressor agents.

7.3 Antihypertensive Agents

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. Monitor blood pressure and adjust the dosage of the antihypertensive drug as needed *[see Warnings and Precautions (5.1)]*.

7.4 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some tricyclic drugs (e.g., imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

7.5 Risperidone

Combined use of methylphenidate with risperidone when there is a change in dosage, whether an increase or decrease, of either or both medications, may increase the risk of extrapyramidal symptoms (EPS). Monitor for signs of EPS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications, including methylphenidate transdermal system, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visit https://womensmentalhealth.org/adhd-medications/.

Risk Summary: Published studies and post-marketing reports on methylphenidate use during pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the fetus associated with the use of central nervous system (CNS) stimulants during pregnancy *(see Clinical Considerations)*.

No effects on morphological development were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis. However, spina bifida was observed in rabbits when given oral doses of 200 mg/kg/day. When methylphenidate was administered orally to rats throughout pregnancy and lactation, offspring growth and survival were decreased at maternally toxic doses *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations: *Fetal/Neonatal Adverse Reactions:* CNS stimulants, such as methylphenidate transdermal system, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data: *Animal Data:* Animal reproduction toxicity studies with transdermal methylphenidate have not been performed. In embryo-fetal development studies conducted in rats and rabbits, methylphenidate was administered orally to pregnant animals during the period of organogenesis, at doses up to 100 and 200 mg/kg/day, respectively. No evidence of morphological development effects was found either of the species; however, increased incidences of fetal skeletal variations were observed in rats at 60 mg/kg or greater and an increase in fetal visceral variations was seen in rabbits at the highest dose. In a previous study, methylphenidate was shown to have malformations (increased incidence of fetal spina bifida) in rabbits when given oral doses of 200 mg/kg/day. When methylphenidate was administered orally

to rats throughout pregnancy and lactation at doses of up to 60 mg/kg/day, offspring growth and survival were decreased at maternally toxic doses.

In a study in which oral methylphenidate was given to rats throughout pregnancy and lactation at doses up to 60 mg/kg/day, offspring weights and survival were decreased at 40 mg/kg/day and above; these doses caused some maternal toxicity.

8.2 Lactation

Risk Summary: Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for methylphenidate transdermal system and any potential adverse effects on the breastfed infant from methylphenidate or from the underlying maternal condition.

Clinical Considerations: Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

8.4 Pediatric Use

Methylphenidate transdermal system should not be used in children under six years of age, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established.

Long Term Suppression of Growth: Growth should be monitored during treatment with stimulants, including methylphenidate transdermal system. Children who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.6)]*.

Juvenile Animal Toxicity Data: Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only.

Studies with transdermal methylphenidate have not been performed in juvenile animals. In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use
Methylphenidate transdermal system has not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Methylphenidate transdermal system is classified as a Schedule II controlled substance by federal regulation.

9.2 Abuse
See warning containing drug abuse information *[see Boxed Warning]*.

9.3 Dependence
See warning containing drug dependence information *[see Boxed Warning]*.

10 OVERDOSAGE
10.1 Signs and Symptoms
Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

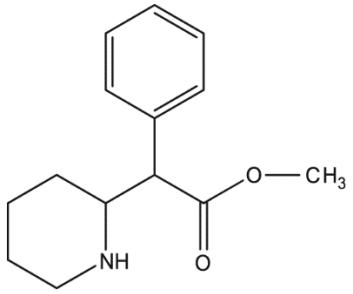
10.2 Recommended Treatment
Remove all transdermal systems immediately and cleanse the area(s) to remove any remaining adhesive. The continuing absorption of methylphenidate from the skin, even after removal of the transdermal system, should be considered when treating patients with overdose. Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate transdermal system overdosage has not been established.

10.3 Poison Control Center
As with the management of all overdosages, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

11 DESCRIPTION
Methylphenidate transdermal system is an adhesive-based matrix transdermal system containing methylphenidate that is applied to intact skin. The chemical name for methylphenidate is α-phenyl-2-piperidineacetic acid methyl ester. It is a white to off-white powder and is soluble in alcohol, ethyl acetate, and ether. Methylphenidate is practically insoluble in water and petrol

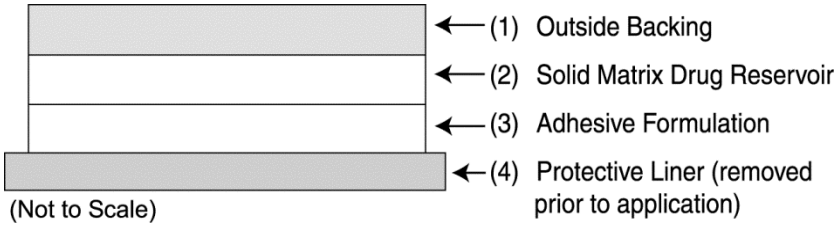
ether. Its molecular weight is 233.31. Its molecular formula is $C_{14}H_{19}NO_2$. The structural formula of methylphenidate is:



11.1 Transdermal System Components

Methylphenidate transdermal system contains methylphenidate in a polyisobutylene adhesive. The composition per unit area of all dosage strengths is identical, and the total dose delivered is dependent on the transdermal system size and wear time.

The transdermal system consists of four layers, as seen in the figure below (cross-section of the transdermal system)



Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a polyester/ethylene vinyl acetate laminate film backing and white ink which contains acrylic polymers, polyethylene wax, polytetrafluoroethylene, polyvinylpyrrolidone, sodium dioctyl sulfosuccinate and titanium dioxide, (2) a solid matrix drug reservoir of methylphenidate, polyisobutylene adhesive, mineral oil and hydrophobic colloidal silica, (3) a skin contact adhesive formulation of polyisobutylene adhesive, mineral oil and hydrophobic colloidal silica, and (4) a fluoropolymer-coated polyester protective liner, which is attached to the adhesive surface and must be removed before the transdermal system can be used.

The active component of the transdermal system is methylphenidate. The remaining components are pharmacologically inactive.

Methylphenidate transdermal systems are packaged with an additional piece of protective film above the system within each pouch. This piece of protective film is removed and discarded at the time of use.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate is a central nervous system (CNS) stimulant. Its mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-enantiomers. The *d*-enantiomer is more pharmacologically active than the *l*-enantiomer. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space.

12.3 Pharmacokinetics

The pharmacokinetics of methylphenidate transdermal system when applied to the hip for 9 hours have been studied in ADHD patients 6 to 17 years old.

Absorption: The amount of methylphenidate absorbed systemically is a function of both wear time and transdermal system size. In patients with ADHD, peak plasma levels of methylphenidate are reached at about 10 hours after single application and 8 hours after repeat transdermal system applications (12.5 cm^2 to 37.5 cm^2) when worn up to 9 hours.

On single dosing of children or adolescents with methylphenidate transdermal system, there was a delay of, on average, 2 hours before *d*-methylphenidate was detectable in the circulation. On repeat dosing, low concentrations (1.2-3.0 ng/mL in children and 0.5-1.7 ng/mL in adolescents, on average across the dose range) were observed earlier in the profile, due to carry-over effect. Following the application of methylphenidate transdermal system once daily with a 9-hour wear time, the mean pharmacokinetic parameters of *d*-methylphenidate in children and adolescents with ADHD after 4 weeks of therapy are summarized in Table 3.

Table 3 Mean Plasma *d*-Methylphenidate Pharmacokinetic Parameters After Repeated 9-Hour Applications of Methylphenidate Transdermal System or Oral ER-MPH for up to 28 days to Pediatric ADHD Patients (Aged 6 - 17 years)

Children				
Parameter	Methylphenidate Transdermal System[1] 12.5 cm^2 (N = 12)	Methylphenidate Transdermal System[2] 37.5 cm^2 (N = 10)	Oral ER-MPH[3] 18 mg	Oral ER-MPH[3] 54 mg
C_{ssmax} (ng/mL)	15.7 ± 9.39	42.9 ± 22.4	8.37 ± 4.14	26.1 ± 11.2
C_{ssmin} (ng/mL)	1.04 ± 1.17	1.96 ± 1.73	0.708 ± 1.08	1.19 ± 1.54
AUC_{ss} (ng·hr/mL)	163 ± 101	447 ± 230	97.7 ± 67.0	317 ± 160
t_{lag} (h)[4]	0 (0 - 2.0)	0 (0 - 1.0)	0	0
Adolescents				

C_{ssmax} (ng/mL)	8.32 ± 4.60	16.5 ± 6.94	5.23 ± 1.72	18.0 ± 6.97
C_{ssmin} (ng/mL)	0.544 ± 0.383	1.02 ± 0.629	0.360 ± 0.478	1.50 ± 0.937
AUC_{ss} (ng·hr/mL)	85.7 ± 50.0	167 ± 66.0	59.7 ± 19.1	216 ± 80.8
t_{lag} (h)[4]	0 (0 - 2.0)	0 (0 - 2.0)	0	0

[1]Dose maintained fixed for 28 days;
[2]Dose escalated at 7 day intervals from 12.5 cm^2 through 18.75 cm^2 and 25 cm^2 to 37.5 cm^2;
[3]Dose escalated at 7 day intervals from 18 mg through 27 mg and 36 mg to 54 mg;
[4]Median (minimum – maximum); t_{lag} = Last Sampling Time Prior to Time of First Quantifiable Plasma Concentration

Following administration of methylphenidate transdermal system 12.5 cm^2 to pediatric and adolescent ADHD patients daily for 7 days, there were 13% and 14% increases, respectively, in steady state area under the plasma concentration-time curve (AUC_{ss}) relative to that anticipated on the basis of single dose pharmacokinetics ($AUC_{0-\infty}$); after 28 days administration, these increments increased to 64% and 76%, respectively. C_{max} increased by nearly 69% and 100% within 4 weeks of daily administration of the starting dose in children and adolescents, respectively.

The observed exposures with methylphenidate transdermal system could not be explained by drug accumulation predicted from observed single dose pharmacokinetics and there was no evidence that clearance or rate of elimination changed between single and repeat dosing. Neither were they explainable by differences in dosing patterns between treatments, age, race, or gender. This suggests that transdermal absorption of methylphenidate may increase with repeat dosing with methylphenidate transdermal system; on average, steady-state is likely to have been achieved by approximately 14 days of dosing.

In the single- and multiple dose study described above, exposure to *l*-methylphenidate was 46% of the exposure to *d*-methylphenidate in children and 40% in adolescents. *l*-methylphenidate is less pharmacologically active than *d*-methylphenidate *[see Pharmacodynamics (12.2)]*.

In a phase 2 PK/PD study in children aged 6-12 years, 2/3 of patients had 2-hour *d*-MPH concentrations < 5 ng/mL on chronic dosing, and at 3 hours 40% of patients had *d*-MPH concentrations < 5 ng/mL *[see Clinical Studies (14)]*.

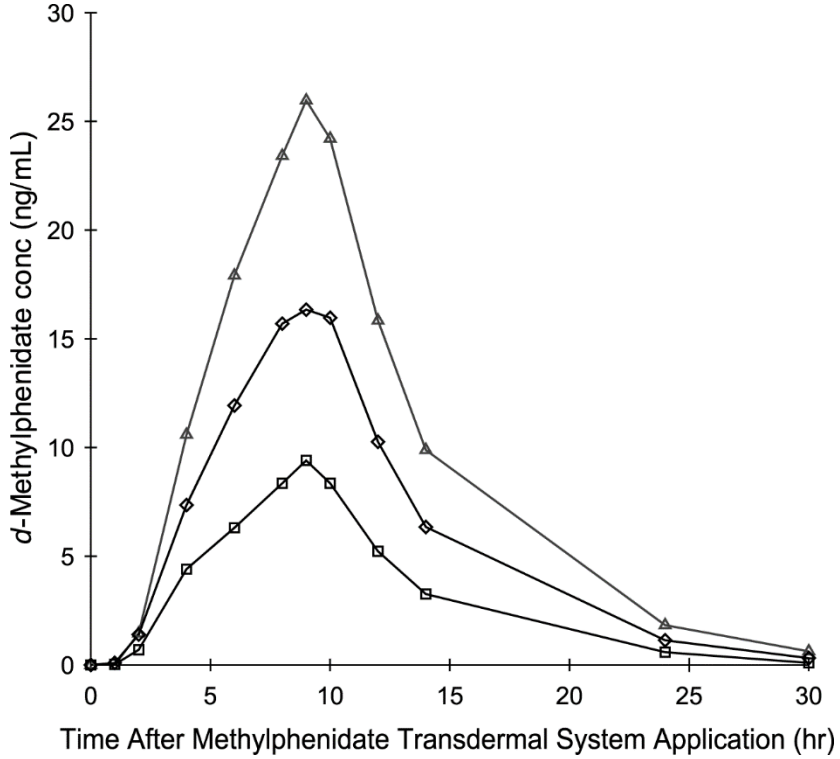
When methylphenidate transdermal system is applied to inflamed skin both the rate and extent of absorption are increased as compared with intact skin. When applied to inflamed skin, lag time is no greater than 1 hour, T_{max} is 4 hours, and both C_{max} and AUC are approximately 3-fold higher.

When heat is applied to methylphenidate transdermal system after transdermal system application, both the rate and the extent of absorption are significantly increased. Median T_{lag} occurs 1 hour earlier, T_{max} occurs 0.5 hours earlier, and median C_{max} and AUC are 2-fold and 2.5-fold higher, respectively.

Application sites other than the hip can have different absorption characteristics and have not been adequately studied in safety or efficacy studies.

Dose Proportionality: Following a single 9-hour application of methylphenidate transdermal system doses of 10 mg/9 hours to 30 mg/9 hours transdermal systems to 34 children with ADHD, C_{max} and AUC_{0-t} of *d*-methylphenidate were proportional to the transdermal system dose. Mean plasma concentration-time plots are shown in Figure 1. C_{max} of *l*-methylphenidate was also proportional to the transdermal system dose. AUC_{0-t} of *l*-methylphenidate was only slightly greater than proportional to transdermal system dose.

FIGURE 1
Mean Concentration-time Profiles for *d*-Methylphenidate in all Patients (N = 34) Following Administration of Single Applications (9-Hour Wear Time) of *d,l*-Methylphenidate Using Methylphenidate Transdermal System 10 mg (□), 20 mg (◊) and 30 mg (Δ) per 9-Hour Transdermal Systems



Distribution: Upon removal of methylphenidate transdermal system, methylphenidate plasma concentrations in children with ADHD decline in a biexponential manner. This may be due to continued distribution of MPH from the skin after transdermal system removal.

Metabolism and Excretion: Methylphenidate is metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity.

Transdermal administration of methylphenidate exhibits much less first pass effect than oral administration. Consequently, a much lower dose of methylphenidate transdermal system on a mg/kg basis compared to oral dosages may still produce higher exposures of *d*-MPH with transdermal administration compared to oral administration. In addition, very little, if any, *l*-methylphenidate is systemically available after oral administration due to first pass metabolism, whereas after transdermal administration of racemic methylphenidate exposure to *l*-methylphenidate is nearly as high as to *d*-methylphenidate.

The mean elimination $t_{1/2}$ from plasma of *d*-methylphenidate after removal of methylphenidate transdermal system in children aged 6 to 12 years and adolescents aged 13-17 years was approximately 4 to 5 hours. The $t_{1/2}$ of *l*-methylphenidate was shorter than for *d*-methylphenidate and ranged from 1.4 to 2.9 hours, on average.

The C_{max} and AUC of *d*-methylphenidate were approximately 50% lower in adolescents, compared to children, following either a 1-day or 7-day administration of methylphenidate transdermal system (10 mg/9 hr). Multiple-dose administration of methylphenidate transdermal system did not result in significant accumulation of methylphenidate; following 7 days of methylphenidate transdermal system administration (10 mg/9 hr) in children and adolescents, the accumulation index of methylphenidate was 1.1, based on the mean steady state area under the plasma concentration-time curve (AUC_{ss}) relative to that anticipated on the basis of single dose pharmacokinetics ($AUC_{0-\infty}$).

Food Effects: The pharmacokinetics or the pharmacodynamic food effect performance after application of methylphenidate transdermal system has not been studied, but because of the transdermal route of administration, no food effect is expected.

Special Populations: *Gender:* The pharmacokinetics of methylphenidate after single and repeated doses of methylphenidate transdermal system were similar between boys and girls with ADHD, after allowance for differences in body weight.

Race: The influence of race on the pharmacokinetics of methylphenidate after administration of methylphenidate transdermal system has not been defined.

Age: The pharmacokinetics of methylphenidate after administration of methylphenidate transdermal system have not been studied in children less than 6 years of age.

Renal Impairment: There is no experience with the use of methylphenidate transdermal system in patients with renal insufficiency.

Hepatic Impairment: There is no experience with the use of methylphenidate transdermal system in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies of transdermal methylphenidate have not been performed. In a lifetime carcinogenicity study of oral methylphenidate carried out in B6C3F1

mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors and the significance of these results to humans is unknown.

Orally administered methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week oral carcinogenicity study in the transgenic mouse strain $p53^{+/-}$, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. In this study, male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis: Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese hamster ovary cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility: Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted at doses up to 160 mg/kg/day.

14 CLINICAL STUDIES

Methylphenidate transdermal system was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in two (2) randomized double-blind, placebo-controlled studies in children aged 6 to 12 years and one (1) randomized, double-blind, placebo-controlled study in adolescents aged 13 to 17 years who met Diagnostic and Statistical Manual (DSM-IV-TR®) criteria for ADHD. The transdermal system wear time was 9 hours in all three (3) studies.

In Study 1, conducted in a classroom setting, symptoms of ADHD were evaluated by school teachers and observers using the Deportment Subscale from the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale which assesses behavior symptoms in the classroom setting. Methylphenidate transdermal system was applied for 9 hours before removal. There was a 5-week open-label methylphenidate transdermal system dose optimization phase using dosages of 10 mg/9 hours, 15 mg/9 hours, 20 mg/9 hours, and 30 mg/9 hours, followed by a 2-week randomized, double-blind, placebo-controlled crossover treatment phase using the optimal transdermal system dose for each patient or placebo. The mean differences between methylphenidate transdermal system and placebo in change from baseline in SKAMP Deportment Scores were statistically significant in favor of methylphenidate transdermal system beginning at 2 hours and remained statistically significant at all subsequent measured time points through 12 hours after application of the methylphenidate transdermal system.

In Study 2, conducted in the outpatient setting, methylphenidate transdermal system or placebo was blindly administered in a flexible-dose design using doses of 10 mg/9 hours, 15 mg/9 hours, 20 mg/9 hours, and 30 mg/9 hours to achieve an optimal regimen over 5 weeks, followed by a 2-week maintenance period using the optimal transdermal system dose for each patient. Symptoms of ADHD were evaluated by the ADHD-Rating Scale (RS)-IV. Methylphenidate transdermal system was statistically significantly superior to placebo as measured by the mean change from baseline for the ADHD-RS-IV total score. Although this study was not designed specifically to evaluate dose response, in general there did not appear to be any additional effectiveness accomplished by increasing the transdermal system dose from 20 mg/9 hours to 30 mg/9 hours.

In Study 3, conducted in the outpatient setting, methylphenidate transdermal system or placebo was blindly administered in a flexible-dose design using doses of 10 mg/9 hours, 15 mg/9 hours, 20 mg/9 hours, and 30 mg/9 hours during a 5-week dose-optimization phase, followed by a 2-week maintenance period using the optimal transdermal system dose for each patient. Symptoms of ADHD were evaluated using the ADHD-Rating Scale (RS)-IV. Methylphenidate transdermal system was statistically significantly superior to placebo as measured by the mean change from baseline in the ADHD-RS-IV total score.

15 REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association 1994.

16 HOW SUPPLIED/STORAGE AND HANDLING

Methylphenidate Transdermal System is supplied in a carton containing 30 individually pouched transdermal systems. See the chart below for information regarding available strengths.

Each dosage form is a translucent rectangular transdermal system with rounded corners consisting of a matte backing film randomly printed with “Methylphenidate Transdermal System” and the “mg/hr” strength in white ink, an adhesive layer and a clear to slightly hazy oversized release liner that is slit. Each transdermal system is overlaid with an additional clear to slightly hazy oversized release liner and is contained in a square, flat pouch that is imprinted with lot number and expiration date.

Nominal Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Transdermal System Size (cm^2)	Methylphenidate Content per Transdermal System** (mg)	Transdermal Systems Per Carton	NDC Number
10	1.1	9.6	10.4	30	0378-8260-93
15	1.6	14.4	15.6	30	0378-8261-93
20	2.2	19.2	20.7	30	0378-8262-93

30	3.3	28.8	31.1	30	0378-8263-93

*Nominal *in vivo* delivery rate per hour in children and adolescents when applied to the hip, based on a 9-hour wear period.
**Methylphenidate content in each transdermal system.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Do not store transdermal systems unpouched. Do not store transdermal systems in refrigerators or freezers.

Apply the transdermal system immediately upon removal from the individual protective pouch. **For transdermal use only**.

PHARMACIST: Dispense a Medication Guide with each prescription.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Priapism: Advise patients, caregivers, and family members of the possibility of painful or prolonged penile erections (priapism). **Instruct the patient to seek immediate medical attention in the event of priapism** *[see Warnings and Precautions (5.4)]*.

Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]:

- Instruct patients beginning treatment with methylphenidate transdermal system about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and its associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red
- Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.
- **Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while using methylphenidate transdermal system**
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Chemical Leukoderma: Advise patients of the possibility of a persistent loss of skin pigmentation at, around and distant from the application site. Advise patients to immediately inform their healthcare provider if changes in skin pigmentation occur *[see Warnings and Precautions (5.7)]*.

Parents and patients should be informed to apply methylphenidate transdermal system to a clean, dry site on the hip, which is not oily, damaged, or irritated. The site of application must be alternated daily. The transdermal system should not be applied to the waistline, or where tight clothing may rub it.

If patients or caregivers experience difficulty separating the transdermal system from the release liner or observe tearing and/or other damage to the transdermal system during removal from the

liner, the transdermal system should be discarded according to the directions provided in this label, and a new transdermal system should be applied *[see Dosage and Administration (2.3)]*. Patients or caregivers should inspect the release liner to ensure that no adhesive containing medication has transferred to the liner. If adhesive transfer has occurred, the transdermal system should be discarded.

Methylphenidate transdermal system should be applied 2 hours before the desired effect. Methylphenidate transdermal system should be removed approximately 9 hours after it is applied, although the effects from the transdermal system will last for several more hours. Methylphenidate transdermal system may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.

The parent or caregiver should be encouraged to use the administration chart included with each carton of methylphenidate transdermal system to monitor application and removal time, and method of disposal. The Medication Guide included at the end of this insert also includes a timetable to calculate when to remove methylphenidate transdermal system, based on the 9 hour application time.

Patients or caregivers should avoid touching the adhesive side of the transdermal system during application, in order to avoid absorption of methylphenidate. If they do touch the adhesive side of the transdermal system, they should immediately wash their hands after application.

In the event that a transdermal system does not fully adhere to the skin upon application, or is partially or fully detached during wear time, the transdermal system should be discarded according to the directions provided in this label, and a new transdermal system should be applied *[see Dosage and Administration (2.3)]*. If a transdermal system is replaced, the total recommended wear time for that day should remain 9 hours, regardless of the number of transdermal systems used.

Transdermal systems should not be applied or re-applied with dressings, tape, or other common adhesives.

Exposure to water during bathing, swimming, or showering can affect transdermal system adherence.

Do not cut transdermal systems. Only intact transdermal systems should be applied.

If there is an unacceptable duration of appetite loss or insomnia in the evening, taking the transdermal system off earlier may be attempted before decreasing the transdermal system dose.

Skin redness or itching is common with methylphenidate transdermal system and small bumps on the skin may also occur in some patients. If any swelling or blistering occurs the transdermal system should not be worn and the patient should be seen by the prescriber. Patients or caregivers should not apply hydrocortisone or other solutions, creams, ointments, or emollients immediately prior to transdermal system application, since the effect on transdermal system adhesion and

methylphenidate absorption has not been established. The potential adverse effects of topical corticosteroid use during treatment with methylphenidate transdermal system are unknown.

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that methylphenidate transdermal system does not adversely affect their ability to engage in such activities.

Transdermal systems should be stored at 20° to 25°C (68° to 77°F) *[see How Supplied/Storage and Handling (16)]*. Patients or caregivers should be advised not to store methylphenidate transdermal system in the refrigerator or freezer.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with methylphenidate transdermal system and should counsel them in its appropriate use. A patient Medication Guide is available for methylphenidate transdermal system. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is printed at the end of this document.

Pregnancy Registry: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications, including methylphenidate transdermal system, during pregnancy *[see Use in Specific Populations (8.1)]*.

For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

Medication Guide
Methylphenidate Transdermal System CII
(meth″ il fen′ i date)

Only Use Methylphenidate Transdermal System on Your Skin
Important: **Methylphenidate transdermal system is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep methylphenidate transdermal system in a safe place to protect it from theft. Selling or giving away methylphenidate transdermal system may harm others and is against the law.** **Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicine or street drugs.**

What is the most important information I should know about methylphenidate transdermal system?

Methylphenidate transdermal system contains methylphenidate which is a central nervous system (brain) stimulant medicine. Serious side effects have been reported with methylphenidate transdermal system or other stimulant medicines, including:

1. Heart problems, including:
- sudden death in people who have heart problems or heart defects
- stroke and heart attack in adults
- increased blood pressure and heart rate

Your doctor should check you carefully for blood pressure and heart problems before you start and while you are using methylphenidate transdermal system.

Remove the methylphenidate transdermal system and call your doctor right away if you have any signs of heart problems such as:
- chest pain
- shortness of breath
- fainting

2. Mental (psychiatric) problems, including:
- new or worse aggressive behavior, hostility, anger, or irritability
- new or worse bipolar illness or mania (an extreme increase in activity or talking)
- new or worse psychosis (hearing or seeing things that are not real, being suspicious or distrustful, believing things that are not true)
- other unusual or extreme changes in behavior or mood

Tell your doctor right away if you have any new or worsening mental problems while using methylphenidate transdermal system.

3. Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red

- Tell your doctor if you have or your child has numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.
- **Call your doctor right away if you have or your child has any signs of unexplained wounds appearing on fingers or toes while taking methylphenidate transdermal system**

What is methylphenidate transdermal system?
Methylphenidate transdermal system is a prescription medication used to treat Attention Deficit Hyperactivity Disorder (ADHD) in people 6 to 17 years old. Methylphenidate transdermal system is a central nervous system (brain) stimulant medicine. Methylphenidate transdermal system may help you have better attention and less impulsive and hyperactive behavior. Methylphenidate transdermal system is a transdermal system that you apply to your skin on your hip. Methylphenidate transdermal system is used as part of a total treatment program for ADHD that may also include counseling or other treatments.

It is not known if methylphenidate transdermal system is safe and effective in children younger than 6 years.

Who should not use methylphenidate transdermal system?
Do not use methylphenidate transdermal system if you:

- are very anxious, tense, or agitated
- have glaucoma
- have tics (involuntary repeated movements or sounds that cannot be controlled)
- have Tourette's Syndrome or a family history of this syndrome
- are taking or have taken a monoamine oxidase inhibitor (MAOI) medicine within the past 2 weeks. Do not take a MAOI medicine for at least 2 weeks before using methylphenidate transdermal system. Ask your doctor or pharmacist if you are not sure if any of your medicines are MAOIs.
- are allergic to methylphenidate or any other ingredients in methylphenidate transdermal system. See **"What are the ingredients in methylphenidate transdermal system?"** for a complete list of ingredients.

Talk to your healthcare provider before taking this medicine if you have any of these conditions.

What should I tell my doctor before using methylphenidate transdermal system?
Before you start using methylphenidate transdermal system, tell your doctor if you:

- have heart problems, heart defects, high blood pressure
- have mental problems including psychosis, mania, bipolar illness, or depression
- have seizures or have had an abnormal brain wave test (EEG)
- have circulation problems in fingers or toes
- have skin problems such as eczema or psoriasis, or have skin reactions to soaps, lotions, make-up, or adhesives (glues)

- are pregnant or plan to become pregnant. It is not known if methylphenidate transdermal system will harm your unborn baby.
    - There is a pregnancy registry for females who are exposed to ADHD medications, including methylphenidate transdermal system during pregnancy. The purpose of the registry is to collect information about the health of females exposed to methylphenidate transdermal system and their baby. If you or your child becomes pregnant during treatment with methylphenidate transdermal system, talk to your healthcare provider about registering with the National Pregnancy Registry of ADHD Medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/adhd-medications/.
- are breast feeding or plan to breast feed. Methylphenidate passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with methylphenidate transdermal system.
- a history of vitiligo and/or a family history of vitiligo

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Methylphenidate transdermal system and certain other medicines may affect each other, causing serious side effects.
Especially tell your doctor if you take:

- a monoamine oxidase inhibitor (MAOI) medicine See **"Who should not use methylphenidate transdermal system?"**
- medicines to treat depression
- medicines to treat seizures
- a blood pressure medicine
- a blood thinner medicine
- cold or allergy medicines that contain decongestants

Know the medicines that you take. Keep a list of them to show your doctor and pharmacist. Do not start any new medicine while using methylphenidate transdermal system without talking to your doctor first.

How should I use methylphenidate transdermal system?

- Read the Patient Instructions for Use at the end of this Medication Guide that comes with your methylphenidate transdermal system for information about the right way to use methylphenidate transdermal system.
- Use methylphenidate transdermal system exactly as your doctor tells you to.
- Your doctor may change your dose if needed.
- Apply methylphenidate transdermal system to your hip 2 hours before an effect is needed.
- Do not wear methylphenidate transdermal system longer than 9 hours a day.
- Apply methylphenidate transdermal system to a different hip each day.
- Do not cut methylphenidate transdermal systems.
- Parents or caregivers should apply and remove methylphenidate transdermal system for their child if the child is not responsible enough to do so.
- Your doctor may stop methylphenidate transdermal system treatment to check your ADHD symptoms.

- Your doctor may do certain blood tests and check your heart and blood pressure while you use methylphenidate transdermal system.
- If you forget to apply a transdermal system in the morning, you may apply the transdermal system later in the day. You should remove your transdermal system at the usual time of day to lower the chance of side effects later in the day.
- If you have loss of appetite or trouble sleeping in the evening, ask your doctor if you can take the transdermal system off earlier in the day.
- Contact with water while bathing, swimming, or showering can make the transdermal system not stick well or make it fall off. If your transdermal system falls off, **do not** touch the sticky side of the transdermal system with your fingers. You may apply a new transdermal system to a different area on the same hip. If you have to replace a transdermal system that has fallen off, the total wear time for the first and second transdermal system should not be more than a total of 9 hours in 1 day. Do not reapply the same transdermal system that fell off.
- **Do not** wear your methylphenidate transdermal system longer than 9 hours.
- If you accidentally apply or wear more than 1 transdermal system at a time, you have used too many methylphenidate transdermal systems. Remove all transdermal systems, wash the application sites right away and call your doctor.
    - Call your Poison Control Center at 1-800-222-1222 -or go to the nearest hospital emergency room right away if you have:
        - vomiting
        - agitation
        - shaking
        - confusion or mental changes
        - see things that are not there (hallucinations)
        - sweating
        - redness in your face
        - headache
        - heartbeat changes

What should I avoid while using methylphenidate transdermal system?

- Do not put any medicine, cream, or lotion on your hip before you apply the methylphenidate transdermal system. Medicines, creams or lotions may affect how the transdermal system sticks to your skin and how the medicine is absorbed from the transdermal system.
- Do not use bandages, tape, or other household adhesives (glue) to hold the transdermal system onto your skin.
- **Do not use hair dryers, heating pads, electric blankets, heated water beds or other heat sources while wearing a methylphenidate transdermal system. Too much medicine can pass into your body and cause serious side effects.**
- Do not drive, operate heavy machinery or do other dangerous activities until you know how methylphenidate transdermal system affects you.

What are possible side effects of methylphenidate transdermal system?
Methylphenidate transdermal system may cause serious side effects, including:

- See **"What is the most important information I should know about methylphenidate transdermal system?"**
- **Seizures.** This usually happens in people with a history of seizures.

- Painful and prolonged erections (priapism) have occurred with methylphenidate. If you or your child develops priapism, seek medical help right away. Because of the potential for lasting damage, priapism should be evaluated by a doctor immediately.
- **Slowing of growth (weight and height)**. You should have your height and weight checked while using methylphenidate transdermal system.
- **Loss of skin color (chemical leukoderma).** Methylphenidate transdermal system may cause a persistent loss of skin-color where the transdermal system is applied or around the transdermal system application site. Loss of skin-color, in some cases, has been reported at locations on the skin far from any application site. The loss of your skin-color may be permanent even after removing the transdermal system or stopping use of methylphenidate transdermal system. Call your doctor immediately if you have changes in your skin-color.
- **Allergic skin rash. Stop using methylphenidate transdermal system and see your doctor right away if you have swelling or blisters at or around the application site.** You may have a skin allergy to methylphenidate transdermal system. People who have skin allergies to methylphenidate transdermal system may develop an allergy to all medicines that contain methylphenidate, even those methylphenidate medicines that are taken by mouth.
- Eyesight changes or blurred vision

The most common side effects of methylphenidate transdermal system include:

- skin problems where you apply methylphenidate transdermal system (redness, small bumps, itching)
- poor appetite
- nausea
- vomiting
- stomach pain
- weight loss
- tics
- trouble sleeping
- mood swings
- dizziness

Tell your doctor if you have any side effect that bothers you or does not go away.
These are not all the possible side effects of methylphenidate transdermal system. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store methylphenidate transdermal system?

- Store methylphenidate transdermal system at room temperature between 20° to 25°C (68° to 77°F).
- Do not store methylphenidate transdermal system in the refrigerator or freezer.
- Keep methylphenidate transdermal systems in their unopened pouches until you are ready to use them.

Keep methylphenidate transdermal system and all medicines out of the reach of children.

General information about the safe and effective use of methylphenidate transdermal system.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use methylphenidate transdermal system for a condition for which it was not prescribed. Do not give methylphenidate transdermal system to other people, even if they have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about methylphenidate transdermal system. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about methylphenidate transdermal system that is written for health professionals.

For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in methylphenidate transdermal system?

Active ingredient: methylphenidate
Inactive ingredients: fluoropolymer-coated polyester release liner, hydrophobic colloidal silica, mineral oil, polyester/ethylene vinyl acetate laminate backing film and polyisobutylene adhesive. The white ink contains acrylic polymers, polyethylene wax, polytetrafluoroethylene, polyvinylpyrrolidone, sodium dioctyl sulfosuccinate and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Instructions for Use
Methylphenidate Transdermal System CII
(meth″ il fen′ i date)

1. Methylphenidate Transdermal System Dosing Chart

Each carton of methylphenidate transdermal systems contains a methylphenidate transdermal system Dosing Chart to help you keep track of your transdermal system including:

- when you apply the transdermal system to the skin on your hip each morning
- when you remove the transdermal system
- how and where you threw the methylphenidate transdermal system away

To use the methylphenidate transdermal system Dosing Chart, follow these instructions:

- Each day, when a new methylphenidate transdermal system is applied to your hip, write down the date and time that you applied the transdermal system.
- Use the methylphenidate transdermal system schedule below so you can decide when to remove the transdermal system. For example, if the transdermal system is applied to the skin at 6:00 a.m., remove the transdermal system at 3:00 p.m. on the same day. After you remove and throw away the transdermal system, write down the time you removed the transdermal system and how and where you threw it away.
- If the transdermal system you placed on your child is missing, ask your child:
  - when the transdermal system came off
  - how the transdermal system came off
  - where the transdermal system is

Methylphenidate Transdermal System Schedule for 9 Hour Dosing

If you put the transdermal system on at:	**On the same day, remove the transdermal system at:**
5:00 a.m.	2:00 p.m.
6:00 a.m.	3:00 p.m.
7:00 a.m.	4:00 p.m.
8:00 a.m.	5:00 p.m.
9:00 a.m.	6:00 p.m.
10:00 a.m.	7:00 p.m.
11:00 a.m.	8:00 p.m.
12:00 p.m.	9:00 p.m.

2. Where to apply methylphenidate transdermal system

- Apply the transdermal system to your hip area. Do not put the transdermal system near your waist. Clothing and movement may make your transdermal system rub off (See Figure A).
- Use your other hip when you apply a new transdermal system the next morning. Make sure there is no redness, small bumps or itching at the site where the transdermal system is going to be applied.

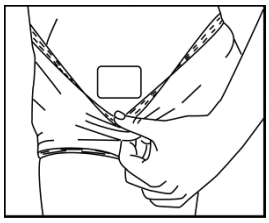


Figure A

3. Before you apply methylphenidate transdermal system

Make sure your skin:

- Is clean (freshly washed), dry, and cool
- Does not have any powder, oil, or lotion
- Does not have any cuts and irritation (rashes, inflammation, redness, or other skin problems).

4. How to apply methylphenidate transdermal system

- Each transdermal system is sealed in its own protective pouch.
- Carefully cut the protective pouch open with scissors, being careful not to cut the transdermal system. **Do not use transdermal systems that have been cut or damaged in any way (See Figure B).**

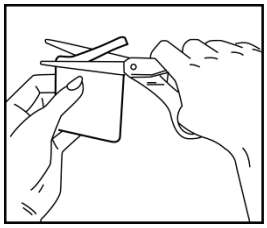


Figure B

- Remove the transdermal system from the protective pouch and discard additional piece of protective film above the transdermal system.
- Look at the transdermal system to make sure it is not damaged. The transdermal system should separate easily from the protective liner. Throw away the transdermal system if the protective liner is hard to remove.

The methylphenidate transdermal system has 4 layers. The 4 layers are pictured below. The pictures show both sides of the transdermal system:

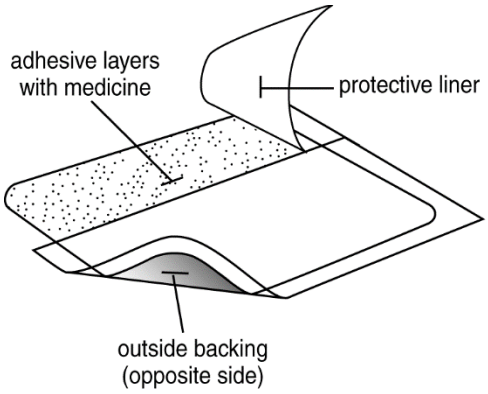


Figure C

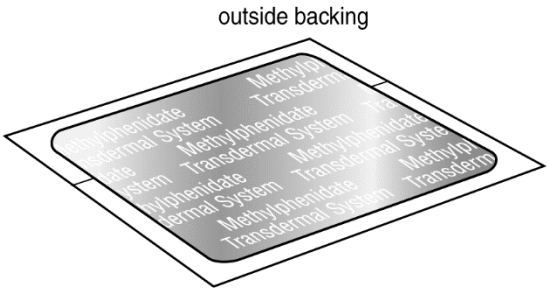


Figure D

Layers:

- **Protective liner:** The protective liner is the layer that you remove before you put the transdermal system on (See Figure C).
- **Adhesive layers with medicine:** The adhesive layers with medicine consist of an adhesive reservoir layer that contains drug and an adhesive layer that sticks to your skin (See Figure C).
- **Outside backing:** The outside backing is the layer that you see after you put the transdermal system on your skin. The words "Methylphenidate Transdermal System" are printed on this layer (See Figure D).

- **Apply the transdermal system right away after you remove the transdermal system from protective pouch**.
- Hold the transdermal system with the hard protective liner facing you. The words "Methylphenidate Transdermal System" will appear backwards.
- **Gently** bend the transdermal system along the faint line and **slowly peel** one side of the liner, which covers the sticky surface of the transdermal system (See Figure E).

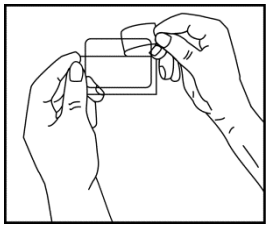


Figure E

- Avoid touching the sticky side of the transdermal system with your fingers.
- If you accidentally touch the sticky side of the transdermal system, apply the transdermal system, then wash your hands right away so that the medicine does not go into the skin on your hands.
- Using the other side of the protective liner as a handle, apply the sticky side of the transdermal system to the selected area of the child's hip (See Figure F).

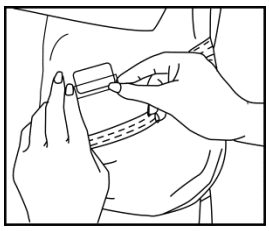


Figure F

- Press the sticky side of the transdermal system firmly into place and smooth it down.
- While you are still holding the sticky side down, gently fold back the other side of the transdermal system.
- Hold an edge of the remaining protective liner and **slowly peel** it off (See Figure G).

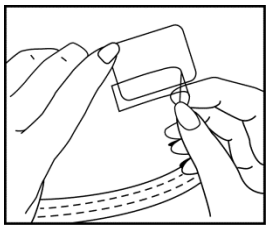


Figure G

- After the protective liner is removed, there should not be any adhesive (glue) sticking to the liner.

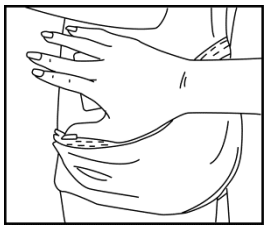


Figure H

- **Press the entire transdermal system firmly into place with the palm of your hand over the transdermal system for about 30 seconds (See Figure H).**
- Make sure that the transdermal system firmly sticks to your skin.
- Gently rub the edges of the transdermal system with your fingers to make sure the transdermal system sticks to your skin.
- Wash your hands after you apply your transdermal system.
- Write the time you applied your transdermal system on the dosing chart on the carton. Use the dosing schedule so you know what time you should remove your transdermal system.

5. How to remove and throw away methylphenidate transdermal system

- When you remove the transdermal system, peel it off slowly. If the transdermal system is too sticky on your skin and you need something to help you remove it:

- Gently apply an oil-based product (petroleum jelly, olive oil, or mineral oil) to the transdermal system edges. Gently spread the oil underneath the transdermal system edges.
- Apply an oil-based product or lotion to your skin if any adhesive (glue) remains after you remove your transdermal system. This will gently loosen and remove any adhesive that is left over.
- If you still cannot easily remove the transdermal system, ask your doctor or pharmacist about what to do for this problem.

- Fold the used methylphenidate transdermal system in half and press it together firmly so that the sticky side sticks to itself. **Flush the used transdermal system down the toilet or put the transdermal system in a container with a lid right away.**
- Do not flush the protective pouches or the protective liners down the toilet. These items should be thrown away in a container with a lid.
- Wash your hands after you handle the transdermal system.
- After you remove the transdermal system and throw the transdermal system away, write down the time on the dosing chart.
- Safely throw away any unused methylphenidate transdermal systems that are left over from the prescription as soon as they are no longer needed.
  To safely throw away the transdermal systems:
  - Remove the leftover transdermal systems from their protective pouches and remove the protective liners.
  - Either fold the transdermal systems in half with the sticky sides together, and flush the transdermal systems down the toilet, **or**
  - Throw the transdermal systems away in a container with a lid.

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.

The brands listed are trademarks of their respective owners.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Revised: 6/2021
MPN:RX2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

LABELING REVIEWS

***** This document contains proprietary information that cannot be released to the public.***V.25**

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	07/21/2021
ANDA Number(s)	206497
Review Number	3
Applicant Name	Mylan Technologies Inc., a Viatris Company
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr
Proposed Proprietary Name	NA
Submission Received Date	02/25/2021 and 07/01/2021
Primary Labeling Reviewer	Charlene Peterson
Secondary Labeling Reviewer	Eunjung Chuh

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C3)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C3)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C3)

The Division of Labeling has no further questions/comments at this time based on your labeling submissions received 02/25/2021, 07/01/2021.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C3)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C3)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C3)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr 1 Transdermal System per container pouch	07/27/2017	Satisfactory
Blister	N/A	N/A		
Carton	Final	1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr 30 (1 x 30) Transdermal Systems	02/25/2021	Satisfactory
Patch (Transdermal System)	Final	1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr 1	07/27/2017	Satisfactory
Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 6/2021	07/01/2021	Satisfactory
Medication Guide	Draft	Revised: 6/2021	07/01/2021	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	Draft	Revised: 6/2021	07/01/2021	Satisfactory
SPL Data Elements				

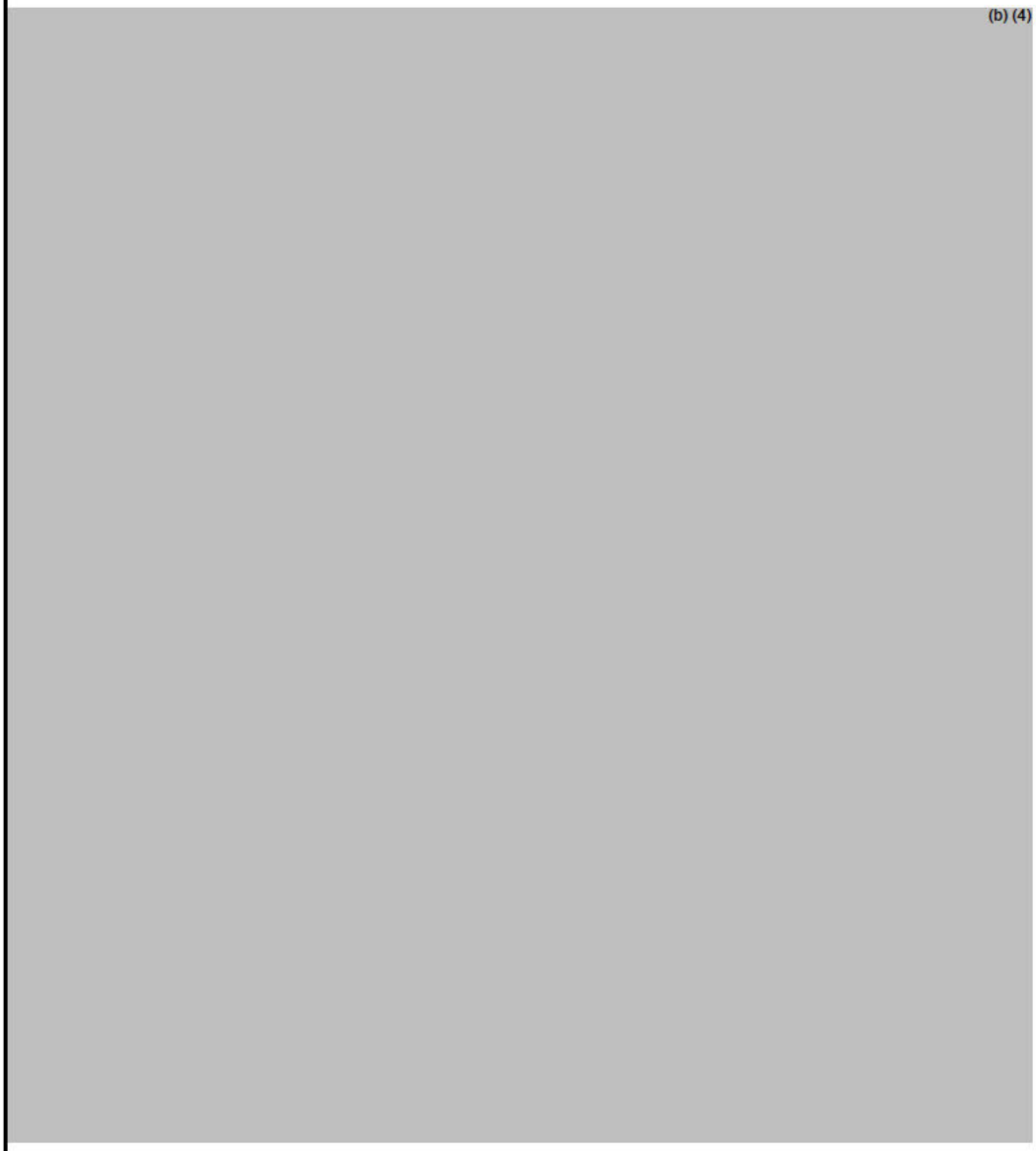
4 LABELING REVIEW INFORMATION(C3)

4.1 REGULATORY INFORMATION (C3)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? **Drug Facts dated 07/03/2019** National Pregnancy Registry for Psychiatric Medications

Yes	No	
		There is a pregnancy registry established by the Massachusetts General Hospital and Havard Medical school for the class of psychiatric medications. There are three different groups under the pregnancy registry but the phone number for the PR is the same for all three. 1. The National Pregnancy Registry for Atypical Antipsychotics 2. The National Pregnancy Registry for Antidepressants 3. The National Pregnancy Registry for ADHD Medications. Per DPMH, this NDA holders are required to list this PR in their insert labeling. We will request all ANDAs for psychiatric medications to list this PR in their labeling to be the same as the RLD. We do NOT need to ask the firm to confirm that they are registred with this organization to participate in the PR. **Updated 4/14/2021: Added active ingredients for Atypical Antipsychotics, Antidepressants, and ADHD Medication. Please update as needed.**

(b) (4)



Drug Facts dated 01/20/2017

Yes	No	(b) (4)
☐	☒	

4.2 MODEL PRESCRIBING INFORMATION (C3)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**
(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)
NDA#/Supplement# (S-000 if original): NDA 021514 / S-032
Supplement Approval Date: 06/25/2021
Proprietary Name: Daytrana
Established Name: Methylphenidate Transdermal System
Description of Supplement:
Please refer to your supplemental new drug application (sNDA) dated and received April 30, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Daytrana (methylphenidate transdermal system) We also refer to our letter dated March 12, 2021, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for methylphenidate products. This information pertains to the risk of extrapyramidal symptoms (EPS) caused by the combined usage of

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
methylphenidate and risperidone. Our March 12, 2021, correspondence also requested revisions, unrelated to the new safety information, to further align the Drug Interaction section of the Prescribing Information. This supplemental new drug application provides for revisions to the labeling for Daytrana consistent with our March 12, 2021, safety labeling change notification letter. **Link:** https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4817651_4409067_090140af805fce41_NDA021514_3285107
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):** NDA 021514/S-033 pending CMC (Acknowledgement letter) dated 06/24/2021 No impact on labeling This supplemental application, submitted as a "Changes Being Effected" supplement, (b) (4) (b) (4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:
The ANDA has used NDA 021514/S-032 approved on 06/25/2021 as their RLD/Model labeling.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C3)

The Orange Book was searched on 07/21/2021

Table 4 provides Orange Book patents for the Model Labeling (NDA021514) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
10MG/9HR (1.1MG/HR), 20MG/9HR (2.2MG/HR), 30MG/9HR (3.3MG/HR), 15MG/9HR (1.6MG/HR)	8632802	10/07/2025			IV	3/4/2014	None
30MG/9HR	9034370	10/07/2025			IV	7/29/2015	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter Carve-out or None)**
(3.3MG/HR), 10MG/9HR (1.1MG/HR), 20MG/9HR (2.2MG/HR), 15MG/9HR (1.6MG/HR)							
30MG/9HR (3.3MG/HR), 10MG/9HR (1.1MG/HR), 15MG/9HR (1.6MG/HR), 20MG/9HR (2.2MG/HR)	9668981	10/07/2025	U-2024	METHOD FOR TRANSDERMALLY DELIVERING A DRUG TO A USER IN NEED THEREOF	IV	9/1/2017	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:

Patent Amendment dated 11/03/2017

In accordance with the August 27, 2015, letter from FDA to Mylan finding the above-identified ANDA acceptable for filing, Mylan is hereby notifying the Agency that Mylan did not receive notice regarding the commencement of an action for patent infringement of U.S. Patent No. 9,668,981 against Mylan within the statutory forty-five (45) day period set forth in 21 U.S.C. § 355(j)(5)(B)(iii) by any person provided notice under 21 U.S.C. § 355(j)(2)(B)(iii) and 21 C.F.R § 314.95(a) with respect to the reference listed drug (DAYTRANA® Extended-release Film, NDA No. 021514).

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C3)

The USP was searched on 07/21/2021

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
		USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

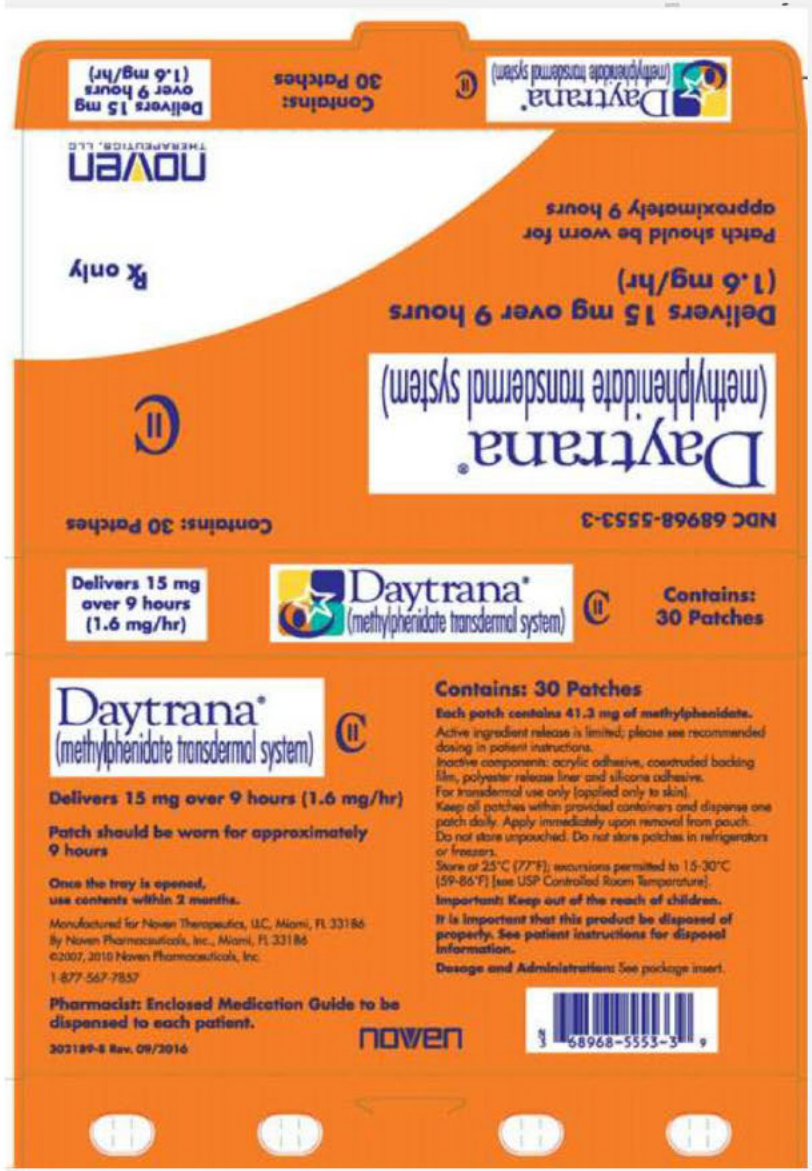
Reviewer Comments:
NA

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C3)

Model container/carton/blister labels (Source: NDA 021514/S-032 SPL submitted on 07/14/2021 (b) (4)
(b) (4)

Carton


Daytrana®
(methylphenidate transdermal system)
Delivers 15 mg over 9 hours
(1.6 mg/hr)
Patch should be worn for
approximately 9 hours
Once the tray is opened,
use contents within 2 months.
Manufactured for Noven Therapeutics, LLC, Miami, FL 33186
By Noven Pharmaceuticals, Inc., Miami, FL 33186
©2007, 2010 Noven Pharmaceuticals, Inc.
1-877-567-7857
Pharmacist: Enclosed Medication Guide to be
dispensed to each patient.
302189-8 Rev. 09/2016
NOVEN
Contains: 30 Patches
Each patch contains 41.3 mg of methylphenidate.
Active ingredient release is limited; please see recommended
dosing in patient instructions.
Inactive components: acrylic adhesive, coextruded backing
film, polyester release liner and silicone adhesive.
For transdermal use only (applied only to skin).
Keep all patches within provided containers and dispense one
patch daily. Apply immediately upon removal from pouch.
Do not store unpouched. Do not store patches in refrigerators
or freezers.
Store at 25°C (77°F); excursions permitted to 15-30°C
(59-86°F) [see USP Controlled Room Temperature].
Important: Keep out of the reach of children.
It is important that this product be disposed of
properly. See patient instructions for disposal
information.
Dosage and Administration: See package insert.
3 68968-5553-3 9
Delivers 15 mg
over 9 hours
(1.6 mg/hr)
Daytrana®
(methylphenidate transdermal system)
Contains:
30 Patches
NDC 68968-5553-3
Contains: 30 Patches
Daytrana®
(methylphenidate transdermal system)
Delivers 15 mg over 9 hours
(1.6 mg/hr)
Rx only
Patch should be worn for
approximately 9 hours
NOVEN
THERAPEUTICS, LLC
Contains:
30 Patches
Delivers 15 mg
over 9 hours
(1.6 mg/hr)
Daytrana®
(methylphenidate transdermal system)

Daytrana®
(methylphenidate transdermal system)
Delivers 15 mg over 9 hours (1.6 mg/hr)
Date of Patch Application MM/DD/YYYY
Time Applied
Time Removed
Application Site
Disposal Method
Fold & flush
Fold & trash
Once the tray is opened, use contents within 2 months.


Delivers 30 mg over 9 hours (3.3 mg/hr)
Daytrana® (methylphenidate transdermal system)
Contains: 30 Patches
Daytrana®
(methylphenidate transdermal system)
Delivers 30 mg over 9 hours
(3.3 mg/hr)
Patch should be worn for approximately 9 hours
Once the tray is opened, use contents within 2 months.
Manufactured for Noven Therapeutics, LLC, Miami, FL 33186
By Noven Pharmaceuticals, Inc., Miami, FL 33186
©2007, 2010 Noven Pharmaceuticals, Inc.
1-877-567-7857
Pharmacist: Enclosed Medication Guide to be dispensed to each patient.
302191-8 Rev. 09/2016
Contains: 30 patches
Each patch contains 82.5 mg of methylphenidate.
Active ingredient release is limited; please see recommended dosing in patient instructions.
Inactive components: acrylic adhesive, coextruded backing film, polyester release liner and silicone adhesive.
For transdermal use only (applied only to skin).
Keep all patches within provided containers and dispense one patch daily. Apply immediately upon removal from pouch.
Do not store unpouched. Do not store patches in refrigerators or freezers.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Important: Keep out of the reach of children.
It is important that this product be disposed of properly. See patient instructions for disposal information.
Dosage and Administration: See package insert.
noven
3 68968-5555-3 7
NDC 68968-5555-3
Rx only
NOVEN THERAPEUTICS, LLC
Contains: 30 Patches
Delivers 30 mg over 9 hours (3.3 mg/hr)
302191-8
04840

Delivers 30 mg over 9 hours (3.3 mg/hr)

Daytrana® (methylphenidate transdermal system) ℞

Date of Patch Application MM/DD/YYYY	Time Applied	Time Removed	Application Site	Disposal Method
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash
	AM PM	AM PM	Left Right	Fold & flush Fold & trash

Once the tray is opened, use contents within 2 months.

5 ASSESSMENT OF ANDA LABELING AND LABELS (C3)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C3)

5.1.1 DRUG PRODUCT REVIEW (C3)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

The last completed Drug Product Review dated 02/09/2018 did not include a Labeling section, but did include a response to previous labeling reviewer's question.
Refer to section 6.

Drug Product Review dated 04/26/2016

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain:

ii) Are the storage conditions acceptable? ☒ Yes, with a comment ☐ No
If "No," explain.

The RLD states to "**Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F)** [see USP Controlled Room Temperature]. Do not store patches unpouched. Do not store patches in refrigerators or freezers".
The proposed product states to "**Store at 20° to 25°C (68° to 77°F).** [See USP Controlled Room Temperature]. Do not store (b) (4) unpouched. Do not store (b) (4) in refrigerators or freezers".

c) DOSAGE AND ADMINISTRATION:

Adequate

Refer to section 6 for CMC communication.

5.1.2 DESCRIPTION (C3)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	NA
ANDA Labeling	(b) (4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	(b) (4)
	Currently Proposed Methylphenidate transdermal system contains methylphenidate in a polyisobutylene adhesive. The composition per unit area of all dosage strengths is identical, and the total dose delivered is dependent on the transdermal system size and wear time. The transdermal system consists of four layers, as seen in the figure below (cross-section of the transdermal system) (1) Outside Backing (2) Solid Matrix Drug Reservoir (3) Adhesive Formulation (4) Protective Liner (removed prior to application) Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a polyester/ethylene vinyl acetate laminate film backing and white ink which contains acrylic polymers, polyethylene wax, polytetrafluoroethylene, polyvinylpyrrolidone, sodium dioctyl sulfosuccinate and titanium dioxide, (2) a solid matrix drug reservoir of methylphenidate, polyisobutylene adhesive, mineral oil and hydrophobic colloidal silica, (3) a skin contact adhesive formulation of polyisobutylene adhesive, mineral oil and hydrophobic colloidal silica, and (4) a fluoropolymer-coated polyester protective liner, which is attached to the adhesive surface and must be removed before the transdermal system can be used. The active component of the transdermal system is methylphenidate. The remaining components are pharmacologically inactive. Methylphenidate transdermal systems are packaged with an additional piece of protective film above the system within each pouch. This piece of protective film is removed and discarded at the time of use. **There is a change** in the information associated with the white ink in the film backing. Per side-by side submitted on 07/01/2021 formulation information added to be consistent with the Chemistry, Manufacturing and Controls

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	section of Mylan's application. ***Acceptable .***

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C3)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	NA
ANDA Labeling	(b) (4) [redacted] **Currently Proposed** Methylphenidate Transdermal System is supplied in a carton containing 30 individually pouched transdermal systems. See the chart below for information regarding available strengths. Each dosage form is a translucent rectangular transdermal system with rounded corners consisting of a matte backing film randomly printed with "Methylphenidate Transdermal System" and the "mg/hr" strength in white ink, an adhesive layer and a clear to slightly hazy oversized release liner that is slit. Each transdermal system

<table>
<tr><th colspan="2">Table 8: Comparison of Model Labeling to ANDA Labeling</th></tr>
<tr><td></td><td>
is overlaid with an additional clear to slightly hazy oversized release liner and is contained in a square, flat pouch that is imprinted with lot number and expiration date.
<table>
<tr><th>Nominal Dose Delivered (mg) Over 9 Hours</th><th>Dosage Rate* (mg/hr)</th><th>Transdermal System Size (cm^2)</th><th>Methylphenidate Content per Transdermal System** (mg)</th><th>Transdermal Systems Per Carton</th><th>NDC Number</th></tr>
<tr><td>10</td><td>1.1</td><td>9.6</td><td>10.4</td><td>30</td><td>0378-8260-93</td></tr>
<tr><td>15</td><td>1.6</td><td>14.4</td><td>15.6</td><td>30</td><td>0378-8261-93</td></tr>
<tr><td>20</td><td>2.2</td><td>19.2</td><td>20.7</td><td>30</td><td>0378-8262-93</td></tr>
<tr><td>30</td><td>3.3</td><td>28.8</td><td>31.1</td><td>30</td><td>0378-8263-93</td></tr>
</table>
*Nominal in vivo delivery rate per hour in children and adolescents when applied to the hip, based on a 9-hour wear period.
**Methylphenidate content in each transdermal system.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Do not store transdermal systems unpouched. Do not store transdermal systems in refrigerators or freezers.

Apply the transdermal system immediately upon removal from the individual protective pouch. For transdermal use only.

There is not a change.
Acceptable.
</td></tr>
</table>

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER(C3)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	NA
Name and Address on ANDA Container/Carton	NA
Name and Address on ANDA Prescribing Information	**Previous Labeling Review** Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. **Currently Proposed** Manufactured for: **Mylan Pharmaceuticals Inc.** Morgantown, WV 26505 U.S.A. There is not a change. ***Acceptable.***

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**
	Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A.		

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		OVERALL ASSESSMENT:
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The container (pouch) label and (b) (4) were acceptable during labeling review C2 based on the submission dated 07/27/2017.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The carton labeling was previously acceptable during labeling review C2 based on the submission dated 07/27/2017.

The applicant updated the carton labeling in the submission dated on 02/25/2021.

CR letter dated 02/25/2021

Mylan's previous submitted final printed carton labels were revised to be consistent with Mylan's current standard format as well as to incorporate a new keyline. The revised final printed carton labels are provided in Section 1.14.2.1. A side-by-side comparison of Mylan's previously submitted final printed cartons to Mylan's proposed final printed carton labels is provided in Section 1.14.1.2 (Carton). Mylan's proposed final printed pouch and final printed patch print labels remain the same as those submitted in a Major Complete Response Amendment on July 27, 2017 (Sequence No. 0014).

The revisions were as follows:

1.Revised the Pharmacist dispensing statement on the top panel to be consistent with Mylan's current standard format.

2. Revised the list of inactive ingredients to alphabetize the list, add specificity to the polyester release liner component and add the white ink composition to be consistent with the Chemistry, Manufacturing and Controls section of Mylan's application and Mylan's current standard format.

3. Relocated the "Mylan.com" web address to place it directly below the Mylan company name to be consistent with Mylan's current standard format.

4. Inserted "(1-877-4-INFO-RX)" after Mylan's company telephone number to be consistent with Mylan's current standard format.

5. Replaced label code to reflect the latest version of final printed labeling.

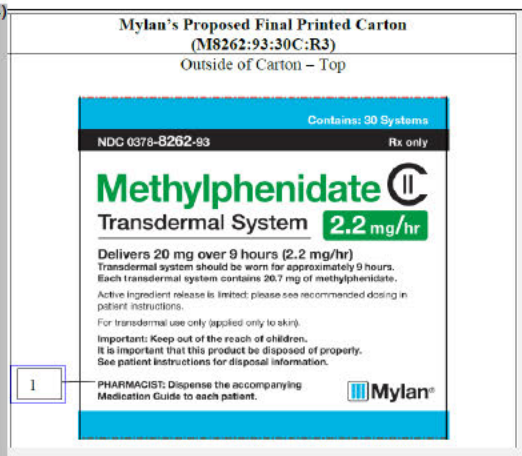
6. Designated area indicated for the Lot Number, Expiration Date and Serialization which is printed onto the carton during the packaging process.

7. Replaced the pharmacode and human readable number to reflect the latest version of final printed labeling. The pharmacode has also been revised to all black to be consistent with Mylan's current packaging site requirements.

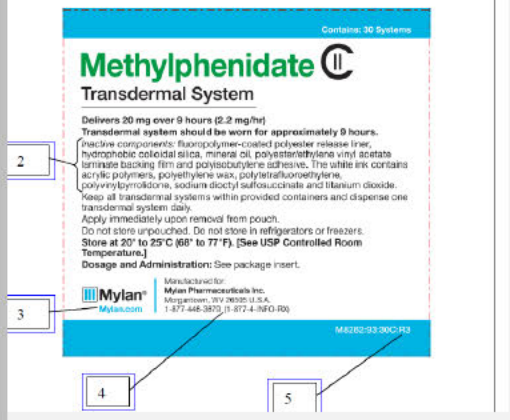
(b) (4)

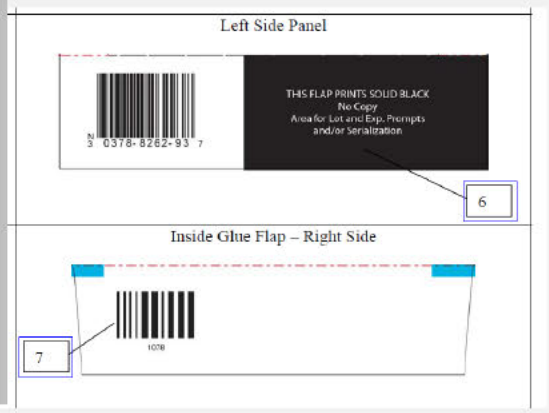
(b) (4)

Mylan's Proposed Final Printed Carton
(M8262:93:30C:R3)
Outside of Carton – Top



Mylan's Proposed Final Printed Carton
(M8262:93:30C:R3)
Outside of Carton – Bottom





The revised carton labeling is acceptable.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The applicant includes a Pregnancy Registry , which is the same as the reference listed drug (RLD) labeling. Refer to section 4.1.

The reason for this review is based on the following;
Complete Response letter submitted on 02/25/2021

Mylan wishes to amend this application to provide final printed Prescribing Information/ Medication Guide/Instructions for Use labeling (MPN:R3; Revised: 1/2021) that has been revised in response to the Agency's Complete Response Letter dated February 26, 2018 and pursuant to the CDER Internet Posting dated October 22, 2019 (NDA 021514/S-030) which contained approved labeling revisions for Reference Listed Drug (RLD), Daytrana® (methylphenidate) transdermal system (Noven Pharmaceuticals, Inc.). A copy of the CDER approval letter for the RLD is provided in Section 1.4.4., References. A copy of the RLD's labeling approved on October 22, 2019 is provided in Section 1.14.3.3.

A side-by-side comparison of Mylan's proposed final printed Prescribing Information/Medication Guide/Instructions for Use to the RLD's labeling approved on October 22, 2019 is provided in Section 1.14.3.1 (Labeling). Mylan's previous submitted final printed carton labels were revised to be consistent with Mylan's current standard format as well as to incorporate a new keyline. The revised final printed carton labels are provided in Section 1.14.2.1. A side-by-side comparison of Mylan's previously submitted final printed cartons to Mylan's proposed final printed carton labels is provided in Section 1.14.1.2 (Carton). Mylan's proposed final printed pouch and final printed patch print labels remain the same as those submitted in a Major Complete Response Amendment on July 27, 2017 (Sequence No. 0014).

FDA COMMENT 1
GENERAL COMMENT

Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-028 approved November 6, 2017.

MYLAN RESPONSE
Since the issuance of the February 26, 2018 Complete Response Letter, subsequent labeling has been approved for the RLD. Accordingly, Mylan has revised our proposed final printed Prescribing Information/Medication Guide/Instructions for Use in accordance with the most recently approved labeling for the RLD, Daytrana® (NDA 021514/S-030), approved on October 22, 2019. Please refer to Mylan's proposed final printed Prescribing Information/Medication Guide/Instructions for Use provided in Section 1.14.2.2.

FDA COMMENT 2
FULL PRESCRIBING INFORMATION: CONTENTS* and FULL PRESCRIBING INFORMATION:

Revise the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of Fertility".

MYLAN RESPONSE
As requested by the Agency, Mylan has revised the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of Fertility" in the FULL PRESCRIBING INFORMATION: CONTENTS* and FULL PRESCRIBING INFORMATION sections of our proposed final printed Prescribing Information/Medication Guide/Instructions for Use. Please refer to Mylan's proposed final printed Prescribi Information/Medication Guide/Instructions for Use provided in Section 1.14.2.2.

In accordance with the Agency's Guidance, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005), Structured Product Labeling (SPL) for Methylphenidate Transdermal System, 10 mg/9 hrs (1.1 mg/hr), 15 mg/9 hrs (1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr) is provided in Section 1.14.2.3. As a review aid, Microsoft Word versions have also been provided for the proposed labeling components.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the RLD. Mylan will monitor FDA's website for any approved labeling changes, where applicable, subject to the provisions of 505(j)(10)(A) which address late stage labeling changes by the RLD.

The applicant has adequately addressed the deficiencies.

Labeling Amendment submitted on 07/01/2021

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Mylan Technologies, a Viatris Company, wishes to amend this application to provide draft labeling (MPN:RX2; Revised: 6/2021) that has been revised pursuant to the CDER Internet Posting dated June 25, 2021 (NDA 021514/S-032) which contained approved labeling revisions for the Reference Listed Drug (RLD), Daytrana® (methylphenidate) Transdermal System (Noven Pharmaceuticals, Inc.). A copy of the CDER approval letter for the RLD is provided in Section 1.4.4, References. A copy of the RLD's labeling approved on June 25, 2021 is provided in Section 1.14.3.3.

In accordance with 21 CFR §314.96(d)(2), Mylan confirms that any changes described in this amendment do not require a patent certification pursuant to 21 CFR §314.96(d)(1).

A side-by-side comparison of Mylan's proposed draft Prescribing Information/Medication Guide/Instructions for Use to the RLD's labeling approved on June 25, 2021 is provided in Section 1.14.3.1 (Labeling). Please note that Mylan's proposed final printed pouch and final printed patch print labels remain the same as those previously submitted in a Resubmission – Major Complete Response Amendment dated July 27, 2017 (Sequence No. 0014). Mylan's proposed final printed carton labels remain the same as those previously submitted in a Resubmission – Major Complete Response Amendment dated February 25, 2021 (Sequence No. 0022).

In accordance with the Agency's Guidance, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005), draft Structured Product Labeling (SPL) for Methylphenidate Transdermal System, 10 mg/9 hrs (1.1 mg/hr), 15 mg/9 hrs (1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr) is provided in Section 1.14.1.3. As a review aid, a Microsoft Word version has also been provided for the proposed labeling component.

The Prescribing Information is adequate.

Deficiency Comments:

5.5 MEDICATION GUIDE (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The Medication Guide and Instructions for Use are combined. Therefore, the revision date is found at the end of the Instructions for Use.

The Medication Guide is acceptable.

Deficiency Comments:

5.6 OTHER PATIENT LABELING (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The minor differences in comparison to the reference listed drug (RLD) labeling do not impact the safe use and substitutability of this drug product.
Refer to section 6.

The Instructions for Use are acceptable.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C3)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:
From: Drug Product Review dated 02/09/2018

Labeling & Package CMC Related Concerns: NONE

The labeling reviewer provided the following update to the CMC reviewer based on the previous concerns and firm's response:

"The applicant added an additional paragraph describing the drug product in the HOW SUPPLIED/STORAGE AND HANDLING section of the labeling. Please see below and confirm that the information is accurate.
Each dosage form is a translucent rectangular transdermal system with rounded corners consisting of a matte backing film randomly printed with "Methylphenidate Transdermal System" and the "mg/hr" strength in white ink, an adhesive layer, and a clear to slightly hazy oversized release liner that is slit. Each transdermal system is overlaid with an additional clear to slightly hazy oversized release liner and is contained in a square, flat pouch that is imprinted with lot number and expiration date."

From: DCR Review dated 06/01/2021

3 APPLICANT'S THRESHOLD ANALYSES

On 02/25/2021, the applicant submitted a comparative threshold analysis report. The Applicant concluded the identified minor differences between the user interfaces of the generic combination product in comparison to the RLD are not expected to affect substitutability of the products.

***Reviewer's Comment**: DCR concludes that there are acceptable minor design differences based on the physical comparison, comparative task analysis, and labeling comparison of the delivery device constituent part between the proposed generic combination product and the RLD. DCR also concludes that the generic product can be substituted for the RLD without the intervention of a health care provider and without additional training prior to use of the generic product. Thus, additional information and data are not necessary to evaluate the identified differences in the user interface.*

4 CONCLUSION

From a clinical safety perspective, there are acceptable minor design differences between the RLD and proposed drug delivery device. Therefore, DCR concludes this generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product.

Deficiency Comments:

Charlene Peterson

Digitally signed by Charlene Peterson
Date: 7/23/2021 04:56:41PM
GUID: 5423006c00721f95e6563eed63495a75

Esther Chuh

Digitally signed by Esther Chuh
Date: 7/23/2021 05:43:36PM
GUID: 508da70700028b78f2f9ebd95bfb4a18

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	January 18, 2018
ANDA Number(s)	206497
Review Number	2
Applicant Name	Mylan Technologies, Inc.
Established Name & Strength(s)	Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr
Proposed Proprietary Name	NA
Submission Received Date	July 27, 2017
Primary Labeling Reviewer	Julie Neshiewat
Secondary Labeling Reviewer	Adolph Vezza

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐YES ☒NO

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on January 18, 2018 based on your submission dated July 27, 2017:

1. GENERAL COMMENT
   Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-028 approved November 6, 2017.
2. FULL PRESCRIBING INFORMATION: CONTENTS* and FULL PRESCRIBING INFORMATION: Revise the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of Fertility".

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

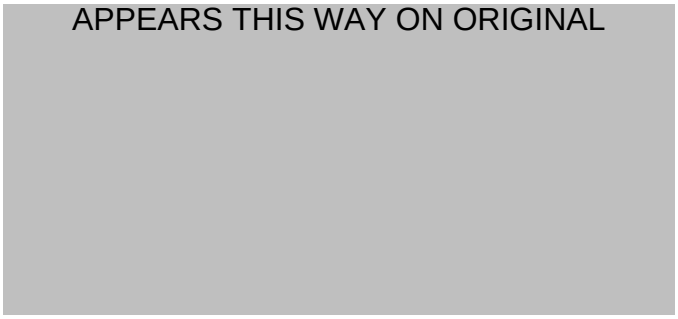
1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

APPEARS THIS WAY ON ORIGINAL

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].



Reviewer Comments:

The below comments are from the labeling review C1 based on the submission dated 12/13/13:

1. GENERAL COMMENTS
    a. Revise your Prescribing Information and Medication Guide to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-023 approved 8/14/15.
    b. Explain how the container closure system for your pouch label and carton labeling meet the tamper evident requirements of 21 CFR 1302.06.
2. PATCH LABEL: Space permitting, revise the established name to read "Methylphenidate Transdermal System".
3. POUCH LABEL
    a. Similar to the carton labeling, we recommend adding a usual dosage statement "**Dosage and Administration:** See package insert.". This statement can appear on the back of the pouch.
    b. The proposed expressions of strength on the pouch label/carton labeling lack adequate differentiation and may lead to medication errors. We recommend using a method(s) (e.g., use of different color, bolding, highlighting and etc.) to help differentiate the expressions of strength. Ensure any colors selected to display the expression of strength are sufficiently differentiated between the pouch labels/carton labeling.
    c. Ensure to include a place holder for the lot number and the expiration date.
4. CARTON LABELING
    a. See comments 3.b. and 2.c. above.
    b. To help further differentiate your drug product strengths, we recommend increasing the middle digits of the NDC number by increasing their size in comparison to the remaining digits in the NDC number (similar to your pouch label). For example: xxxxx-XXXX-xx.
    c. We recommend relocating the pharmacist instructions for the Medication Guide to the principal display panel (PDP). In order to accommodate this information on the PDP, the "**Dosage and Administration:** See package insert." statement can appear on the back panel.
5. PRESCRIBING INFORMATION (PI)
    a. GENERAL COMMENTS
        i. We recommend revising instances of "patch" or "transdermal patch" to read "transdermal system". For example, HIGHLIGHTS OF PI, **DOSAGE FORMS AND STRENGTHS**, we recommend revising "Transdermal Patch" to read "Transdermal System".
        ii. When stating strengths and dosages, we recommend placing a space between the number and its associated unit of measurement. For example, HIGHLIGHTS OF PI, **DOSAGE FORMS AND STRENGTHS**, we recommend revising "10mg/9 hours (1.1 mg/hr), …" to read "10 mg/9 hours (1.1 mg/hr), …" [added space between "10" and "mg"].
        iii. When stating strengths and dosages, we recommend having a unit of measurement after every number. For example, FULL PI, **14 CLINICAL STUDIES**, second paragraph, third sentence, we recommend revising "… 10, 15, 20, and 30 mg / 9 hours…" to read "… 10 mg/9 hours, 15 mg/9 hours, 20 mg/9 hours, and 30 mg/9 hours…" [please also note that the spaces were deleted before and after the "/"].
        iv. When stating strengths and dosages, we recommend keeping the number and its associated unit of measurement in the same line of text. For example, FULL PI, **14 CLINICAL STUDIES**, third paragraph, last sentence, we recommend placing "20" and "mg/9 hours" hours in the same line of text vs. two separate lines of text.
    b. HIGHLIGHTS OF PI
        i. Revise the first paragraph to read "**These highlights do not include all the information needed to use METHYLPHENIDATE TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for METHYLPHENIDATE**

TRANSDERMAL SYSTEM."

ii. Revise the title to read "**METHYLPHENIDATE transdermal system, CII**"

iii. Extend the solid line that separates the HIGHLIGHTS OF PI and FULL PI: CONTENTS* to appear across both columns (vs. just the right column).

iv. (b) (4)

v. Revise the subsection title to read: "**DOSAGE FORMS AND STRENGTHS**".

c. FULL PI: CONTENTS*

i. Revise the section title for "3" to read "**DOSAGE FORMS AND STRENGTHS**".

ii. Revise the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of Fertility".

d. FULL PI

i. Revise the section title for "3" to read "**DOSAGE FORMS AND STRENGTHS**".

ii. Revise the subsection title for "13.1" to read: "**Carcinogenesis, Mutagenesis, Impairment of Fertility**".

iii. Revise the spelling of "*vaculopathy*" in subsection 17.1 "**Information for Patients**" to read "*vasculopathy*".

6. MEDICATION GUIDE

a. **Before you start using methylphenidate transdermal system, tell your doctor if you have:**,

b. (b) (4)

7. STRUCTURED PRODUCT LABELING (SPL), Data Elements: (b) (4) (b) (4) to read "methylphenidate transdermal system".

Applicant's response: For comment 1.b., the applicant provided the following information –

Mylan acknowledges the Agency's comment and confirms that the intended container closure system (pouch and carton) for the drug product meets the requirements of 21 CFR 1302.06. (b) (4) *In addition, the labeling states "This pouch is Child Resistant. Cut Here." with a scissors icon and dashed line to indicate where to cut the pouch open. Mylan's proposed carton containing 30 pouched transdermal systems will be securely sealed with glue and would consequently show signs of tampering upon opening. The labeling indicates "OPEN HERE" on the proposed carton's Front Tuck Flap. For comment 7., the applicant indicates that the data elements cannot be revised as "transdermal system" is not a dosage form option within the FDA's stylesheet used to generate the SPL. The applicant acknowledged all other comments and submitted revised labels and labeling.*

Assessment: (b) (4) *We will continue to recommend these comments. The applicant adequately addressed all other comments.*

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:
The revised labels and labeling are satisfactory.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:
NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review A consult was completed by DCR for differences in patch removal instructions (peel patch slowly for RLD vs. quickly for ANDA). This issue is not applicable to the ANDA under review, as the patch removal instructions are the same as the RLD (peel patch slowly).
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** NDA021514/S-028 **Supplement Approval Date:** 11/6/17 **Proprietary Name:** Daytrana **Established Name:** methylphenidate transdermal system **Description of Supplement:** provides for the addition of the term "depression" into the Postmarketing Experience – Psychiatric Disorders subsection (6.2)
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):**
☐ **OTHER (Describe):** Supplement 029 approved 11/22/17 is a CMC supplement that does not impact labeling. (b) (4) Supplement 026 are CMC supplements that do not impact labeling.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO** Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES** Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

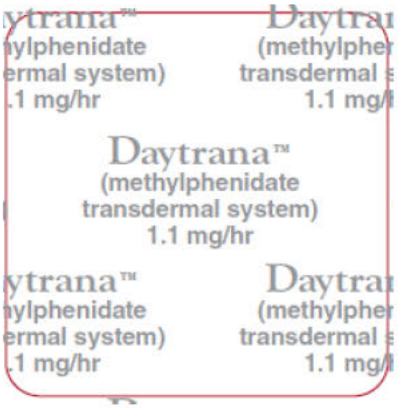
Reviewer Comments:

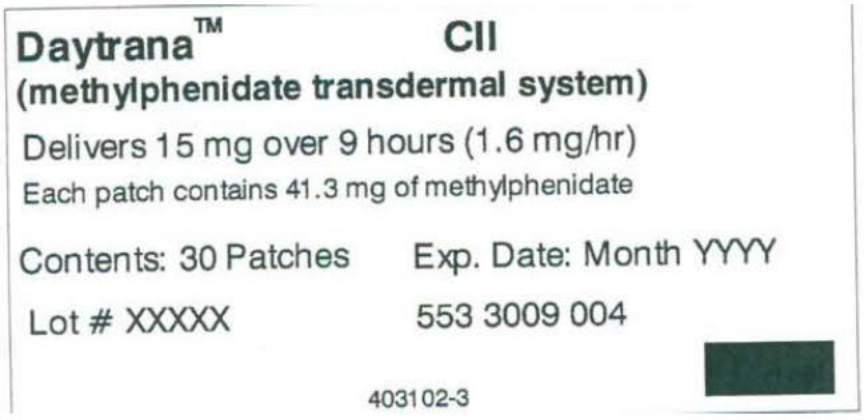
Recommendations for the applicant:

- Revise your Prescribing Information and Medication Guide to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-028 approved November 6, 2017.
- FULL PI: CONTENTS* and FULL PI: Revise the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of Fertility".

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: Annual Report 002 – 6/6/08**)**






This pouch is Child Resistant
Cut Here
NDC 54092-553-01
Contains: 1 Patch
Daytrana™
(methylphenidate transdermal system)
Delivers 15 mg over 9 hours (1.6 mg/hr)
Patch should be worn for approximately 9 hours.
Each patch contains 41.3 mg of methylphenidate.
Active ingredient release is limited; please see recommended dosing in patient instructions.
Inactive components: acrylic adhesive, coextruded backing film, polyester release liner and silicone adhesive.
For transdermal use only (applied only to skin).
Keep all patches within provided containers and dispense one patch daily. Apply immediately upon removal from pouch.
Do not store unpouched. Do not store patches in refrigerators or freezers. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Important: Keep out of the reach of children.
It is important that this product is disposed of properly.
See patient instructions for disposal information.
Rx only
Manufactured for Shire US Inc., Wayne, PA 19087
by Noven Pharmaceuticals, Inc., Miami, FL 33186
1-800-828-2088 ©2007 Shire Pharmaceuticals Ireland Limited.
Daytrana™ is a trademark of
Shire Pharmaceuticals Ireland Limited.
Once the tray is opened, use contents within 2 months.
202113-4 553 0102 006 Rev. 11/2007
LOT:
EXP:
*
Shire


302191-4
04B40
Daytrana™
(methylphenidate transdermal system)
NDC 54092-555-30
Contains: 30 Patches
Delivers 30 mg over 9 hours
(3.3 mg/hr)
Patch should be worn for approximately 9 hours
Rx only
Shire
Contains: 30 patches
Each patch contains 82.5 mg of methylphenidate.
Active ingredient release is limited; please see recommended dosing in patient instructions.
Inactive components: acrylic adhesive, coextruded backing film, polyester release liner and silicone adhesive.
For transdermal use only (applied only to skin).
Keep all patches within provided containers and dispense one patch daily. Apply immediately upon removal from pouch.
Do not store unpouched. Do not store patches in refrigerators or freezers.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Important: Keep out of the reach of children.
It is important that this product be disposed of properly. See patient instructions for disposal information.
Dosage and Administration: See package insert.
Delivers 30 mg over 9 hours (3.3 mg/hr)
Patch should be worn for approximately 9 hours
Once the tray is opened, use contents within 2 months.
Manufactured for Shire US Inc., Wayne, PA 19087
by Noven Pharmaceuticals, Inc., Miami, FL 33186
© 2007 Shire Pharmaceuticals Ireland Limited.
Daytrana™ is a trademark of Shire Pharmaceuticals Ireland Limited.
Pharmacist: Enclosed Medication Guide to be dispensed to each patient.
302191-4 555 3004 007 Rev. 11/2007
Once the tray is opened, use contents within 2 months.
LOT:
EXP:
Date of Patch Application MM/DD/YYYY
Time Applied
Time Removed
Application Site
Disposal Method
AM PM
Right Left
Fold & Flush
Fold & Trash
Delivers 30 mg over 9 hours (3.3 mg/hr)
Daytrana™
(methylphenidate transdermal system)

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 1/19/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	NO		NA	NA
Pending Monograph Proposed	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

NA

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/19/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 021514 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
6210705	Sep 30, 2018	U-727	For the treatment of Attention Deficit Hyperactivity Disorder (ADHD)	IV	12/13/13	None
6348211	Sep 30, 2018	U-727	For the treatment of Attention Deficit Hyperactivity Disorder (ADHD)	IV	12/13/13	None
8632802	Oct 7, 2025			IV	3/4/14	None
9034370	Oct 7, 2025			IV	7/29/15	None
9668981	Oct 7, 2025	U-2024	Method for transdermally delivering a drug to a user in need thereof	IV	9/1/17	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

In the 11/6/15 submission, the applicant informed the Agency of two actions filed against them for patent infringement of the '705 patent, '211 patent, '802 patent, and '370 patent. In the 11/9/16 submission, the applicant informed the Agency of the dismissal of the actions for patent infringement. In the 11/3/17 submission, the applicant indicated that no legal action was taken within the 45-day statutory period for the '981 patent.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

NA

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
		(b) (4)

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
(b) (4)	Methylphenidate transdermal system is supplied in a carton containing 30 individually pouched transdermal systems. See the chart below for information regarding available strengths. Each dosage form is a translucent rectangular transdermal system with rounded corners consisting of a matte backing film randomly printed with "Methylphenidate Transdermal System" and the "mg/hr" strength in white ink, an adhesive layer, and a clear to slightly hazy oversized release liner that is slit. Each transdermal system is overlaid with an additional clear to slightly hazy oversized release liner and is contained in a square, flat pouch that is imprinted with lot number and expiration date.	(b) (4)

Nominal Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Transdermal System Size (cm^2)	Methylphenidate Content per Transdermal System** (mg)	Transdermal Systems Per Carton	NDC Number
10	1.1	9.6	10.4	30	0378-8260-93
15	1.6	14.4	15.6	30	0378-8261-93
20	2.2	19.2	20.7	30	0378-8262-93
30	3.3	28.8	31.1	30	0378-8263-93

*Nominal in vivo delivery rate per hour in children and adolescents when applied to the hip, based on a 9-hour wear period.
**Methylphenidate content in each transdermal system.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Do not store transdermal systems unpouched. Do not store transdermal systems in refrigerators or freezers. Apply the transdermal system immediately upon removal from the individual protective pouch. For transdermal use only.

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
Mylan Pharmaceuticals Inc. Morgantown, WV 26505	Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A.	**The highlighted change is acceptable.**

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB) reviewer(s):

Reviewer Comments:

CMC:

The applicant added an additional paragraph describing the drug product in the HOW SUPPLIED/STORAGE AND HANDLING section of the labeling. Please see below and confirm that the information is accurate.

Each dosage form is a translucent rectangular transdermal system with rounded corners consisting of a matte backing film randomly printed with "Methylphenidate Transdermal System" and the "mg/hr" strength in white ink, an adhesive layer, and a clear to slightly hazy oversized release liner that is slit. Each transdermal system is overlaid with an additional clear to slightly hazy oversized release liner and is contained in a square, flat pouch that is imprinted with lot number and expiration date.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (Pouch)	Final	1s	7/27/17	Satisfactory
Patch	Final		7/27/17	Satisfactory
Carton (including Dosing Chart)	Final	1 X 30	7/27/17	Satisfactory
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	7/2017	7/27/17	Revise
Medication Guide (including Instructions for Use)	Draft	7/2017	7/27/17	Revise
Patient Information	NA			
SPL Data Elements	NA	7/2017	7/27/17	Satisfactory

Julie Neshiewat

Digitally signed by Julie Neshiewat
Date: 1/19/2018 04:46:20PM
GUID: 50814c7000007a4b6143ee494842a538

Adolph Vezza

Digitally signed by Adolph Vezza
Date: 1/22/2018 10:37:24AM
GUID: 508da70600028a9e6a494d73e6454d09

*** This document contains proprietary information that cannot be released to the public.***V.9

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	2/22/16
ANDA Number(s)	206497
Review Number	1
Applicant Name	Mylan Technologies, Inc.
Established Name & Strength(s)	Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr
Proposed Proprietary Name	NA
Submission Received Date	12/13/13
Labeling Reviewer	Julie Neshiewat
Labeling Team Leader	Adolph Vezza

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on 2/22/16 based on your submission dated 12/13/13:

1. GENERAL COMMENTS
    a. Revise your Prescribing Information and Medication Guide to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-023 approved 8/14/15.
    b. Explain how the container closure system for your pouch label and carton labeling meet the tamper evident requirements of 21 CFR 1302.06.
2. PATCH LABEL: Space permitting, revise the established name to read "Methylphenidate Transdermal System".
3. POUCH LABEL
    a. Similar to the carton labeling, we recommend adding a usual dosage statement "**Dosage and Administration:** See package insert.". This statement can appear on the back of the pouch.
    b. The proposed expressions of strength on the pouch label/carton labeling lack adequate differentiation and may lead to medication errors. We recommend using a method(s) (e.g., use of different color, bolding, highlighting and etc.) to help differentiate the expressions of strength. Ensure any colors selected to display the expression of strength are sufficiently differentiated between the pouch labels/carton labeling.
    c. Ensure to include a place holder for the lot number and the expiration date.
4. CARTON LABELING
    a. See comments 3.b. and 3.c. above.
    b. To help further differentiate your drug product strengths, we recommend increasing the middle digits of the NDC number by increasing their size in comparison to the remaining digits in the NDC number (similar to your pouch label). For example: xxxxx-XXXX-xx.
    c. We recommend relocating the pharmacist instructions for the Medication Guide to the principal display panel (PDP). In order to accommodate this information on the PDP, the "**Dosage and Administration:** See package insert." statement can appear on the back panel.
5. PRESCRIBING INFORMATION (PI)
    a. GENERAL COMMENTS
        i. We recommend (b) (4) "transdermal system". For example, HIGHLIGHTS OF PI, **DOSAGE FORMS AND STRENGTHS**, (b) (4) to read "Transdermal System".
        ii. When stating strengths and dosages, we recommend placing a space between the number and its associated unit of measurement. For example, HIGHLIGHTS OF PI, **DOSAGE FORMS AND STRENGTHS**, we recommend revising "10mg/9 hours (1.1 mg/hr), …" to read "10 mg/9 hours (1.1 mg/hr), …" [added space between "10" and "mg"].
        iii. When stating strengths and dosages, we recommend having a unit of measurement after every number. For example, FULL PI, **14 CLINICAL STUDIES**, second paragraph, third sentence, we recommend revising "… 10, 15, 20, and 30 mg / 9 hours…" to read "… 10 mg/9 hours, 15 mg/9 hours, 20 mg/9 hours, and 30 mg/9 hours…" [please also note that the spaces were deleted before and after the "/"].
        iv. When stating strengths and dosages, we recommend keeping the number and its associated unit of measurement in the same line of text. For example, FULL PI, **14 CLINICAL STUDIES**, third paragraph, last sentence, we recommend placing "20" and "mg/9 hours" hours in the same line of text vs. two separate lines of text.

b. HIGHLIGHTS OF PI
    i. Revise the first paragraph to read "**These highlights do not include all the information needed to use METHYLPHENIDATE TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for METHYLPHENIDATE TRANSDERMAL SYSTEM.**"
    ii. Revise the title to read "**METHYLPHENIDATE transdermal system, CII**"
    iii. Extend the solid line that separates the HIGHLIGHTS OF PI and FULL PI: CONTENTS* to appear across both columns (vs. just the right column).
    iv. (b) (4)
    v. Revise the subsection title to read: "**DOSAGE FORMS AND STRENGTHS**".
c. FULL PI: CONTENTS*
    i. Revise the section title for "3" to read "**DOSAGE FORMS AND STRENGTHS**".
    ii. Revise the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of Fertility".
d. FULL PI
    i. Revise the section title for "3" to read "**DOSAGE FORMS AND STRENGTHS**".
    ii. Revise the subsection title for "13.1" to read: "**Carcinogenesis, Mutagenesis, Impairment of Fertility**".
    iii. Revise the spelling of "*vaculopathy*" in subsection 17.1 "**Information for Patients**" to read "*vasculopathy*".

6. MEDICATION GUIDE
    a. **Before you start using methylphenidate transdermal system, tell your doctor if you have:**
    b. (b) (4)
7. STRUCTURED PRODUCT LABELING (SPL), Data Elements: (b) (4) (b) (4) to read "methylphenidate transdermal system".

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

1.3 POST APPROVAL REVISIONS

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES
Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain. Methylphenidate ER – Revised BE guidance No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead No IR/ECD/CC for OBE Broad policy issue covering multiple products containing extended-release methylphenidate. Contact OGDP Lead prior to any communication or action. *Based on this information, it appears the labeling review can continue.*

2.2 MODEL LABELING

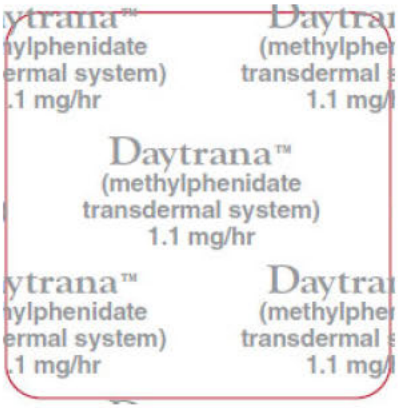
2.2.1 MODEL PRESCRIBING INFORMATION

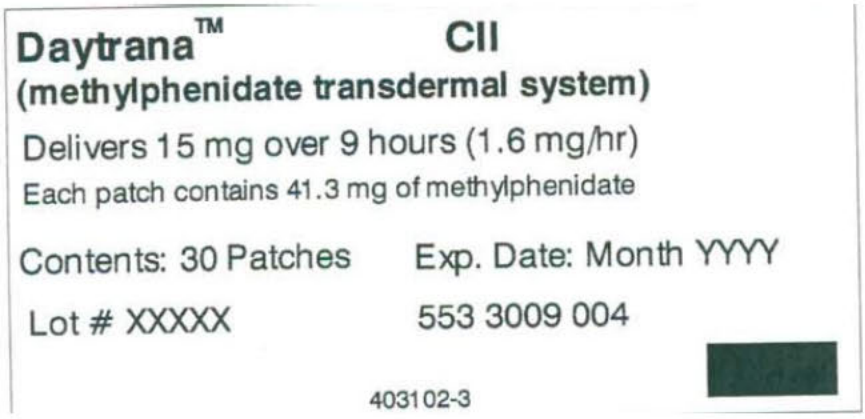
Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if original):** NDA 021514/S-023 **Supplement Approval Date:** 8/14/15 **Proprietary Name:** Daytrana **Established Name:** methylphenidate transdermal system **Description of Supplement:** Provides for the addition of new subsection under WARNINGS AND PRECAUTIONS entitled "Chemical Leukoderma", addition of new subsection under PATIENT COUNSELING INFORMATION – Information for Patients entitled "Chemical Leukoderma" , and revisions to the Medication Guide relating to chemical leukoderma to the labeling for Daytrana (methylphenidate transdermal system) consistent with the Agency's June 23, 2015 letter
☐ MOST RECENTLY APPROVED ANDA RLD LABELING **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out):

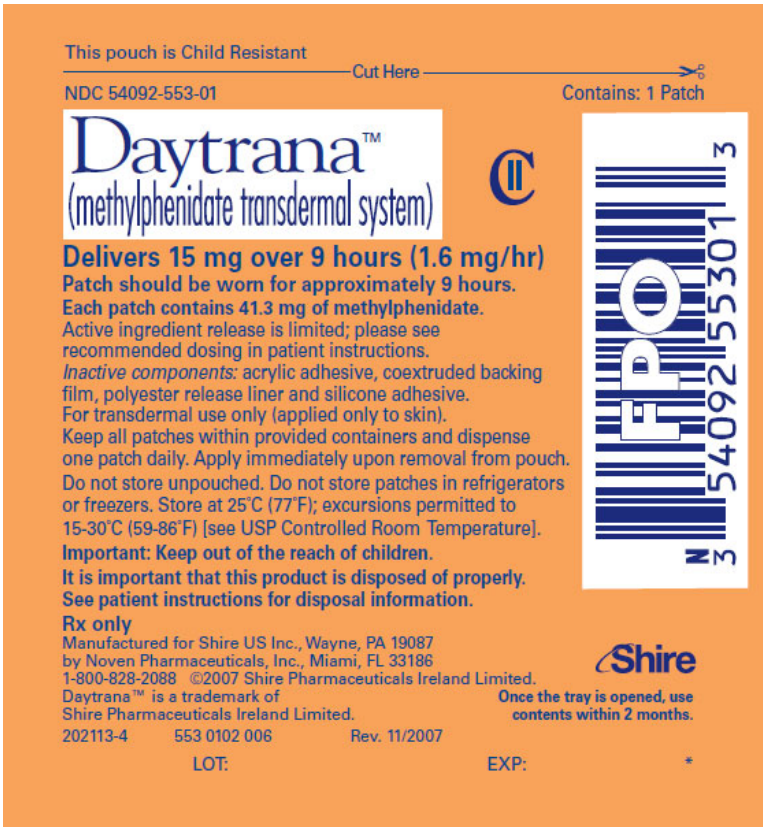
Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ OTHER (Describe): Supplement 018, approved 11/9/15, is a CMC supplement that does not impact labeling.
(b) (4)

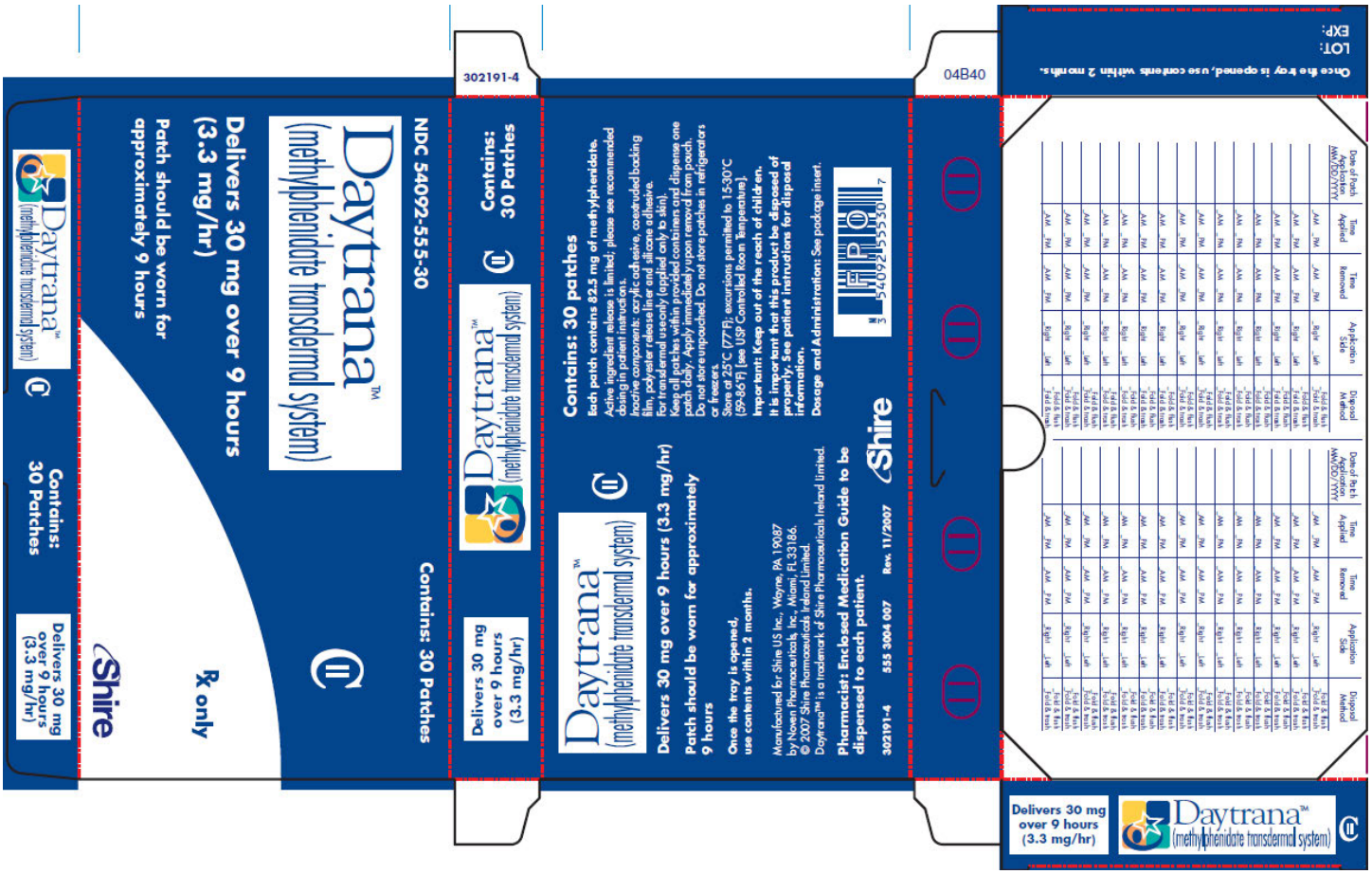
2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: Annual Report 002 – 6/6/08**)**






This pouch is Child Resistant
Cut Here
NDC 54092-553-01
Contains: 1 Patch
Daytrana™
(methylphenidate transdermal system)
Delivers 15 mg over 9 hours (1.6 mg/hr)
Patch should be worn for approximately 9 hours.
Each patch contains 41.3 mg of methylphenidate.
Active ingredient release is limited; please see recommended dosing in patient instructions.
Inactive components: acrylic adhesive, coextruded backing film, polyester release liner and silicone adhesive.
For transdermal use only (applied only to skin).
Keep all patches within provided containers and dispense one patch daily. Apply immediately upon removal from pouch.
Do not store unpouched. Do not store patches in refrigerators or freezers. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Important: Keep out of the reach of children.
It is important that this product is disposed of properly.
See patient instructions for disposal information.
Rx only
Manufactured for Shire US Inc., Wayne, PA 19087
by Noven Pharmaceuticals, Inc., Miami, FL 33186
1-800-828-2088 ©2007 Shire Pharmaceuticals Ireland Limited.
Daytrana™ is a trademark of
Shire Pharmaceuticals Ireland Limited.
202113-4 553 0102 006 Rev. 11/2007
LOT: EXP:
Shire
Once the tray is opened, use contents within 2 months.


Daytrana™
(methylphenidate transdermal system)
Delivers 30 mg over 9 hours
(3.3 mg/hr)
Patch should be worn for approximately 9 hours
Rx only
Shire
Contains: 30 Patches
Delivers 30 mg over 9 hours (3.3 mg/hr)
NDC 54092-555-30
Contains: 30 Patches
302191-4
Contains: 30 patches
Each patch contains 82.5 mg of methylphenidate.
Active ingredient release is limited; please see recommended dosing in patient instructions.
Inactive components: acrylic adhesive, coextruded backing film, polyester release liner and silicone adhesive.
For transdermal use only (applied only to skin).
Keep all patches within provided containers and dispense one patch daily. Apply immediately upon removal from pouch.
Do not store unpouched. Do not store patches in refrigerators or freezers.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Important: Keep out of the reach of children.
It is important that this product be disposed of properly. See patient instructions for disposal information.
Dosage and Administration: See package insert.
Pharmacist: Enclosed Medication Guide to be dispensed to each patient.
302191-4 555 3004 007 Rev. 11/2007
Manufactured for Shire US Inc., Wayne, PA 19087
by Noven Pharmaceuticals, Inc., Miami, FL 33186
© 2007 Shire Pharmaceuticals Ireland Limited.
Daytrana™ is a trademark of Shire Pharmaceuticals Ireland Limited.
04B40
Once the tray is opened, use contents within 2 months.
LOT:
EXP:
Date of Patch Application MM/DD/YYYY
Time Applied
Time Removed
Application Site
Disposal Method
AM PM
Right Left
3-Fold & Flush
Delivers 30 mg over 9 hours (3.3 mg/hr)
Daytrana™
(methylphenidate transdermal system)

2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	2/22/2016	NO	NA	NA
PF	2/22/2016	NO	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/22/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6210705	Sep 30, 2018	U-727	For the treatment of Attention Deficit Hyperactivity Disorder (ADHD)	IV	12/13/13	None
6348211	Sep 30, 2018	U-727	For the treatment of Attention Deficit Hyperactivity Disorder (ADHD)	IV	12/13/13	None
8632802	Oct 7, 2025			IV	3/4/14	None
9034370	Oct 7, 2025			IV	7/29/15	None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufactured (Cite Source)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
(b) (4)	Mylan Pharmaceuticals Inc. Morgantown, WV 26505	Mylan Pharmaceuticals Inc. Morgantown, WV 26505

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **NO**
Is the established name for this ANDA acceptable? **YES**
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Are the required USP recommendations reflected in the labeling? **NA**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **YES**

Reviewer Comments:
In the 11/6/15 submission, the applicant provided the complaint for patent infringement (all four patents).

Recommendations for the applicant:

- Revise your Prescribing Information and Medication Guide to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-023 approved 8/14/15.
- GENERAL COMMENTS
  - We recommend (b) (4) "transdermal system". For example, HIGHLIGHTS OF PI, **DOSAGE FORMS AND STRENGTHS**, (b) (4) (b) (4) to read "Transdermal System".
  - When stating strengths and dosages, we recommend placing a space between the number and its associated unit of measurement. For example, HIGHLIGHTS OF PI, **DOSAGE FORMS AND STRENGTHS**, we recommend revising "10mg/9 hours (1.1 mg/hr), …" to read "10 mg/9 hours (1.1 mg/hr), …" [added space between "10" and "mg"].
  - When stating strengths and dosages, we recommend having a unit of measurement after every number. For example, FULL PI, **14 CLINICAL STUDIES**, second paragraph, third sentence, we recommend revising "… 10, 15, 20, and 30 mg / 9 hours…" to read "… 10 mg/9 hours, 15 mg/9 hours, 20 mg/9 hours, and 30 mg/9 hours…" [please also note that the spaces were deleted before and after the "/"].
  - When stating strengths and dosages, we recommend keeping the number and its associated unit of measurement in the same line of text. For example, FULL PI, **14 CLINICAL STUDIES**, third paragraph, last sentence, we recommend placing "20" and "mg/9 hours" hours in the same line of text vs. two separate lines of text.
- HIGHLIGHTS OF PI
  - Revise the first paragraph to read "**These highlights do not include all the information needed to use METHYLPHENIDATE TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for METHYLPHENIDATE TRANSDERMAL SYSTEM.**"
  - Revise the title to read "**METHYLPHENIDATE transdermal system, CII**"
  - Extend the solid line that separates the HIGHLIGHTS OF PI and FULL PI: CONTENTS* to appear across both columns (vs. just the right column).
  - (b) (4)
  - Revise the subsection title to read: "**DOSAGE FORMS AND STRENGTHS**".
- FULL PI: CONTENTS*
  - Revise the section title for "3" to read "**DOSAGE FORMS AND STRENGTHS**".
  - Revise the subsection title for "13.1" to read: "Carcinogenesis, Mutagenesis, Impairment of

Fertility".

- FULL PI
  - Revise the section title for "3" to read "**DOSAGE FORMS AND STRENGTHS**".
  - Revise the subsection title for "13.1" to read: "**Carcinogenesis, Mutagenesis, Impairment of Fertility**".
  - (b) (4)

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
Daytrana contains methylphenidate in a multipolymeric adhesive. The methylphenidate is dispersed in acrylic adhesive that is dispersed in a silicone adhesive. The composition per unit area of all dosage strengths is identical, and the total dose delivered is dependent on the patch size and wear time. The patch consists of three layers, as seen in the figure below (cross-section of the patch). (1) Outside backing (2) Adhesive containing methylphenidate (3) Protective liner (removed prior to application) Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a polyester/ethylene vinyl acetate laminate film backing, (2) a proprietary adhesive formulation incorporating Noven Pharmaceuticals, Inc.'s DOT Matrix™ transdermal technology consisting of an acrylic adhesive, a silicone adhesive, and methylphenidate, and (3) a fluoropolymer-coated polyester protective liner which is attached to the adhesive surface and must be removed before the patch can be used. The active component of the patch is methylphenidate. The remaining components are pharmacologically inactive.	(b) (4)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling Memorandum of Understanding (MOU)?
YES, chemistry review pending (as of 2/22/16)
(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **PENDING CHEMISTRY REVIEW (as of 2/22/16)**

For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:
NA

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling

Model Labeling

Daytrana is supplied in a sealed tray or outer pouch containing 30 individually pouched patches. See the chart below for information regarding available strengths.

Nominal Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Patch Size (cm^2)	Methylphenidate Content per Patch** (mg)	Patches Per Carton	NDC Number
10	1.1	12.5	27.5	30	68968-5552-3
15	1.6	18.75	41.3	30	68968-5553-3
20	2.2	25	55	30	68968-5554-3
30	3.3	37.5	82.5	30	68968-5555-3

*Nominal *in vivo* delivery rate per hour in children and adolescents when applied to the hip, based on a 9-hour wear period.
**Methylphenidate content in each patch.

Store at 25º C (77º F); excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]. Do not store patches unpouched. Do not store patches in refrigerators or freezers.
Once the sealed tray or outer pouch is opened, use contents within 2 months. Apply the patch immediately upon removal from the individual protective pouch. **For transdermal use only.**

ANDA Labeling

(b) (4)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **YES, chemistry review pending (as of 2/22/16)**
If the chemistry review does NOT follow the MOU, is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **See comment below**
Is the storage or dispensing statement acceptable as compared to the USP? **NA**

Reviewer Comments:
We note that the RLD states "Once the sealed tray or outer pouch is opened, use contents within 2 months." (b) (4)

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **YES**
Is the Medication Guide same as the model labeling, except for allowable differences? **NO**
Does the Medication Guide meet the requirements of 21 CFR 208.20? **YES**
Has the Applicant committed to provide a sufficient number of medication guides? **See comment below**
Is the phonetic spelling of the proprietary or established name present? **YES**
Is FDA 1-800-FDA-1088 phone number included? **YES**

Reviewer Comments:
The carton labeling for the drug product states (b) (4) Since the carton contains 30 patches, which is unit-of-use packaging, the one enclosed Medication Guide would be a sufficient number of Medication Guides for the packaging.

Recommendations for the applicant:

- Revise your Prescribing Information and Medication Guide to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Daytrana, NDA 021514/S-023 approved 8/14/15.
- **Before you start using methylphenidate transdermal system, tell your doctor if you have:**, (b) (4) (b) (4)
-

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **NA**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:
NA

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES (Pouch)**
(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
Is container label too small to contain all required information? **NO** If yes, does the container meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**

Is the following information properly displayed?

- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **YES**
- Warnings (if any) or cautionary statements (if any): **YES**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **See comment below**
- Controlled substance symbol: **YES**
- Usual Dosage statement: **NO**
- Product strength equivalency statement: **NA**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **See comment below**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

Are multiple strengths differentiated by use of different color or other acceptable means? **See comment below**
Are the labels of related products differentiated to avoid selection errors? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NO**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments:
The Medication Guide Pharmacist instructions appear only on the carton labeling. Since the carton contains 30 patches, which is unit-of-use packaging, the Medication Guide Pharmacist instructions appear more appropriate on the carton labeling and not the pouch label.

The pouch label has the following statement "Active ingredient release is limited; please see recommended dosing in patient instructions." However, we will request the applicant to add a usual dosage statement, similar to the carton labeling – "**Dosage and Administration:** See package insert." This information can appear on the back of the pouch label.

In 1.14.1.5. Labeling History submission, the applicant states that the bar code on their final printed pouch and carton will contain the drug's NDC number. In addition, the applicant states that the container labels will contain contrasting colors to differentiate the product strengths.

(b) (4)

Recommendations for the applicant:

- Similar to the carton labeling, we recommend adding a usual dosage statement "**Dosage and Administration:** See package insert.". This statement can appear on the back of the pouch.
- The proposed expressions of strength on the pouch label/carton labeling lack adequate differentiation and may lead to medication errors. We recommend using a method(s) (e.g., use of different color, bolding, highlighting and etc.) to help differentiate the expressions of strength. Ensure any colors selected to display the expression of strength are sufficiently differentiated between the pouch labels/carton labeling.
- Ensure to include a place holder for the lot number and the expiration date.

(b) (4)

The following recommendation is for the applicant: Space permitting, revise the established name to read "Methylphenidate Transdermal System".

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
NA

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
NA

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
NA

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **NA**

Reviewer Comments:
NA

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **YES** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**
If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Reviewer Comments:
Recommendations for the applicant:

- Ensure to include a place holder for the lot number and the expiration date.
- To help further differentiate your drug product strengths, we recommend increasing the middle digits of the NDC number by increasing their size in comparison to the remaining digits in the NDC number (similar to your pouch label). For example: xxxxx-XXXX-xx.
- We recommend relocating the pharmacist instructions for the Medication Guide to the principal display panel (PDP). In order to accommodate this information on the PDP, the "**Dosage and Administration:** See package insert." statement can appear on the back panel.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? **NA**
Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**

Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the established name for this ANDA acceptable? **NA**
Is title case used in expressing the established name? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **NA**
Is the following information properly displayed?
- Pharmacological category: **NA**
- Net quantity statement: **NA**
- Route(s) of administration (other than oral): **NA**
- Warnings (if any) or cautionary statements (if any): **NA**
- NDC: **NA**
- Bar code per 21 CFR 201.25(c)(2): **NA**

Is the Manufacturer/Distributor/Packager statement acceptable? **NA**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected in the labeling? **NA**
Is the storage statement acceptable? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**

Reviewer Comments:
NA

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
NA	NA

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **NA**
Are the inactive ingredients listed in alphabetical order? **NA**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:
NA

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	NA
ANDA (enter source of information of product description on the right hand column; e.g., chemistry Review & date, Module 3.2.P.5.1)	NA

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **NA**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **NA**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **NA**

Reviewer Comments:
NA

3.2.2 OTC: OTHER PATIENT LABELING

Are other patient labeling required? **NA**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was other patient labeling submitted? **NA**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:
NA

3.3 CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **NO**
Are the tamper evident requirements met for OTC and Controlled Substances? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **NO**

For ophthalmic products:
Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:
Is there text on the cap/ferrule overseal of this injectable product? **NA**

If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap and ferrule color? **NA**
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

(b) (4)

Recommendation for the applicant:

- Explain how the container closure system for your pouch label and carton labeling meet the tamper evident requirements of 21 CFR 1302.06.

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**
If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
NA	NA	NA

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **NA**
Are the stated contents in the table above acceptable? **NA**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **NA**
Are the labeling requirements met per 21 CFR 201.323? **NA**

Reviewer Comments:
NA

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (Cite source of information such as the chemistry review that follows the MOU, Product Specification in 3.2.P.5.1, Commercial Batch Record in 3.2.P.3.3. etc.)**
NA	NA	NA

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **See comment below**

Reviewer Comments:
We note that the inactive ingredient "polyisobutylene adhesive" is not listed in the FDA substance registration system – unique ingredient identifier, and therefore is not listed in the SPL: Data Elements.

Recommendation for the applicant:

- In the title, [redacted] (b) (4) to read "methylphenidate transdermal system".

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:
NA

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

Reviewer Comments:
NA

6. SPECIAL CONSIDERATIONS

NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (Pouch)	Draft	1s	12/13/13	Revise
Patch	Draft		12/13/13	Revise
Carton	Draft	1 X 30	12/13/13	Revise
(Other – specify) Dosing Chart	Draft		12/13/13	Satisfactory
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	October 2013	12/13/13	Revise
Medication Guide (including Instructions for Use)	Draft	October 2013	12/13/13	Revise
Patient Information	NA			
SPL Data Elements	NA	11/2013	12/13/13	Revise

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

CLINICAL REVIEWS

Clinical Review of Comparative (Threshold) Analyses for Drug-Device Combination Products

Division of Clinical Review (DCR)
Office of Safety and Clinical Evaluation (OSCE), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA	206497-Amendment 23
Drug Product/Strength(s)	Methylphenidate transdermal system 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3 mg/hr).
ANDA Applicant	Mylan Technologies Inc.
Product Name RLD/Reference Standard#/	Daytrana® (methylphenidate) transdermal film, extended release, 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3 mg/hr) Reference Standard is 30 mg/9 hours (3.3 mg/hr) NDA 021514, Approved on 04/06/2006
RLD/RS Sponsor	Noven Pharms Inc
Primary Reviewer	Sharon K. Ahluwalia, MD Physician, ANDA Team 1, DCR, OSCE
Secondary Reviewer	Carol Kim, Pharm.D. Team Leader, ANDA Team 1, DCR, OSCE
Tertiary Reviewer	Kimberly Witzmann, MD Deputy Director, OSCE
Submission Date	02/25/2021
Materials Reviewed	ANDA original submission: 12/13/2013 ANDA amendment-14: 11/9/2016 ANDA amendment-15: 07/27/2017 Division of Labeling Review (DLR) review dated 01/22/2018 ANDA amendment-23: 02/25/2021 (Comparative Threshold Analyses Report)
Date of Review	05/24/2021
GDUFA Goal Date	08/24/2021

DCR Comparative Analyses Conclusion	☐ No Design Differences ☒ Minor Design Differences ☒ Acceptable ☐ Not acceptable ☐ Other Design Differences
Deficiency Classification	☐ Major ☐ Minor **(See section 5 for Recommendation)** ☒ N/A (Review is Adequate) ☐ **Comments to the Applicant thru OPQ DRL** ☐ **Labeling Comments**

1 INTRODUCTION AND BACKGROUND

1.1 Summary of Drug Product Information Pertinent to Review

This review evaluates the delivery device constituent part of the combination product intended to administer the drug product and any associated product labeling and packaging. This review focuses on the analysis of the user interface[1] for the drug-device combination product (drug and a delivery device intended to administer a drug) comparing the proposed generic and the Reference Listed Drug (RLD).

Mylan Technologies Inc. (Applicant) submitted ANDA 206497 Amendment-23 for Methylphenidate Transdermal System 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3 mg/hr) on 02/25/2021. The reference listed drug (RLD), Daytrana® (methylphenidate) transdermal film, extended release 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3 mg/hr) was approved on 04/06/2006. The Orange Book[2] lists the 30 mg/9 hours (3.3 mg/hr) strength of the RLD as the Reference Standard (RS). The RLD and the proposed generic are delivered to the user via extended release film and therefore, the proposed generic is considered a complex drug-device combination product.

The original product label for the RLD, Daytrana® (methylphenidate) extended release transdermal film, was first approved on July 27, 2006.[3] The current label was approved on October 22, 2019 (SUPPL-30).[4] The RLD labeling includes Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU). The primary user group for Daytrana® (methylphenidate) extended release transdermal film is patients or their caregivers.

According to the most recent FDA approved label dated 10/22/2019,[5] Daytrana® (methylphenidate) transdermal film, extended release, 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3 mg/hr), is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in ages 6 to 17 years. The recommended starting dose for patients new to or converting from another formulation of methylphenidate is 10 mg. Daytrana should be applied to the hip area (using alternating sites) 2 hours before an effect is needed and should be removed 9 hours after application. Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. Dosage should be titrated to effect. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient. The RLD label has a boxed warning as follows:

[1] User interface refers to all components of the combination product with which a user interacts.
[2] https://www.accessdata fda.gov/scripts/cder/ob/search_product.cfm
[3] https://www.accessdata fda.gov/drugsatfda_docs/label/2006/021514s001lbl.pdf
[4] https://www.accessdata fda.gov/drugsatfda_docs/label/2019/021514s030lbl.pdf
[5] Daytrana®, NDA 021514, label. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021514s030lbl.pdf

WARNING: DRUG DEPENDENCE
See full prescribing information for complete boxed warning

Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior.

1.2 Other Relevant Information

As of 05/06/2021, there are no approved ANDAs for Daytrana® (methylphenidate) transdermal film, extended release, 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3 mg/hr), listed in the Orange Book.[6]

DARRTS[7] lists (b) (4) ANDA submissions:

ANDA Number	Applicant	Status Date	Status
(b) (4)			
206497*	Mylan Technologies, Inc.	02/25/2021	Pending
(b) (4)			

*Current application, under review

Of note ANDA 206497 was originally submitted on 12/13/2013, and it received a complete response (CR) on 07/27/2016. The application was resubmitted on 07/27/2017 and received a complete response on 02/26/2018. The current submission was received on 02/25/2021.

DCR has not completed any other comparative analyses on ANDAs referencing the RLD, Daytrana® (NDA 021514).

As of 05/06/2021, there have been seven controlled correspondences (CCs) submitted that reference the RLD, Daytrana® (NDA 021514), as below. There have been no CCs submitted by this firm. No pre-ANDA meetings have been submitted for this RLD. None of the prior CCs was related to the product's user interface.

GDRP[8] lists 11 CC submissions referencing NDA 021514. See Appendix for detail.

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW AND DISCUSSION

DCR conducted a comparative analysis of the user interface of the proposed generic combination product and its RLD Daytrana® (methylphenidate) transdermal film, extended release, 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3

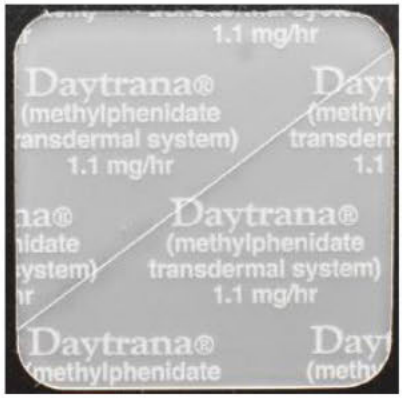
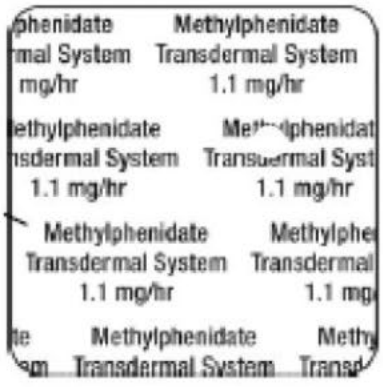
[6] Orange Book search on 03/31/2021: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm
[7] DARRTS, NDA 021514, accessed 05/06/2021.
[8] GDRP, NDA 012514, accessed 05/06/2021.

mg/hr), (NDA 021514). DCR also reviewed the comparative analyses report provided by the Applicant.[9]

2.1 Physical comparison of the product samples: RLD vs. Proposed

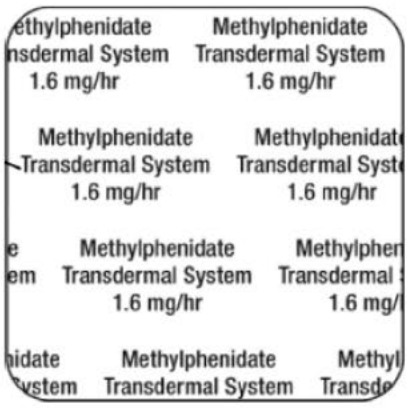
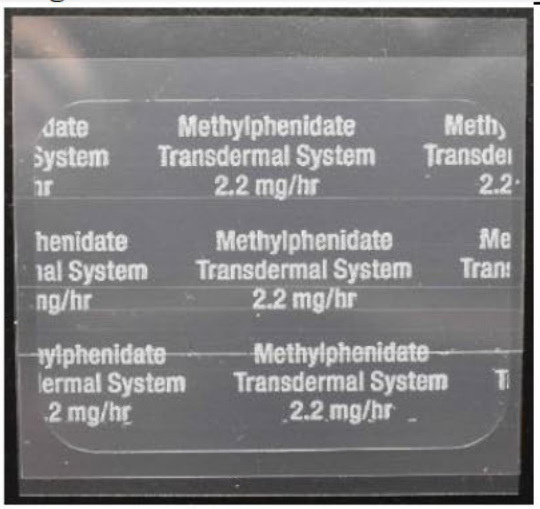
DCR was not able to perform an evaluation of the proposed product samples (proposed generic product and RLD) due to the current COVID-19 pandemic. Instead, DCR performed the physical comparison based on the information including pictures provided by the Applicant in their comparative threshold analyses report. Table 1 provides a physical comparison of the RLD and proposed generic product by the Applicant.

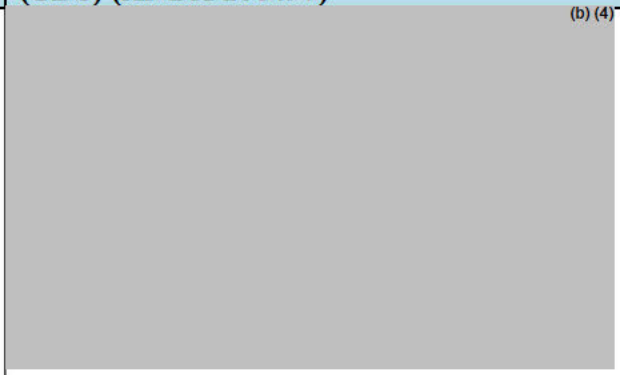
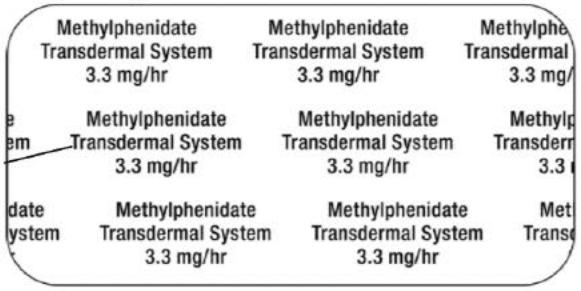
Table 1: Physical Comparison Between the RLD and Proposed Generic Product

RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (TDS) (ANDA 206497)
TDS with Protective Liner	
1.1 mg/hr	
	(b) (4) Proposed generic Methylphenidate TDS Artwork: 
1.6 mg/hr	

[9] Source: DocuBridge. ANDA 206497. Module 3.2.P.2 Comparative Analyses Report for Methylphenidate Transdermal System. Sequence 0021.

ANDA 206497
Methylphenidate Transdermal System 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3 mg/hr)

RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (TDS) (ANDA 206497)
	(b) (4) Proposed Generic's TDS Artwork: 
2.2 mg/hr	
	
3.3 mg/hr	

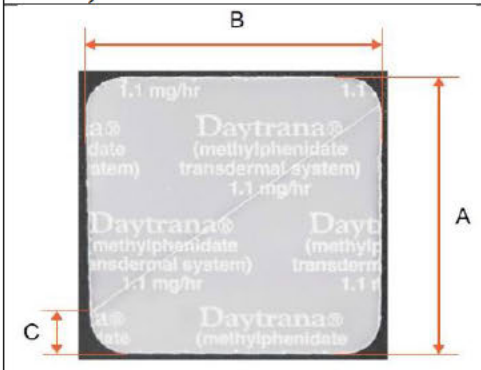
RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (TDS) (ANDA 206497)
	(b) (4)  Proposed generic's TDS Artwork: 
Additional Protective Film (representative of all strengths)	
N/A	(b) (4) 
Diagram of TDS Components	

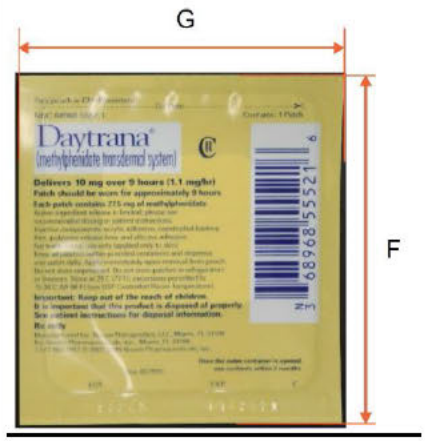
RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (TDS) (ANDA 206497)
N/A	(b) (4)

Dimensional Analysis

Annotated Illustration of the TDS Dimensions for 1.1 mg/hr Strength of the RLD (Left) and the Proposed Generic Methylphenidate TDS (right)
(According to the applicant, the strength 1.1 mg/hr TDS is representative of 1.1 mg/hr TDS and 1.6 mg/hr TDS; the strength 3.3 mg/hr TDS is representative of 2.2 mg/hr TDS and 3.3 mg/hr TDS.)

(b) (4)





Dimensional Comparison of 1.1 mg/hr RLD and 1.1 mg/hr Proposed Generic Methylphenidate TDS (Mean of five samples of each product)

RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (TDS) (ANDA 206497)

Dimension	RLD (n=5) (Mean) (mm)	Mylan's Methylphenidate TDS (n=5) (Mean) (mm)	Difference (mm)
A: TDS Height	(b) (4)		
B: TDS Width			
C: Distance of protective liner split line from bottom left of protective liner			
D: Protective liner Height			
E: Protective liner Width			
F: Protective pouch Height			
G: Protective pouch Width			

Dimensional Comparison of 3.3 mg/hr RLD and 3.3 mg/hr Proposed Generic Methylphenidate TDS (Mean of five samples of each product)

Dimension	RLD (n=5) (Mean) (mm)	Mylan's Methylphenidate TDS (n=5) (Mean) (mm)	Difference (mm)
A: TDS Height	(b) (4)		
B: TDS Width			
C: Distance of protective liner split line from bottom left of protective liner			
D: Protective liner Height			
E: Protective liner Width			
F: Protective pouch Height			
G: Protective pouch Width			

Photos and tables provided by applicant.

The proposed generic Methylphenidate TDS has a horizontal split line. The RLD has a diagonal split line. This difference in split line for removal of the (b) (4) *from the adhesive liner is an acceptable minor difference, as it is easy and intuitive to use.*

According to the adhesion study (#MPTP-12130) review dated 3/26/16, DCR concluded that the adhesion performance of the proposed generic product is at least as good as the RLD. (b) (4)

In conclusion, the physical comparison indicates that, ***from a user interface perspective, there are minor acceptable differences*** *between the RLD and the proposed generic Methylphenidate TDS with regard to the design of the protective film in the proposed generic, the placement of the split line,* (b) (4). *These minor acceptable differences should not impact the ability of patients to use the drug product.*

Table 2: Comparison of Carton for 1.1 mg/hr Strength Between the RLD and Proposed Generic Product

Carton Comparison	
1.1 mg/hr (The Applicant notes that the Carton depiction is representative of all four TDS strengths.)	
RLD Daytrana® (NDA 021514)	**Proposed Methylphenidate Transdermal System (ANDA 206497)**
(b) (4)	

Photos provided by applicant.

Reviewer Comments: *The applicant has provided images of the physical carton for one strength (1.1 mg/hr) of the RLD and has indicated that it is representative of the physical carton for all strengths of the RLD. The RLD carton is composed of an outer carton and a sealed inner carton, in which moisture permeable pouches are sealed along with a drying agent. The proposed generic Methylphenidate TDS's carton consists only of an outer carton, in which non-breathable pouches are directly placed. The applicant indicates that a drying agent is not required because the proposed generic is packaged in non-breathable pouches. As seen in the TDS and Protective Liner comparison above, the RLD pouch only contains the TDS while the proposed generic pouch contains the TDS along with a protective film. This is a minor difference in packaging that should not interfere with a patient's ability to use this product.*

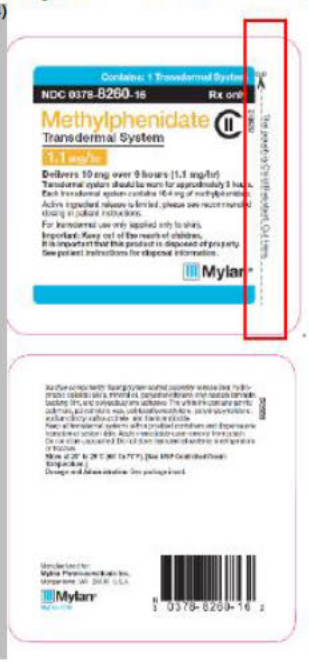
Therefore, from the user interface perspective, there is a ***minor acceptable difference*** *in the packaging of the RLD and the proposed generic Methylphenidate TDS.*

Table 3: Comparison of Protective Pouch Between the RLD and Proposed Generic Product

RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (ANDA 206497)
Protective Pouch (1.1 mg/hr) Front (top), Back (bottom)	

RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (ANDA 206497)
(b) (4)	Mylan's TDS (b) (4)

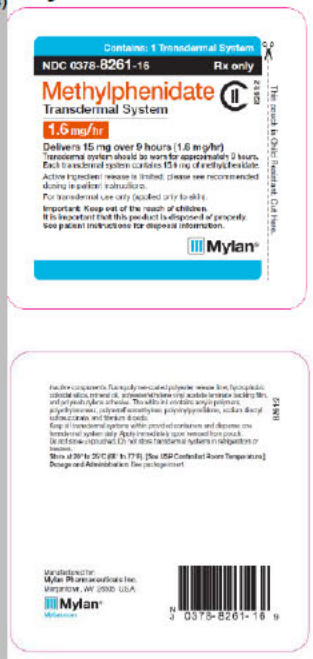
Mylan's TDS Artwork



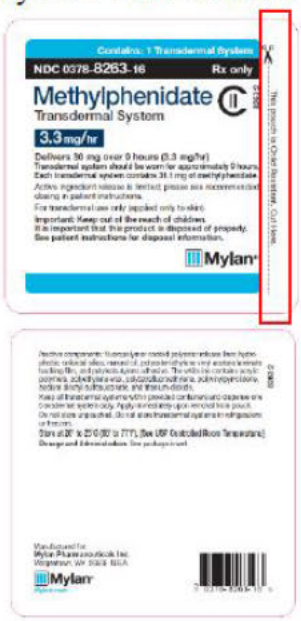
Protective Pouch (1.6 mg/hr)
Front (top), Back (bottom)

(b) (4)	Mylan's TDS (b) (4)

Mylan's TDS Artwork



RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (ANDA 206497)
Protective Pouch (2.2 mg/hr) Front (top), Back (bottom)	
(b) (4)	 
Protective Pouch (3.3 mg/hr) Front (top), Back (bottom)	

RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (ANDA 206497)	
(b) (4)	Mylan's TDS (b) (4)	Mylan's TDS Artwork 

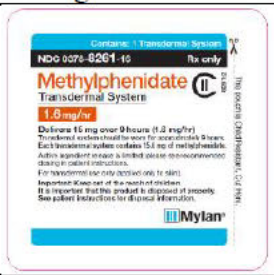
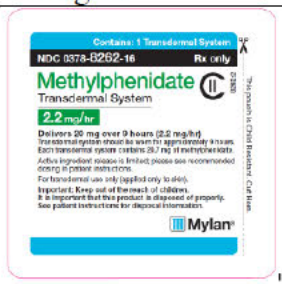
Photos provided by applicant.

Reviewer Comments: *The RLD is packaged in a pouch with transparent backing. The proposed generic Methylphenidate TDS is packaged in a non-permeable pouch that is not transparent. All required product information is printed on the front of the pouch for the RLD. For the proposed generic Methylphenidate TDS, some information, including the bar code, is printed on the back of the pouch. This minor difference in opacity of the back of the pouch is considered acceptable from a user interface perspective, as it does not affect use of the product.*

Both pouches contain visual instructions, a scissor icon and a sashed line with the text "This pouch is Child Resistant. Cut Here." For the RLD pouch, this is written across the top of the pouch. For the proposed generic Methylphenidate TDS pouch, this is printed lengthwise along the side of the pouch. From a user interface perspective, the change of the location of this warning and instruction is a minor acceptable difference, as it does not affect a patient's ability to use the product.

The difference in the transparency vs. opacity of the back of the protective pouch and the differences in where information is printed on the pouches are both considered ***minor acceptable differences*** *from the user interface perspective, as use of the product remains intuitive for patients.*

Table 4: Comparison of Visual Color of the Protective Pouch for Multiple Strengths Between the RLD and the Proposed Generic

RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (ANDA 206497)
Visual Color of Pouches	
1.1 mg/hr (b) (4)	1.1 mg/hr 
1.6 mg/hr (b) (4)	1.6 mg/hr 
2.2 mg/hr (b) (4)	2.2 mg/hr 
3.3 mg/hr (b) (4)	3.3 mg/hr 

Photos provided by applicant.

Reviewer Comments: *The visual color of the pouches for the RLD is different for each strength. For the RLD, the entire pouch for each strength is the designated color for that strength, with printed information in white boxes or in white text. For the proposed generic Methylphenidate TDS, the strengths are differentiated by the color of the text for "Methylphenidate" on the pouch, and by the color of the box surrounding the printed strength on the pouch. The colors correspond to the colors used by the RLD (i.e. 1.1 mg/hr in yellow, 1.6 mg/hr in orange, 2.2 mg/hr in green, and 3.3 mg/hr in blue). The strengths are easily distinguished. Similar to the RLD, the proposed product's strengths are also color coded and are easily distinguished.*

Thus, from the user interface perspective, the difference in visual color of the pouches between the RLD and the proposed generic is an acceptable minor difference that should not impact a user's ability to correctly use the drug product.

Overall, the physical analysis comparison provided by the applicant supports that the ***proposed generic product can be substituted for the RLD without additional training*** *by the healthcare provider prior to use of the proposed generic product.*

2.2 Applicant's Comparative Task Analysis

Table 5: Comparative Task Analysis provided by Applicant.

User Task	Task Sequence of RLD	Task Sequence of Mylan's Methylphenidate TDS	Critical Task	Threshold Analysis Outcome
Open Carton	Open carton	(b) (4)	Yes	No Design Difference
Prepare Site	Ensure skin on hip is clean (freshly washed), dry, and cool. Ensure skin doesn't have any powder, oil or lotion, cuts or irritation.		Yes	No Design Difference
User Task	Task Sequence of RLD	Task Sequence of Mylan's Methylphenidate TDS	Critical Task	Threshold Analysis Outcome
Access the TDS	Open the sealed tray or outer pouch and throw away drying agent.	(b) (4)	Yes	Minor design difference
	Carefully cut the protective pouch open with scissors, being careful not to cut the transdermal system.		Yes	No Design Difference
Remove TDS	Remove the transdermal system from the protective pouch.		Yes	No Design Difference

User Task	Task Sequence of RLD	Task Sequence of Mylan's Methylphenidate TDS	Critical Task	Threshold Analysis Outcome
Prepare TDS	N/A	(b) (4)	Yes	Minor design difference
	Look at the transdermal system to make sure it is not damaged.		Yes	No Design Difference
	Hold the transdermal system with the hard-protective liner facing the user.		Yes	No Design Difference
	Gently fold the transdermal system in half along the faint line and remove one half of the liner.		Yes	No Design Difference
	Avoid touching sticky side of the transdermal system. If the transdermal system is touched accidentally, wash hands immediately.		Yes	No Design Difference

User Task	Task Sequence of RLD	Task Sequence of Mylan's Methylphenidate TDS	Critical Task	Threshold Analysis Outcome
Apply TDS	Using second side of the protective liner as a handle, apply the sticky side of the transdermal system to the skin.	(b) (4)	Yes	No Design Difference
	Press the sticky side of the transdermal system firmly into place and smooth it down.		Yes	No Design Difference
	While holding the sticky side down, gently fold back the other side of the transdermal system.		Yes	No Design Difference
	Hold an edge of the remaining protective liner and slowly peel it off.		Yes	No Design Difference
	After the protective liner is removed, check that there is no adhesive sticking to the liner.		Yes	No Design Difference

Methylphenidate Transdermal System 10 mg/9 hours (1.1 mg/hr), 15 mg/9 hours (1.6 mg/hr), 20 mg/9 hours (2.2 mg/hr), and 30 mg/9 hours (3.3 mg/hr)

User Task	Task Sequence of RLD	Task Sequence of Mylan's Methylphenidate TDS	Critical Task	Threshold Analysis Outcome
	Press the entire transdermal system firmly into place with the palm of the hand over the transdermal system for 30 seconds.	(b) (4)	Yes	No Design Difference
Check TDS is attached firmly to the skin	Check that TDS is firmly attached to the skin.		Yes	No Design Difference
	Gently rub the edges of the TDS to make sure the TDS is stuck to the skin.		Yes	No Design Difference
Wash hands	Wash hands		Yes	No Design Difference
Write time of application	Write time the TDS was applied on the dosing chart.		Yes	No Design Difference
TDS Removal	To remove, peel off the transdermal system slowly.		Yes	No Design Difference

User Task	Task Sequence of RLD	Task Sequence of Mylan's Methylphenidate TDS	Critical Task	Threshold Analysis Outcome
Fold TDS	Fold the transdermal system in half and press it together firmly so that the sticky side sticks to itself.	(b) (4)	Yes	No Design Difference
Dispose of TDS	Flush transdermal system down the toilet or put in a container with a lid on it, out of the reach of children.		Yes	No Design Difference
Wash hands	Wash hands		Yes	No Design Difference
Write time of removal	Write time of removal on the dosing chart.		Yes	No Design Difference

Table provided by applicant.

Reviewer Comments: *There are two minor task differences identified by the applicant in the comparative task analysis: 1) Accessing the TDS from the carton box and 2) Discarding additional piece of protective film after removing the TDS from the protective pouch. Both of these steps involve accessing the TDS, and the differences arise from the differences in the packaging of the TDS. The RLD patches are packaged in protective pouches and a sealed tray with drying agent that is then packaged inside the cardboard carton. The proposed generic Methylphenidate TDS is packaged in a non-breathable protective pouch directly inside the cardboard box.*

- *For the RLD, the user sees the tray and opens it. The user understands that he/she must take the protective pouch out of the carton. The user also sees the drying agent and must discard it. The user then takes one pouch and opens it to reveal the transdermal patch.*
- *For the proposed generic Methylphenidate TDS, the user sees the pouch in the cardboard carton and understands to remove one pouch from the carton. The user then opens the pouch, removes the additional piece of protective clear film and sees the transdermal patch.*

Thus, the step of opening the tray and discarding the drying agent for the RLD is replaced by the step of opening the pouch and discarding the additional clear protective film in the proposed generic Methylphenidate TDS which does not interfere with peeling and application of the patch. Thus, this is not considered as an added critical step required to use the generic drug product. .

This is a minor acceptable difference. From a user interface perspective, this should not prevent correct use of the product because use remains intuitive.

*Overall, **the task comparison supports that the proposed generic product can be substituted for the RLD without the intervention of a health care provider and without additional training** prior to use of the proposed generic product.*

2.3 Labeling comparison of the delivery device constituent part: RLD vs. Proposed

The original product label for the RLD, Daytrana® (methylphenidate) extended release transdermal film, was first approved on July 27, 2006.[10] The current label was approved on October 22, 2019 (SUPPL-30).[11] The RLD labeling includes Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU).

Side-by-side, line-by-line labeling comparison of the Instructions for Use (IFU) was conducted between the RLD and the proposed generic product. Except for the delivery device constituent part labeling, the review of the remainder of the label is deferred to the Division of Labeling Review (DLR). Table 6 shows results of the comparison of delivery device constituent part of labeling between the proposed generic and the RLD.

Table 6: **Labeling Comparison of the Delivery Device Constituent Part: RLD vs. Proposed**

Delivery device constituent part labeling: RLD vs. Proposed	**Yes/No/NA**
(1) Any difference in the **description/design**?	Yes, minor*
(2) Any difference in the **administration or directions for use**?	Yes, minor*
(3) Any difference in the **illustration(s)/figure(s)**?	Yes, minor*
(4) Any differences in the end-user **IFU**?	Yes, minor*
(5) Other	N/A

* minor differences in physical features of drug-device and in picture illustrations between the proposed generic product and the RLD are observed. See detail in the side-by-side labeling comparison in original ANDA submitted on 02/25/2021.

The following tables present side-by-side comparison of the labeling differences. The differences are highlighted in yellow.

Table 7: Labeling Comparison of the Instructions for Use: RLD vs. Proposed

[10] https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021514s001lbl.pdf
[11] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021514s030lbl.pdf

RLD Daytrana® (NDA 021514) IFU Section ---	Proposed Methylphenidate Transdermal System (ANDA 206497) IFU Section ---
Instructions for Use **Daytrana® (day-TRON-ah)** **(methylphenidate transdermal system) CII**	(b) (4)

1. Daytrana Dosing Chart

Each carton of Daytrana contains a Daytrana Dosing Chart to help you keep track of your patch includin
- when you apply patch to the skin on your hip each morning
- when you remove the patch
- how and where you threw the Daytrana patch away

To use the Daytrana Dosing Chart, follow these instructions:
- Each day, when a new Daytrana patch is applied to your hip, write down the date and time that you a the patch.
- Use the Daytrana schedule below so you can decide when to remove the patch. For example, if the p applied to the skin at 6:00 a.m., remove the patch at 3:00 p.m. on the same day. After you remove an away the patch, write down the time you removed the patch and how and where you threw it away.
- If the patch you placed on your child is missing, ask your child:
  - when the patch came off
  - how the patch came off
  - where the patch is

Daytrana Schedule for 9 Hour Dosing

If you put the patch on at:	On the same day, remove the patch at:
5:00 a.m.	2:00 p.m.
6:00 a.m.	3:00 p.m.
7:00 a.m.	4:00 p.m.
8:00 a.m.	5:00 p.m.
9:00 a.m.	6:00 p.m.
10:00 a.m.	7:00 p.m.
11:00 a.m.	8:00 p.m.
12:00 p.m.	9:00 p.m.

2. Where to apply Daytrana

- Apply patch to your hip area. Do not put the patch near your waist. Clothing and movement may patch rub off (See Figure A).
- Use your other hip when you apply a new patch the next morning. Make sure there is no redness, bumps or itching at the site where the patch is going to be applied.

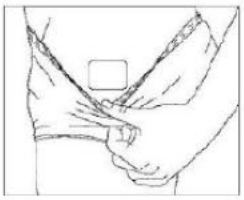
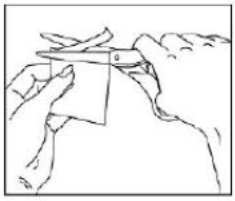
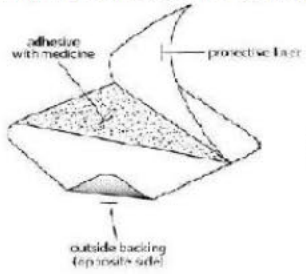
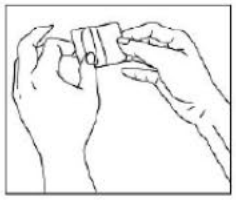
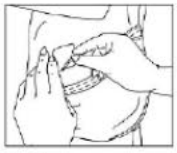
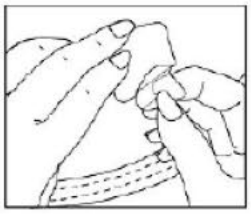
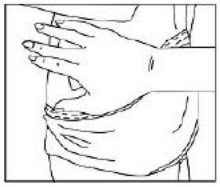


Figure A

3. Before you apply Daytrana

Make sure your skin:
- Is clean (freshly washed), dry, and cool
- Does not have any powder, oil, or lotion
- Does not have any cuts and irritation (rashes, inflammation, redness, or other skin

RLD Daytrana® (NDA 021514) IFU Section ---	Proposed Methylphenidate Transdermal System (ANDA 206497) IFU Section ---
4. How to apply Daytrana • Open the sealed tray or outer pouch and throw away the small packet (drying agent). • Each patch is sealed in its own protective pouch. • Carefully cut the protective pouch open with scissors, being careful not to cut the patch. **Do not use that have been cut or damaged in any way (See Figure B).**	(b) (4)
 Figure B • Remove the patch from the protective pouch. • Look at the patch to make sure it is not damaged. The patch should separate easily from the protecti Throw away the patch if the protective liner is hard to remove.	
The Daytrana patch has 3 layers. The 3 layers are pictured below. The pictures show both sides of th  Figure C  Figure D Layers: • **Protective liner:** The protective liner is the layer that you remove before you put the patch on (See C) • **Adhesive with medicine:** The adhesive with medicine is the layer that sticks to your skin (See Figu • **Outside backing:** The outside backing is the layer that you see after you put the patch on your skin word "Daytrana" is printed on this layer (See Figure D).	
• **Apply the patch right away after you remove the patch from protective pouch.** • Hold the patch with the hard protective liner facing you. The word Daytrana will appear backwards • Gently bend the patch along the faint line and slowly peel half the liner, which covers the sticky su the patch (See Figure E).  Figure E	
• Avoid touching the sticky side of the patch with your fingers. • If you accidentally touch the sticky side of the patch, apply the patch, then wash your hands right awa that the medicine does not go into the skin on your hands. • Using the other half of the protective liner as a handle, apply the sticky side of the patch to the selecte of the child's hip (See Figure F).  Figure F	

RLD Daytrana® (NDA 021514) IFU Section ---	Proposed Methylphenidate Transdermal System (ANDA 206497) IFU Section ---
• Press the sticky side of the patch firmly into place and smooth it down. • While you are still holding the sticky side down, gently fold back the other half of the patch. • Hold an edge of the remaining protective liner and slowly peel it off (See Figure G).  Figure G	(b) (4)
• After the protective liner is removed, there should not be any adhesive (glue) sticking to the liner.  Figure H • Press the entire patch firmly into place with the palm of your hand over the patch for about 30 seconds (See Figure H). • Make sure that the patch firmly sticks to your skin. • Gently rub the edges of the patch with your fingers to make sure the patch sticks to your skin. • Wash your hands after you apply your patch. • Write the time you applied your patch on the dosing chart on the carton. Use the dosing schedule so you know what time you should remove your patch.	

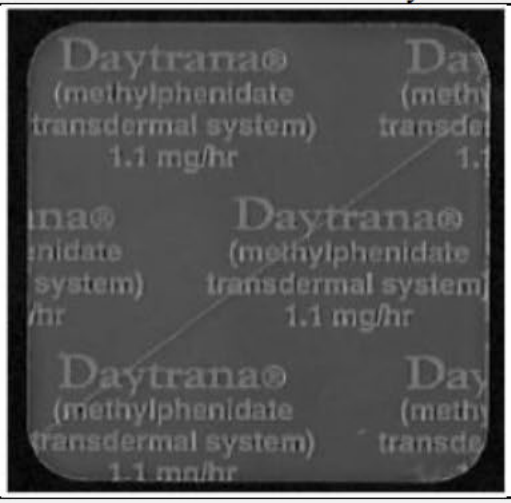
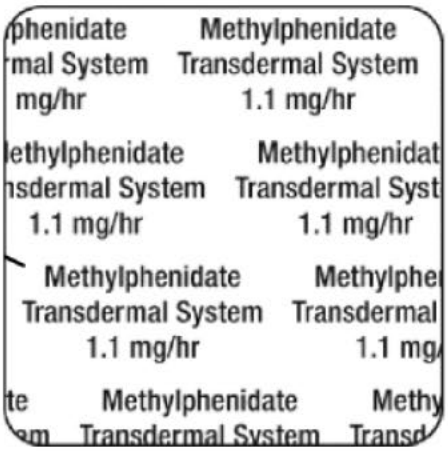
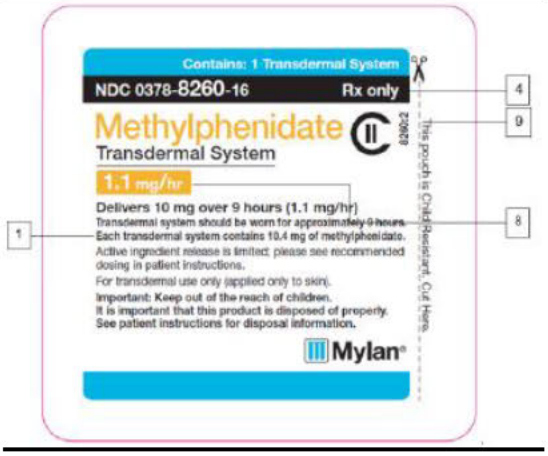
RLD Daytrana® (NDA 021514) IFU Section ---	Proposed Methylphenidate Transdermal System (ANDA 206497) IFU Section ---

5. How to remove and throw away Daytrana
• When you remove the patch, peel it off slowly. If the patch is too sticky on your skin and you need something to help you remove it:
  ○ Gently apply an oil-based product (petroleum jelly, olive oil, or mineral oil) to the patch edges. Gently spread the oil underneath the patch edges.
  ○ Apply an oil-based product or lotion to your skin if any adhesive (glue) remains after you remove your patch. This will gently loosen and remove any adhesive that is left over.
  ○ If you still can not easily remove the patch, ask your doctor or pharmacist about what to do for this problem.
• Fold the used Daytrana patch in half and press it together firmly so that the sticky side sticks to itself. Flush **the used patch down the toilet or put the patch in a container with a lid right away.**
• Do not flush the protective pouches or the protective liners down the toilet. These items should be thrown away in a container with a lid.
• Wash your hands after you handle the patch.
• After you remove the patch and throw the patch away, write down the time on the dosing chart.
• Safely throw away any unused Daytrana patches that are left over from the prescription as soon as they are no longer needed.
To safely throw away the patches:
  • Remove the leftover patches from their protective pouches and remove the protective liners.
  • Either fold the patches in half with the sticky sides together, and flush the patches down the toilet, or
  • Throw the patches away in a container with a lid.
 	
Manufactured for: Noven Therapeutics, LLC, Miami, FL 33186.
 	
By: Noven Pharmaceuticals, Inc., Miami, FL 33186.
© 2009, 2013, 2015, 2016 Noven Pharmaceuticals, Inc.
This Medication Guide has been approved by the U.S. Food and Drug Administration.
 	
Revised 10/2019
 	
102086-18
	(b) (4)

Source: Applicant Submission.

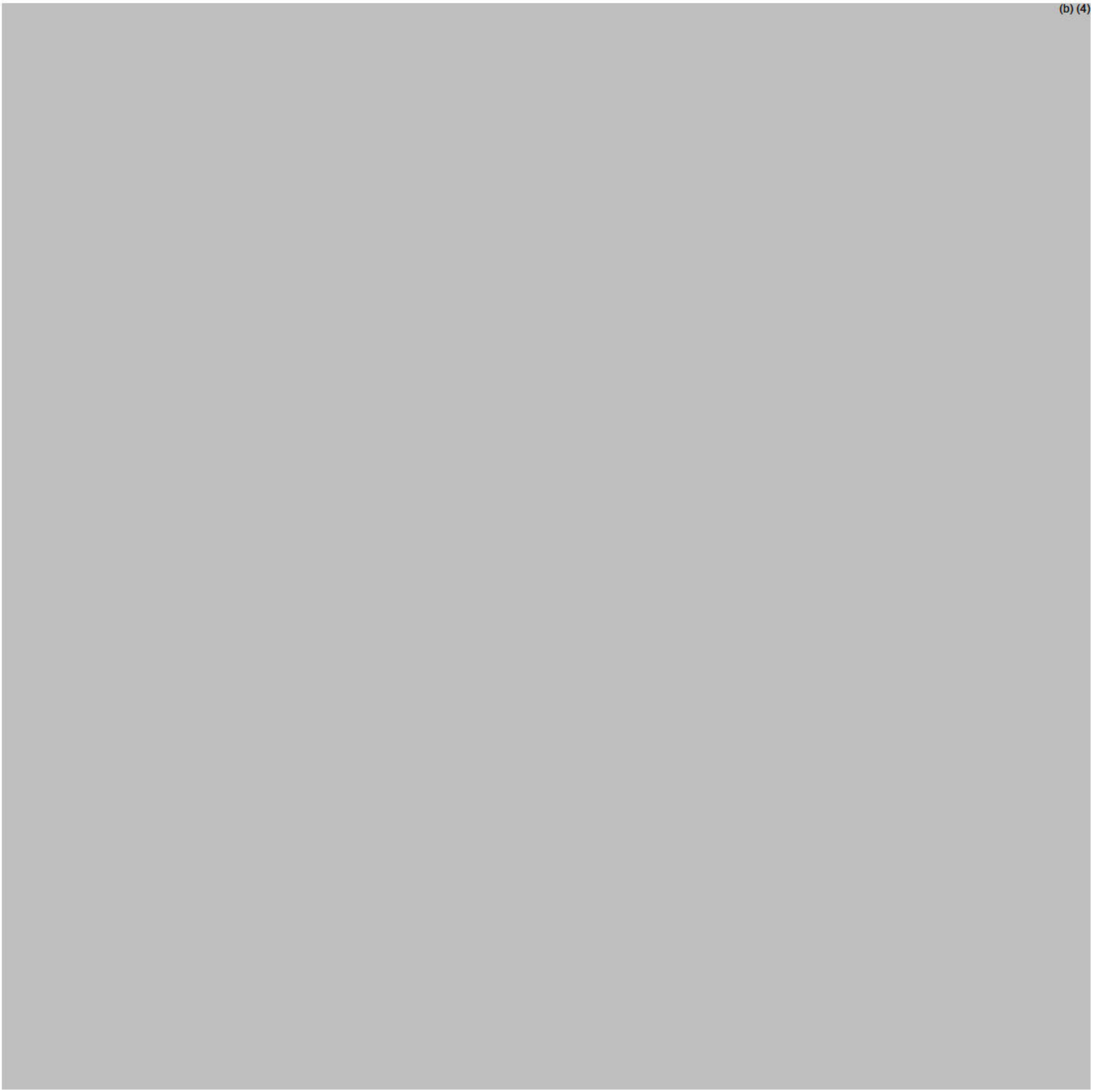
Reviewer Comments: *The proposed IFU accurately reflects the use of the proposed product based on acceptable minor design differences between products.*

Table 8: Comparison of Transdermal System Label and Pouch Label Between the RLD and Proposed Generic Product

RLD Daytrana® (NDA 021514)	**Proposed Methylphenidate Transdermal System (ANDA 206497)**
RLD Transdermal System Label	Proposed Methylphenidate Transdermal System Label
	
RLD Pouch Label Comparison (One Strength is displayed for both the RLD and for the proposed generic. All strengths of the RLD and of the proposed generic contain the same type of information in the same location for all strengths.)	
RLD Pouch Label—Front and Back	Proposed Methylphenidate Transdermal System Pouch Label—Front and Back
 Back of pouch is void of text.	

RLD Daytrana® (NDA 021514)	Proposed Methylphenidate Transdermal System (ANDA 206497)
	(b) (4)
Carton Labels 1.1 mg/hr	
1.1 mg/hr	
	(b) (4)
1.6 mg/hr	

(b) (4)



Reviewer Comments: *From a clinical perspective, the minor design differences in the protective pouch label and the carton label between the RLD and proposed generic product are acceptable. Both carton labels contain similar information including the drug name, strength, control number, Rx only, expiration date, lot number, company name, medication administration record*

table, and storage information. Final acceptability of the labeling is deferred to the Division of Labeling.

*Overall, the labeling comparison supports that the **proposed generic product can be substituted for the RLD without the intervention of a health care provider and without additional training** prior to use of the proposed generic product.*

3 APPLICANT'S THRESHOLD ANALYSES

On 02/25/2021, the applicant submitted a comparative threshold analysis report. The Applicant concluded the identified minor differences between the user interfaces of the generic combination product in comparison to the RLD are not expected to affect substitutability of the products.

Reviewer's Comment: *DCR concludes that there are acceptable minor design differences based on the physical comparison, comparative task analysis, and labeling comparison of the delivery device constituent part between the proposed generic combination product and the RLD. DCR also concludes that the generic product can be substituted for the RLD without the intervention of a health care provider and without additional training prior to use of the generic product. Thus, additional information and data are not necessary to evaluate the identified differences in the user interface.*

4 CONCLUSION

From a clinical safety perspective, there are acceptable minor design differences between the RLD and proposed drug delivery device. Therefore, DCR concludes this generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product.

5 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative (threshold) analyses and has n**o comments at this time.**

Appendix

List of Controlled Correspondences referencing NDA 021514 is shown below.

CC #	Firm	Discipline Category	Status	Completion Date
487905	(b) (4)	Batches, BE		(b) (4)
878509		Batches, BE		
7924678		Inactive ingredients		
7925726		BE study design		
7929128		Unavailability of RLD strength		
9236663		BE study design		
18160447		BE, route of submission		

Kimberly Witzmann

Digitally signed by Kimberly Witzmann
Date: 5/28/2021 03:18:54PM
GUID: 508da6ee0002782694c8988b30c071f3

Sharon Ahluwalia

Digitally signed by Sharon Ahluwalia
Date: 6/01/2021 09:42:48AM
GUID: 5da8a6f80068a79e2dd3cd43ee84756a

Carol Kim

Digitally signed by Carol Kim
Date: 6/01/2021 11:08:48AM
GUID: 508da70a00028df5288765ab0807f9a5

Review of Complete Response Amendment-15
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

ANDA number	206497
Drug Product	Methylphenidate Transdermal System
Strength(s)	10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
Applicant Name	Mylan Technologies, Inc.
Treatment Indication	treatment of Attention Deficit Hyperactivity Disorder
Reference Listed Drug (RLDs)	Daytrana® Transdermal System, 1.1 mg, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr
NDA number for RLD	NDA 021514
RLD Applicant Name	Noven Pharmaceuticals, Inc.
Original Submission Date	12/13/2013
Date of Completion	2/7/2018
GDUFA Goal Date	02/27/2018
Primary Reviewer	Sunny Tse, PhD
Secondary Reviewer	Ying Fan, PhD, Team Leader, ANDA Team
Tertiary Reviewer	Sarah Yim, MD, Division Director
Materials Reviewed	**07/27/2017 (eCTD Sequence 0014):** complete response amendment Office of Biostatistics Review: Wanjie Sun, PhD completed on 1/29/2018
DCR Conclusion	Irritation/sensitization/adhesion study # MPTP-12130 data are adequate to support approval of Mylan Technologies, Inc.'s Methylphenidate Transdermal System.
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)
Justification of Major Designation	N/A

1 INTRODUCTION

On 07/27/2017, the applicant submitted a complete response amendment addressing the clinical bioequivalence deficiency regarding irritation/sensitization/adhesion study MPTP-12130 in the Complete Response (CR) Letter dated 07/26/2016. In this post CR Amendment-15 response, the applicant provided justifications that their sensitization data for study MPTP-12130 were adequate.

2 BACKGROUND / REGULATORY HISTORY

According to the original Division of Clinical Review (DCR) review dated 03/28/2016, the applicant's sensitization data from irritation/sensitization/adhesion study MPTP-12130 were inadequate to support approval of ANDA 206497. The following clinical deficiencies were issued to the applicant in a Complete Response (CR) Letter dated 07/26/2016:

"The sensitization data in Study MPTP 12130 is not adequate to ensure that the sensitization potential of the proposed generic methylphenidate transdermal system (Test) is no worse than that of the reference listed drug product (RLD) as follows:

We do not agree with your numbers of subjects sensitized or potentially sensitized to each product. When we applied the four criteria described in the FDA product-specific bioequivalence guidance to your data,1 of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the RLD, respectively, with 100% more test sites than reference sites showing potential sensitization.

We note that you interpreted the term generally higher in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we reevaluated your data using your interpretation. Using your interpretation of generally higher, 33 test versus 27 RLD skin sites showed potential sensitization. The proportions are 50% for test versus 40.9% for RLD, with 22% more test sites than RLD sites showing sensitization.

The point estimate for the proportion of skin sites showing potential sensitization was higher for the test product compared with the RLD regardless of which interpretation of generally higher we used.

We note that there are several formulation differences between your product and the RLD, which makes a difference in potential sensitization biologically plausible.

To address these deficiencies, we recommend one of the following.

1. Provide adequate justification and evidence that potential sensitization of your proposed methylphenidate transdermal system is no worse than that of the reference listed drug.

2. Conduct new sensitization study with the to-be-marketed product. Please refer to the Product-Specific Recommendation for Methylphenidate Film, Extended

Release/Transdermal recommended in July 2010 on FDA's guidance page: http://www.fda.gov/ucm/groups/fdagov-public/@fdagovdrugsgen/documents/document/ucm220196.pdf"

In response to the CR, on 08/10/2016, the applicant submitted a meeting request. This meeting request included the following three questions: "

1. Mylan notes from FDA COMMENT 1 that the Agency "…applied the four criteria described in the FDA product-specific bioequivalence guidance to your data, of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the RLD, respectively…" Would the Agency please clarify the exact method employed to identify the reported 18 and 9 potential sensitization results?

2. As noted in FDA COMMENT 2, the Agency states, "We note that you interpreted the term generally higher in one of the four sensitization criteria differently from FDA." Would the Agency please clarify the method employed to identify the 33 versus 27 potential sensitization results?

3. Please clarify how the investigator opinion should be considered for the determination of a potential sensitization reaction. Has the use of the independent investigator's clinical judgement in the determination of potential subject sensitization been replaced with the four criteria described in the FDA product-specific bioequivalence guidance? If so, we will need to understand the specific details for using a numerical algorithm in place of a clinical interpretation of sensitization."

On 09/09/2016, the Agency responded to the applicant's three 08/10/2016 meeting request questions.

"FDA Response 1

The Agency responded to the applicant's first question by referring to the four criteria given in the product specific guidance for sensitization.

a. *The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.*
b. *The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.*
c. *The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.*
d. *If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.*

The scores obtained during the Challenge Phase were considered to be "generally higher" than the Induction Phase if the maximum score in the Challenge and Re-Challenge (if applicable) Phase was higher than the maximum score in the Induction Phase.

FDA Response 2

The Agency responded to the applicant's second question by reevaluating the data using the four criteria for sensitization given in the product specific guidance. For the reevaluation of the data, the FDA statistician followed the applicant's interpretation and considered the scores obtained during the Challenge Phase to be "generally higher" than the Induction Phase if the mean score in the Challenge and Re-Challenge Phase (if applicable) was higher than the mean score in the Induction Phase. The applicant was asked to provide their justification of their interpretation of the term "generally higher" in criterion c and also provide the methods used to identify 36 (TEST) versus 32 (RLD) potential sensitization results.

FDA Response 3

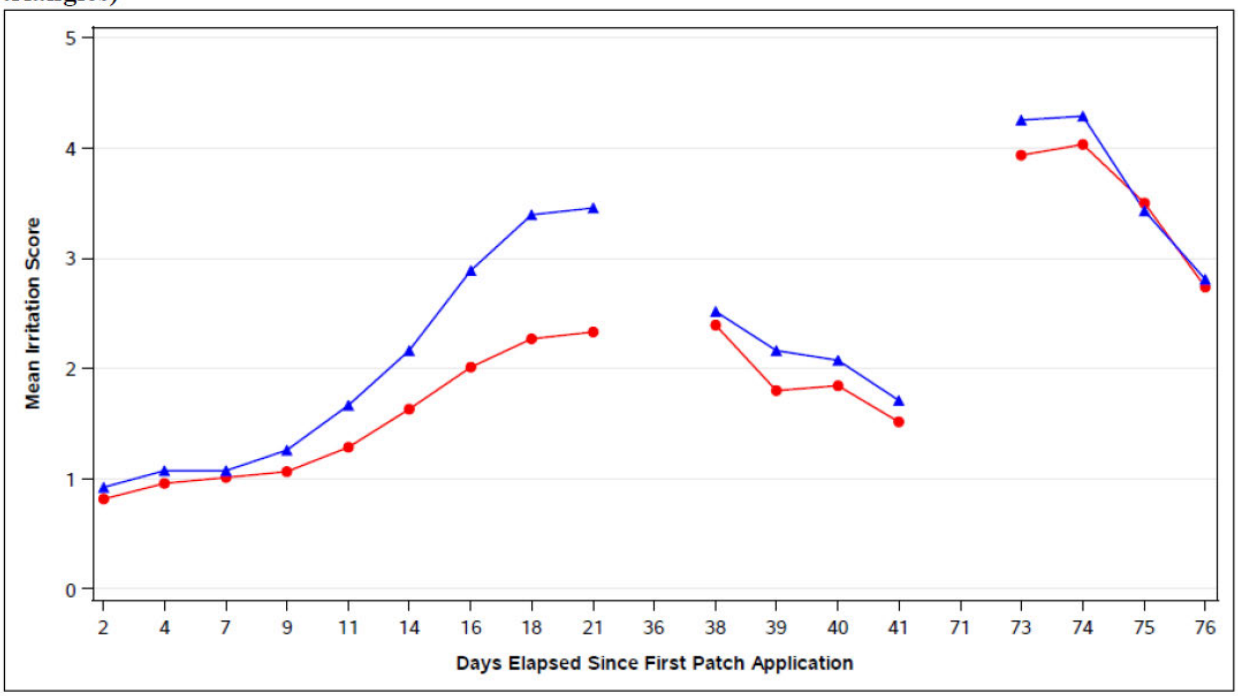
The Agency responded to the applicant's third question by reiterating the four criteria for sensitization given in the product specific guidance. The investigator's opinion was considered as a factor when adequately supported by a sound scientific rationale. Absent adequate scientific justification of the investigator's opinion in determining sensitization, the Agency puts more weight on the four criteria stated in the product specific guidance for Methylphenidate. If the applicant thought that the Agency should put more weight on the opinion of the investigator to determine sensitization, the they should provide justification when submitting an amendment to this ANDA."

3 REVIEW OF CURRENT AMENDMENT

On 07/27/2017, the applicant submitted the amendment providing justifications on why their study demonstrated noninferiority of their test product's sensitization compared with the reference product. This review focused on these justifications.
The applicant's justifications in this amendment are summarized as follows:

1. The applicant cited several literature references indicating that it can take 7-10 days to develop sensitization and asserted that 7 days should be a boundary for induction phase irritation response assessment. The applicant also provided a figure (Figure 1) from the data in Study MPTP-12130 indicating that the irritation profiles are relatively flat and comparable before day 7, whereas after day 7, a deviation in profiles was seen, such that by Day 21 the RLD has a higher mean irritation level than the test product. Therefore, the applicant recommends referencing the leading irritation scores from either test article up to day 7.

Figure 1 - Mean cumulative irritation scores over the induction, challenge and re-challenge phases of Study MPTP-12130, for Mylan product (red filed circles) and the RLD (blue triangles)



Note: Population includes all subjects who finished either the 48 or 72-hour evaluation in the Challenge Phase. Induction Phase (n = 66; Day 2-21), Challenge Phase (n = 66; Days 38-41), Re-Challenge Phase (n = 31; Days 73-76).

Source: 07/27/2017 CR amendment cover letter page 45

Reviewer's comments:

Regarding the optimal duration of the induction phase, the applicant's perspective is to limit the time of observation to minimize noise and ensure accurate identification of sensitization reactions. While this has its place, FDA's perspective is based in being comprehensive and better capturing the extent of irritation and sensitization between the Test and Reference products for the comparison, i.e., if the data are captured, then we can evaluate the data, and then make a decision about whether sensitization is occurring during the induction phase. If only 7 days of data are captured, there may be less noise, but there may also be underestimation of irritation. At this time, we are not prepared to make a wholesale change in the practice of using 21 days as an induction phase for irritation/sensitization studies. However, we acknowledge that in the case of Mylan's study data, the higher scores occurring later in the induction phase may have represented sensitization events that occurred more for the RLD, and that because the RLD has this pattern, it may have artifactually led to fewer qualified sensitization events (i.e., "generally higher") for the RLD in the challenge phase.

2. In a post-hoc analysis, the applicant demonstrated that the test product shows less irritation than the RLD product in the induction phase. For the challenge and re-challenge phase, the test product also has lower mean cumulative irritation scores than the RLD. The applicant

evaluated the data by interpreting the sensitization 'criterion c'[1] on the basis of comparing maximum irritation scores from the Challenge and Re-Challenge Phases to the maximum irritation score observed during Induction, up to Day 7.

Comparing the differences in maximum scores observed at the Challenge and Re-Challenge phases versus the maximum score in the initial 7 days of induction, the applicant claims non-inferiority of the test product to the RLD with respect to sensitization.

Table 1 - Evaluation of Sensitization based on difference in maximum scores observed at Challenge and Re-Challenge versus the maximum score in the initial 7 days of Induction

	Test – Mylan		RLD	
Difference in Maximum Scores	**Challenge and Re-Challenge (N=31)**	**Challenge Only (N=35)**	**Challenge and Re-Challenge (N=31)**	**Challenge Only (N=35)**
≥1	27	8	26	8
≥2	18	6	21	6
≥3	17	5	17	5
≥4	4	2	6	2

Source: 07/27/2017 CR amendment cover letter page 46

Reviewer's comments:

In the current product specific guidance for this drug product, the sensitization determination is as follows:

"Consider a subject to be potentially sensitized if all of the following criteria are met:

a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
b. The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.
d. If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.

Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization. Provide the total number of subjects considered sensitized to the test product and RLD."

[1] The sensitization criterion c referred to by the applicant is listed in the product specific guidance as follows: The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.

As suggested by Figure 1 above, criterion c does appear to allow for the circumstance that occurred in this case, where the RLD appears to have higher (i.e. worse) irritation scores in the induction phase, which then helps the RLD have a lower likelihood of meeting criteria c in the challenge phase evaluations. This would put any product with an improved irritation performance during the induction phase at a disadvantage, which is counterintuitive. However, the applicant's post-hoc analysis is based on a 7-day cut off, which is selected after knowing the study results and may also be biased.

Instead, FDA statistical reviewers performed a different sensitivity analysis conducted by excluding criterion c from the definition of potential sensitization. After excluding criterion c from the definition of potential sensitization, the Test product had 53% with potential sensitization compared with 56% in the RLD group, which is essentially no different (refer to the FDA statistical review and review amendment by Dr. Wanjie Sun for further details). This result supports the conclusion that criterion c drove the primary analysis results and in this case the primary analysis results are not indicative of truly inferior sensitization results for the Test product, but are an artifact of the higher irritation scores observed for the RLD in the induction phase.

3. (b) (4)

Reviewer's comments:

(b) (4)

(b) (4) *However, as there is also drug in a TDS that may not be in contact with the skin, it is not clear how much of a difference in irritation or sensitization one would expect with these changes. In any case, this is a hypothesis for the Test product's lower irritation scores, but does not add to the primary issues described in items 1 and 2 above.*

4. The applicant pointed out the criteria in the product specific guidance to determine the potential for sensitization is biased for the drug product which has the less irritation in the induction phase compares with the RLD. This is due to the requirement to compare the irritation observed in the Challenge Phase and Re-challenge Phase (if applicable) to the irritation observed over the full 21 day Induction Phase. In the case of methylphenidate transdermal systems, development of sensitization in some individuals during Induction

[2] NDA 021514 labelling revision 1/2017; https://www.accessdata fda.gov/drugsatfda_docs/label/2017/021514s025lbl.pdf

[3] \\cdsesub1\evsprod\anda206497\0000\m3\32-body-data\32p-drug-prod\mptp-td-p-mti\32p1-desc-comp\description-and-composition.pdf; pages 2-4 of 6

appears to confound the clinical interpretation of sensitization, based on skin reactions observed during Challenge Phases relative to those observed during Induction Phase. For this reason, the dermatological clinician should limit reference to Induction to the initial scores observed during Induction that relate purely to irritation reactions on naïve skin for comparison to skin reactions observed at Challenge, following single application to naïve skin which represent a composite of irritation and sensitization reactions.

Reviewer's comments:

Item #4 is essentially a general argument summarizing the applicant's concerns raised in points 1 through 3 above. Based on the results of Study MPTP-12130, a reasonable argument could be made that revisions to the current approach and definitions for irritation and sensitization studies may be needed, e.g., criterion "c," particularly if a recurrent issue has been observed. This will be evaluated outside the auspices of this particular ANDA review.

By considering all the factors above, this reviewer concludes that the clinical data (MPTP-12130) are adequate to support that the skin sensitization potential of Mylan Technologies Inc.'s Methylphenidate Transdermal System, 10 mg/9 hrs is no worse than that of the RLD.

3.1 Conclusion and Recommendation

3.1.1 Conclusion

The clinical data (MPTP-12130) submitted to ANDA 206497 are adequate to support that the skin irritation and sensitization potential of Mylan Technologies Inc.'s Methylphenidate Transdermal System, 10 mg/9 hrs is no worse than that of the RLD. The clinical data (MPTP-12130) demonstrate that the adhesive performance of Mylan Technologies Inc.'s Methylphenidate Transdermal System is at least as good as that of the RLD.

3.1.2 Recommendations

DCR recommends approval of this application.

CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

The Clinical Discipline has completed its review of ANDA 206497 and has no comments at this time.

APPEARS THIS WAY ON ORIGINAL

Sunny Tse

Digitally signed by Sunny Tse
Date: 2/07/2018 01:48:05PM
GUID: 508da6ff0002855c7da84880bd716ed2

Sarah Yim

Digitally signed by Sarah Yim
Date: 2/07/2018 02:01:09PM
GUID: 50841a8900009e1fe2b0e31699e4e531

Skin Irritation, Sensitization and Adhesion Studies Review

ANDA number	206497
Drug Product	Methylphenidate Transdermal System
Strength(s)	10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
Applicant Name	Mylan Technologies, Inc.
Treatment Indication	treatment of Attention Deficit Hyperactivity Disorder
Reference Listed Drug (RLD)	Daytrana® Transdermal System, 3.3 mg/hr
NDA number for RLD	NDA 021514
RLD Applicant Name	Noven Pharmaceuticals, Inc.
Original Submission Date	12/13/2013
Materials Reviewed	12/13/2013 (eCTD Sequence 0000): Original Submission 06/19/2014 (eCTD Sequence 0002): Response to Refuse to Receive letter- submission of clinical datasets, tables, results, formulation for Study MPTP-12130 11/17/2015 (eCTD Sequence 0007): Response to Easily Correctible Deficiency (ECD)-submission of formulations 02/02/2016 (eCTD Sequence 0009): Response to ECD - listing of rationale for determining sensitization potential for subject treatments for Study MPTP-12130 02/18/2016 (eCTD Sequence 0010): Response to ECD – explanation of 02/02/2016 ECD narrative FDA Statistical review by Wanjie Sun, Ph.D. completed on 01/15/2016, addendum 02/26/2016 OSIS inspection pending Draft Guidance recommended in Jul 2010
Primary Reviewer	Sunny Tse, PhD Clinical Reviewer Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office Generic Drugs (OGD)
Secondary Reviewer	Ying Fan, PhD Acting Team Leader, ANDA Team DCR, OB, OGD
Tertiary Reviewer	Lesley-Anne Furlong, MD Director DCR, OB, OGD
Date of Completion	3/25/2016
DCR Conclusion	The Division of Clinical Review concludes that the skin irritation/sensitization/adhesion study (MPTP-12130) is **not adequate** to support approval of the application pending OSIS inspection findings.

Table of Contents

Skin Irritation, Sensitization and Adhesion Review for ANDA 206497

1 EXECUTIVE SUMMARY

1.1 Approval Recommendation

The Division of Clinical Review (DCR) does NOT recommend approval of this application. The applicant's submitted irritation and adhesion data are acceptable. However, the clinical data are NOT adequate to demonstrate that sensitization potential of the proposed generic methylphenidate transdermal system is no worse than the reference listed drug product. Therefore, the DCR concludes that the submitted evaluable skin irritation, sensitization, and adhesion study (Study MPTP-12130) is Not adequate to support approval of this application.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

This review focuses on the studies submitted to ensure that the skin irritation and sensitization potentials of the applicant's Methylphenidate Transdermal System (test product) are no greater than those of the RLD, Daytrana®, and that the test product adheres to the skin as well as the RLD over the intended duration of wear. The review of the pharmacokinetic data is deferred to the Division of Bioequivalence II.

On 12/13/2013, the applicant Mylan submitted an original abbreviated new drug application (ANDA) for Methylphenidate Transdermal System. On 05/15/2014, the Agency sent a refuse to receive letter to the applicant which included requests for information from DCR and statistical reviewers. On 06/19/2014, the applicant provided a response to the refuse to receive letter dated 05/15/2014, which included clinical datasets, tables, results, and formulation for Study MPTP-12130 (irritation/sensitization/adhesion study) and Study MPTP-11030 (Fed BE).

The applicant conducted six studies. Studies MPTP-11030 (fed BE, n=24) and MPTP-11007 (cumulative irritation study, n=32) (b) (4) Study MPTP-11125 (fasting BE, n=34) allowed overlay and was not evaluated for adhesion. Study MPTP-12012, 30mg/9 hrs, (fasting BE, n=37) duration was only for 9 hours, included an overlay, and therefore was not evaluated for adhesion. Study MPTP-12046 (cumulative irritation and sensitization, n=100) was not evaluated because the applicant noted a data integrity issue and deficiencies in procedure by Novum Pharmaceutical Research Service.

Only Study MPTP-12130 (irritation/sensitization/adhesion) was evaluated in this review. It was an irritation evaluator blinded, multiple-dose, randomized application site, 2-treatment, 3-phase study of the human dermal safety of a formulation of Mylan's methylphenidate transdermal system, 10 mg/9 hours to Daytrana® patch, 10 mg/9 hours following administration of multiple transdermal doses of 10 mg/9 hours (1 × 10 mg/9 hours patch applied to both sides of the hip). The Test product is 23% smaller than the RLD (9.6 cm^2 versus 12.5 cm^2), which may have had an impact on study blinding.

The applicant assessed adhesion on day 1 at 1, 3, 5, 7, and 9 hours (± 10 minutes) after patch application.
One hundred healthy, adult subjects were enrolled in the study. Ninety-one subjects completed the Irritation (Induction) Phase of the study. Sixty-six subjects completed the Challenge Phase, and 31 subjects completed the Re-Challenge Phase. Seven subjects had fewer than 7 valid irritation scores and were excluded from the irritation analysis. Ninety three subjects were available to be included in the irritation analysis. Sixty six subjects were available to be included in the sensitization analysis. The 01/2008 RLD product label states that at least 13.5% of the 133 adult subjects in the challenge phase of the RLD sensitization study were confirmed to have been sensitized. The product draft guidance indicates that enrollment for the sensitization challenge phase may be lower than the usual 200 subjects. The applicant's sample size of 100 is acceptable as it is already known the drug product is sensitizing and unnecessary exposure is to be avoided. In general, the overall study design for Study MPTP-12130 is consistent with the product draft guidance.

1.2.2 Comparative Irritation

For Study MPTP-12130, both the applicant's and FDA's statistical analyses show that the test product is shown to be non-inferior to the RLD with regard to irritation.

1.2.3 Comparative Sensitization

In aggregate, the data on sensitization show both the RLD and the Test product to have substantial potential for sensitization. The data are not adequate to assure that the Test product is no more sensitizing than the RLD.

Assessing sensitization was complicated by a number of factors:

1. The RLD is known to be sensitizing. Up to 13.5% of adults became sensitized in a study performed under the RLD NDA.
2. For one of the four elements used to diagnose sensitization, the FDA BE guidance leaves room for interpretation. While the applicant chose a reasonable interpretation, the applicant's interpretation differed from the usual FDA interpretation and favored the Test product. The applicant's prespecified statistical plan was not sufficiently detailed to determine if its interpretation of this element was pre-planned or post hoc.
3. FDA guidance recommends descriptive statistics to describe sensitization, leaving interpretation of sensitization to clinical judgment.

Regarding (2) above, one of the four FDA criteria for diagnosing sensitization reads "The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are *generally higher* than the combine "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase. The applicant interpreted *generally higher* as the average irritation score from the challenge/rechallenge phase being higher than the average irritation score from the induction phase. In contrast, FDA has interpreted *generally higher* as the maximum irritation score from the challenge/rechallenge phase being higher than all irritation scores from the induction phase. FDA cannot determine if the applicant's interpretation was or was not a post hoc choice to favor their product: the applicant's

prespecified statistical plan does not provide any more detail than the FDA BE guidance. Therefore, FDA considered both interpretations.

The point estimate for the proportion of skin sites showing potential sensitization was higher for the Test product compared with the RLD regardless of whether the applicant's or the FDA's interpretation of *generally higher* was used. There were 66 subjects in FDA's per-protocol population for sensitization (FPPSEN) in Study MPTP 12130. Using the applicant's interpretation of *generally higher*, 33 Test versus 27 RLD skin sites showed potential sensitization. The proportions are 50% for Test versus 40.9% for RLD, with 22% more Test sites than RLD sites showing sensitization. Both products showed a substantial potential for sensitization.

Using the FDA's interpretation of *generally higher*, 18 Test versus 9 RLD skin sites showed potential sensitization. The proportions are 27.3% for Test versus 13.6% for RLD, with 100% more Test sites than reference sites showing sensitization. Again, both products showed a substantial potential for sensitization.

There are several formulation differences between the two products, which makes a difference in potential sensitization biologically plausible.

1.2.4 Comparative Adhesion

According to the FDA's analysis, the data from Study MPTP-12130 demonstrates non-inferiority of the Test product compared to the reference with regard to adhesion.

1.2.5 Comparative Safety

Eight-five subjects experienced a total of 816 AEs over the course of the study. Adverse events were mild to moderate in intensity. No deaths, other serious adverse events, or other significant adverse events occurred over the course of the study. Twenty-one subjects were discontinued because of adverse events. Seventeen subjects were discontinued due to skin events, with all seventeen of these subjects having the skin events with both the test and reference products simultaneously.

Both the test and reference product exhibited comparable application site adverse events. The most frequently reported application site adverse events (AEs) were application site pruritus (Test 52%, RLD 56%).

Subject (b) (6) was discontinued by the Investigator after Day 18 activities due to skin evaluation. Subject (b) (6) completed exit procedures on (b) (6) and had an elevated serum β-HCG value of 5207.70 mIU/mL (reference range <5.00 mIU/mL). The elevated value was confirmed on (b) (6) with a value of 13063.00 mIU/mL. Subject (b) (6) underwent an elective termination of the pregnancy on (b) (6) Subject (b) (6) was included in the irritation and adhesion analyses and excluded from the sensitization analysis.

2 CLINICAL REVIEW

2.1 Introduction and Background

2.1.1 Summary of Drug Information

Reference Listed Drug	Daytrana® Transdermal System, 30mg/9hr (3.3 mg/hr)
RLD Applicant Name	Noven Pharmaceuticals, Inc.
RLD NDA Number	021514
Date of RLD Approval	04/06/2006
Current Label[1]	08/14/2015
Approved Indication(s)	the treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Recommended Dose/Administration	• Daytrana should be applied to the hip area (using alternating sites) 2 hours before an effect is needed and should be removed 9 hours after application. Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. • Exposure to water during bathing, swimming, or showering can affect patch adherence. • Patches should not be applied or re-applied with dressings, tape, or other common adhesives. In the event that a patch does not fully adhere to the skin upon application, or becomes partially or fully detached during wear time, the patch should be discarded and a new patch may be applied at a different site.
Application site	the hip area
Maximal Daily Dose	30mg/9hrs
Boxed Warnings	Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior.
Commonly reported Adverse Events	Children (ages 6-12):The most commonly (≥5% and twice the rate of placebo) reported adverse reactions in a placebo-controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affective lability, and anorexia. Adolescents (ages 13-17): The most commonly (≥5% and twice

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021514s023lbl.pdf

	the rate of placebo) reported adverse reactions in a placebo-controlled trial in adolescents aged 13-17 included appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain, and anorexia. The majority of subjects in these trials had erythema at the application site. The most common (≥2% of subjects) adverse reaction associated with discontinuations in controlled clinical trials in children or adolescents was application site reactions.
Contraindications	• Hypersensitivity to methylphenidate • Agitation • Glaucoma • Tics • Monoamine Oxidase Inhibitors
Prominent Warnings/ Precautions	Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. Psychiatric Adverse Events: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior. Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking

	stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. Psychiatric Adverse Events: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior. Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. Priapism: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. Peripheral Vasculopathy, including Raynaud's phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients. Chemical Leukoderma: Daytrana use may result in a persistent loss of skin pigmentation at and around the application site. Loss of pigmentation, in some cases, has been reported at other sites distant from the application site. Monitor for signs of skin depigmentation. Discontinue Daytrana if it occurs. Contact Sensitization: Use of Daytrana may lead to contact sensitization. Treatment should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana and is not by itself an indication of sensitization.

	However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. External Heat: Patients should be advised to avoid exposing the Daytrana application site to direct external heat sources. When heat is applied to Daytrana after patch application, both the rate and extent of absorption are significantly increased. Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy.
Mechanism of Action	Methylphenidate is a CNS stimulant. Its mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known, but methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space.
Absorption	The amount of methylphenidate absorbed systemically is a function of both wear time and patch size. In patients with ADHD, peak plasma levels of methylphenidate are reached at about 10 hours after single application and 8 hours after repeat patch applications (12.5 cm^2 to 37.5 cm^2) when worn up to 9 hours. On average, steady-state is likely to have be achieved by approximately 14 days of dosing. Following a single 9-hour application of Daytrana patch doses of 10 mg / 9 hours to 30 mg / 9 hours patches to 34 children with ADHD, C_{max} and AUC_{0-t} of d-methylphenidate were proportional to the patch dose.

2.1.2 Regulatory Background

2.1.2.1 Guidance on Drug Product

A Draft Guidance for this drug product is available. Table 1 provides a brief overview of the Draft Guidance recommendations.

Table 1. Drug Product Guidance

Draft Guidance[2]	Draft Guidance on Methylphenidate Film, Extended Release/Transdermal [NDA 021514]
Date Posted	*Recommended Jul 2010*
Recommended Studies	1. Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints Study 2. Skin Irritation, Sensitization and Adhesion Study
[PK BE Study]	**Design**: Single-dose, fasting, two-treatment, two-period crossover in vivo **Subject population**: Healthy males and nonpregnant females, general population. **Treatment dosing**: The 30 mg/9 hr transdermal patch should be applied to the hip, as recommended in the approved reference listed drug (RLD) and worn for 9 hours.
[Skin Irritation, Sensitization and Adhesion Study]	**Design**: Skin Irritation, Sensitization and Adhesion Study **Subject population**: Healthy males and nonpregnant females, general population. **Treatment dosing**: *Induction phase* – sequential, same skin site, 48-72-hour patch applications for a total of 21 consecutive days of the test and reference patches (plus optional vehicle patch and optional negative control) simultaneously. Evaluate the adhesion performance of only the first applied test product and reference at 9 hours after application. No patch reinforcement should be permitted for the first applied test product and reference patches for their first 9 hours of application. *Rest period* – no patch application for 14-17 days. *Challenge phase* – single 48-hour application of the test and reference patches (plus optional vehicle patch and optional negative control) to a naive site. **Pertinent additional comments**: • Adhesion should be evaluated prior to patch removal throughout the entire study period to ensure adequate skin contact for maximal induction of irritation and sensitization. • Patch reinforcement is allowed after first 9 hours of application. • Irritation evaluation: Induction phase – at each patch removal. Challenge phase – 30 minutes and at 24, 48, and 72 hours after challenge patch removal. • For subjects who experience irritation consistent with a combined score of ≥ 3, or who experience symptomatic intolerable irritation, the patch may be moved to a new site in order to complete the 21-day Induction Phase and continue with the sensitization part of the study. • If a patch completely detaches, it should be replaced within 24 hours and the subject should continue in the study. During the 21-day Induction Phase, if a patch is completely detached for more than 24 hours (unless the patch was removed for an unacceptable degree of irritation), the subject should be excluded from both the irritation and

[2] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm220196.pdf

	sensitization analyses for that product. During the 48-hr Challenge Phase, if a patch is completely detached for more than 24 hours, the subject should be excluded from the sensitization analysis.

2.1.2.2 Generic Product Development

There are no relevant bio-INDs in (b) (4) There are no relevant protocol reviews in the DBE database or (b) (4) There are no relevant controlled correspondences in the OGD database or (b) (4)

On 02/20/2008, the Agency received from the applicant a request for BE recommendations and the drug release method (Control Document OGD#08-0184). The communication was closed 7/ 30/2010 indicating the BE draft guidance was posted on the OGD website July 2010.
On 12/13/2013, the applicant provided the original submission. On 06/19/2014, the applicant provided a response to a refuse to receive letter dated 05/15/2014. This included submission of datasets, tables, results, formulation for Study MPTP-12130 (irritation/sensitization/adhesion study) and Study MPTP-11030 (Fed BE). On 11/17/2015, the applicant submitted a response to an ECD dated 11/04/2015. This included submission of formulation information for Study MPTP-11030 (Fed BE), (b) (4) On 02/02/2016, the applicant submitted a response to an ECD dated 01/20/2016. This included an explanation of how the applicant determined sensitization potential of 17 subject treatments where the applicant had a conflicting conclusion regarding sensitization potential when compared with the FDA statistician's assessment. On 02/18/2016, the applicant submitted a response to an ECD dated 02/12/2016 in which the applicant further attempted to clarify their determination of sensitization potential of the 17 subject treatments in the 02/02/2016 ECD response.

2.1.2.3 Relevant Communications with Other Generic Applicants

none

2.1.2.4 Other ANDA submissions for same or related product

ANDA 206497 is a potential first generic for Methylphenidate TDS. There are other ANDAs submitted to OGD. (See Table 2 below).

Table 2. Other ANDA Submissions for Same or Related Product

ANDA	Applicant	Current Status	Status Date
(b) (4)			

2.1.3 Other Relevant Information

none

2.2 Description of Clinical Data and Sources

The applicant conducted six studies MPTP-12130 (irritation/sensitization/adhesion study), MPTP-11030 (Fed BE), MPTP-11007 (cumulative irritation study), MPTP-11125 (fasting BE), MPTP-12012 (fasting BE), and MPTP-12046 (cumulative irritation and sensitization). Only MPTP-12130 (irritation/sensitization/adhesion study) was evaluated in this review. Table 3 provides reasons for not reviewing the other studies.

Table 3. Non-Evaluable Studies

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
MPTP-11030 - Single-Dose Pilot Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fed BE (n=24)	(b) (4)
MPTP-11007 - Comparative Evaluation of the Cumulative Irritation of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) following a 48 to 72 hour Wear in Healthy Adult Volunteers	Cumulative Irritation Study (n=32)	(b) (4)
MPTP-11125 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fasting Bioequivalence (n=34)	Overlay is allowed
MPTP-12012 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr;	Fasting Bioequivalence (n=37)	The applicant evaluated irritation. However, the study duration is only for 9 hours.

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
Shire) in Healthy Adult Volunteers		
MPTP-12046 - Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Shire) in Healthy Adult Volunteers	Cumulative Irritation and Sensitization (n=100)	The applicant noted data integrity issue and deficiencies in procedure by Novum Pharmaceutical Research Service. Due to data integrity issue, not recommended for the review.

Table 4. Source of Clinical Data

Study #	MPTP-12130
Study Type	irritation/sensitization/adhesion study
CRO	PRACS Institute 4801 Amber Valley parkway Fargo, ND 58104, USA Tel: 701-239-4750 Fax: 701-239-4955
Study Period	October 7, 2012 to February 19, 2013
Study Centers[3]	PRACS Institute 4801 Amber Valley parkway Fargo, ND 58104, USA Tel: 701-239-4750 Fax: 701-239-4955
Enrollment	100

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

ANDA Submission(s)	**12/13/2013 (eCTD Sequence 0000):** Original Submission **06/19/2014 (eCTD Sequence 0002):** Response to Refuse to Receive letter- submission of clinical datasets, tables,

[3] \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf, page 5 of 81

	results, formulation for Study MPTP-12130 **11/17/2015 (eCTD Sequence 0007):** Response to Easily Correctible Deficiency (ECD)-submission of formulations **02/02/2016 (eCTD Sequence 0009):** Response to ECD - listing of rationale for determining sensitization potential for subject treatments for Study MPTP-12130 **02/18/2016 (eCTD Sequence 0010):** Response to ECD – explanation of 02/02/2016 ECD narrative This ANDA is submitted in eCTD format and entirely electronic. The ANDA submission is archived at the following location: \\cdsesub1\evsprod\ANDA206497\206497.enx
FDA Statistical Review	ANDA 206497 Statistical Primary Review by Wanjie Sun, Ph.D., completed on 01/15/2016, addendum 02/26/2016

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Study #	**MPTP-12130**
Office of Study Integrity and Surveillance	**Inspection pending**
Blinding	irritation evaluator blinded All clinic staff, study monitors, and subjects were not blinded to the randomization scheme.
Randomization	site of patch application (either the left or right hip)
Retention of Reserve Samples	Applicant expected to supply sufficient quantities for retention. Once the retention period passed, any remaining unused drug was to be returned to applicant in original containers, or destroyed.

Reviewer's Comments:

- *The applicant's method of blinding is acceptable.*
- *Randomization is acceptable.*
- *The applicant's method for retention of reserve samples is acceptable.*

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

Study # MPTP-12130 appears to have been conducted in accordance with accepted ethical standards. The IRB approved the original protocol and the Informed Consent Form prior to the start of the study.

2.3.4 Evaluation of Financial Disclosure

The applicant submitted a combined Form FDA 3454 for MPTP-11007, MPTP-11030, MPTP-11125, MPTP-12046, MPTP-12130, and MPTP-12012. For the only evaluable study, MPTP-12130 Principal Investigator and sub-investigators were the same and all are listed. The applicant had no financial arrangements with the investigators to disclose.

Reviewer's Comment:
The Form FDA 3454 was signed 12/12/2013.

2.4 Review of Skin Irritation, Sensitization, and Adhesion

2.4.1 General Approach to Review of Skin Irritation, Sensitization and Adhesion

MPTP-12130 was reviewed to verify:

- that the test product is no more irritating than the reference product
- that the skin sensitization potential of the test product is no worse than those expected with use of the reference product
- that the adhesion performance of the test product is no worse than the reference product

2.4.2 Detailed Review of Skin Irritation, Sensitization and Adhesion Studies

2.4.2.1 Skin Irritation, Sensitization, and Adhesion Study (MPTP-12130)

Applicant's Study #	MPTP-12130
Title	Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Noven) in Healthy Adult Volunteers
Objectives	The primary objectives of this study was to evaluate the cumulative irritation and sensitization potential of a single formulation of Mylan's Methylphenidate Transdermal Systems 10mg/9hours compared to Noven's Daytrana® 10 mg (releasing 10 mg/9hours) in healthy male and female volunteers. In addition, the adhesive quality of Mylan's Methylphenidate Transdermal System was compared to Noven's Daytrana® in all enrolled subjects during the first patch application. A secondary objective was to assess patch legibility.

2.4.2.1.1 Protocol Review

Protocol Version	Protocol Date	IRB Approval Date
Original	September 21, 2012	September 26, 2012

Reviewer's Comments:
There were no protocol amendments for this study. The protocol lists a 14 day rest phase and the study report lists a 15 rest phase. This difference has no impact on the outcome of the study.

2.4.2.1.2 Study Design

Overall Study Design and Plan

This was an irritation evaluator blinded, multiple-dose, randomized application site, 2-treatment, 3-phase, 1-period study of the human dermal safety of a formulation of Mylan's methylphenidate transdermal system, 10 mg/9 hours to Daytrana® patch, 10 mg/9 hours following administration of multiple transdermal doses of 10 mg/9 hours (1 × 10 mg/9 hours patch applied to both sides of the hip) in 100 healthy, adult subjects.

On Day 1, each subject received a single transdermal application of 10 mg/9 hours (1 × 10 mg/9 hours patch) of the test product, methylphenidate transdermal system, and a single transdermal dose of 10 mg/9 hours (1 × 10 mg/9 hours patch) of the reference product, Daytrana® patch, to either the left or right side of the hip based on the randomization. On Day 1 only, adhesion was assessed in all subjects every 2 hours(± 10 minutes) starting 1 hour after the first patch application until 9 hours post patch application. After the 9 hour adhesion assessment, subjects were released from confinement and continued in the study on an outpatient basis (returning for patch application and removal and irritation and adhesion assessments). Patches were placed for a 2 to 3-day wear cycle per application over a total of 9 applications (21 days), followed by a 15-day rest phase and a subsequent 48 hour Challenge Phase, which was followed by a 3-day observation and irritation evaluation. Patches were applied on Days: 1, 4, 6, 9, 11, 13, 16, 18, and 20 with the last patches removed on Day 22 for the Induction Phase and were applied once for a 48 hour wear period during the Challenge and Re-Challenge Phases (if applicable). Only those subjects who demonstrated possible sensitization were re-challenged 4 to 8 weeks after completion of the Challenge Phase.

In addition to the patch adhesion performance measured on Day 1, adhesion compliance was also assessed prior to each patch removal. An irritation evaluation occurred 30 to 45 minutes after each patch application removal during the Induction Phase and at 0.5, 24, 48, and 72 hours after patch removal during the Challenge and Re-Challenge Phases. On Day 1 only, print legibility was assessed at the time of patch application and at 3, 6, and 9 hours (± 10 minutes) after patch application.

Table 5. Overall Study Design

Study/Protocol Number	MPTP-12130		
Subject Population	100 healthy adult subjects		
Blinding	Open label, irritation evaluator blinded		
Randomization	Patch application site (both sides of the hip) randomized		
Treatment arms	**Test**		**Reference**
Reinforced	(b) (4) Soft Cloth Surgical Tape (b) (4) was applied to 2 edges of each dermal patch at the time of every application except for the first 9 hours of the first application.		
Number of period/phase	**Induction**	**Rest**	**Challenge**
Duration	21 days	15 days	5 days
Dose administered		none	
Dosing regimen	2 to 3-day wear cycle	none	2 days

Number of applications	9	0	1
Application site	both sides of the hip	none	both sides of the hip (naïve site)
Adhesion assessment times	1, 3, 5, 7, and 9 hours (± 10 minutes) on study day 1	none	Just prior to patch removal
Irritation assessment times	30-45 min after each application was removed	none	0.5, 24, 48, and 72 hours after removal of transdermal systems

Reviewer's Comments:

- *The applicant assessed adhesion on day 1 every 2 hours after patch application. The product draft guidance recommended adhesion assessment on day 1 at 9 hours after patch application. This single difference is acceptable. With the exception of the small sample size of n=100, the overall study design for Study MPTP-12130 is consistent with the product draft guidance.*
- *The treatment administrations are consistent with the approved RLD label and the product draft guidance.*
- *Subjects were instructed to keep the transdermal systems as dry as possible by keeping showering to a minimum and avoiding baths, soaking, or swimming altogether.*

Treatment Arms

Details of each treatment are provided in the table below.

Table 6. Treatment Arms (MPTP-12130)

Treatment arms	Test	Reference
Product Name	Methylphenidate Transdermal System	Daytrana®
Strength	10 mg/9 hours	10 mg/9 hours
Patch size	9.6 cm^2	12.5 cm^2
Manufacturer	Mylan Technologies Inc.	Noven Pharmaceuticals, Inc.
Lot No.	R6D0023	59375
Manufacture Date	04/2012	-
Expiration Date	-	02/2013
Dosage Form	transdermal system	transdermal system
Route of administration	topical	topical

Study Population Selection

MPTP-12130 enrolled non-tobacco using, healthy males and females between the ages of 18 and 45 (inclusive) into the clinical phase of this study. See applicant's Integrated Clinical and

Statistical Study Report[4] sections 9.4.1 and 9.4.2 for the full list of the applicant's inclusion and exclusion criteria.

Reviewer's Comments:

- *The applicant's inclusion and exclusion criteria are consistent with the product draft guidance.*
- *The applicant added additional inclusion and exclusion criteria, all of which are acceptable.*

Restrictions during the study	Subjects were not allowed to use prescription or OTC products per Protocol Medication Exclusion Criteria.
Treatment compliance	Patch application was completed by PRACS Institute staff. Once the patch was applied, it was held in place with the palm of the hand for about 30 seconds. Application compliance was monitored by PRACS Institute staff on Day 1 only by assessing patch adhesion performance at 1, 3, 5, 7, and 9 hours (± 10 minutes). After all other patch applications were applied, tape was applied to 2 edges of each dermal patch and patch adhesion compliance was assessed prior to patch removal (48 or 72 hours after patch application).

Reviewer Comments

- *The applicant's restrictions during the study and treatment compliance measures are acceptable.*

Assessments

The Applicant used the following scales and sensitization definition during MPTP-12130:

Irritation

Table 7. Dermal Response Scoring System

Scale	Irritation
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test (ie, application) site

[4] \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf pages 34-37 of 81

Table 8. Other Effects Scoring System

Scale	Appearance
A (0)	Slightly glazed appearance
B (1)	Marked glazed appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudates covering all or part of the patch site
H (3)	Small petechial erosions and/or scabs

Sensitization Definition

- The subject had at least 1 evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.

- The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.

- The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.

- If the subject completed a Re-Challenge Phase, the above 3 criteria were met during both the Challenge Phase and the Re-Challenge Phase.

- Scores that resolved before 48 hours were generally considered to be due to irritation instead of sensitization. The total number of subjects considered sensitized to the test product and reference listed drug were provided.

Adhesion

Patch adhesion performance was assessed by suitably trained personnel at 1, 3, 5, 7, and 9 hours (± 10 minutes) after the Day 1 patch application using the following adhesion scoring system:

Table 9. Applicant Adhesion Scoring System

Adhesion	Score
100%	100
>90% to <100%	95
>80% to 90%	85
>70% to 80%	75
>60% to 70%	65
>50% to 60%	55
>40% to 50%	45
>30% to 40%	35
>20% to 30%	25
>10% to 20%	15
>0% to 10%	5
Fall off	0

Reviewer's Comments:

- *The applicant's Dermal Response Scoring System and Other Effects Scoring System are the same as the product draft guidance.*
- *The applicant's sensitization definition is the same as the product draft guidance.*
- *The applicant's adhesion scoring system is different than the product draft guidance. The FDA statistical reviewer used a different adhesion scoring system to account for the applicant's more detailed scoring system. Please see Table 10 below.*

Table 10. FDA Statistical Reviewer Adhesion Scoring System

Sponsor's Score	Description	FDA's Score
100	Adhesion: 100%	0
95	Adhesion: >90% to <100%	0
85	Adhesion: >80% to 90%	1
75	Adhesion: >70% to 80%	1
65	Adhesion: >60% to 70%	2
55	Adhesion: >50% to 60%	2
45	Adhesion: >40% to 50%	3
35	Adhesion: >30% to 40%	3
25	Adhesion: >20% to 30%	3
15	Adhesion: >10% to 20%	3
5	Adhesion: >0% to 10%	3
0	Adhesion: 0%	4

Endpoints

Primary Endpoint(s)	Mean Cumulative Irritation Mean Adhesion Sensitization

Reviewer's Comment:
The primary endpoints for the skin irritation, sensitization, and adhesion study are consistent with the product draft guidance.

Statistical Analysis Plan
See applicant's Study Report, Section 9.8 (pages 43-44) and the 15-Jan-2016 FDA Statistical Review, Section 3 (pages 8-9) for details of the statistical analysis plan. The Applicant's per-protocol (PP) population definition is provided below.

Per-Protocol Population

- **Irritation**:

The Per-Protocol (PP) Population for evaluation of skin irritation is defined as follows: the test articles need to be applied sequentially to the same site for the entire 21 day induction phase (without any period of detachment longer than 24 hours) to be evaluated for the cumulative irritation effect OR if a patch is moved or removed due to excessive irritation, it should be included using Last Observation Carried Forward (LOCF).

- **Sensitization**:

Sensitization Analysis will include all test articles worn (without any period of detachment longer than 24 hours) for the full 21 day induction phase AND the entire 48-hour challenge phase AND the subject must return for at least one of the scheduled evaluations at 48 and 72 hours after removal of the challenge patch. If a test article is removed prior to the end of the 48-hour challenge phase due to an intolerable reaction, the application site should be evaluated at 24, 48, and 72 hours after patch removal and be included in the sensitization analysis using LOCF.
For each test article, individually evaluate each Per Protocol subject with a combined score of 2 or greater at 48 or 72 hours after patch removal during the

Challenge Phase for potential sensitization. A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. Consider a subject to be potentially sensitized if all of the following criteria are met:

a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
b. The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.
d. If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.
e. Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization. The total number of subjects considered sensitized to the test product and RLD will be provided.

- **Adhesion**:

The Per-Protocol (PP) Population evaluation for adhesion for each test article is defined as follows: Valid adhesion score for statistical analysis should include all patches except those removed early for unacceptable irritation or those that dropped out of the study before the end of the first 9-hour wear period of the 1st patch application.

Reviewer's Comment:

- *The applicant's definitions for the irritation, sensitization, and adhesion per-protocol populations are consistent with the product draft guidance.*

2.4.2.1.3 Study Subjects

Subject Disposition

Table 11 below provides a summary of subject disposition and subjects analyzed by the applicant.

Table 11. Summary of Subject Disposition

	Total
Subjects Randomized	100
Subjects Successfully Completed all Dose Applications Intended Per Protocol	66
Subjects Who Elected to Withdraw	8
Subjects Discontinued by the Investigator	26
Subjects Discontinued by Sponsor	0
Subjects Available to be Included in Adhesion Analysis	100
Subjects Available to be Included in Irritation Analysis	93
Subjects Available to be Included in Sensitization Analysis	66

Treatment A: Methylphenidate Transdermal System, 10 mg/9 hours, (Lot No.: R6D0023)
Treatment B: Daytrana® 10 mg, (10 mg/9 hours, (Lots No.: 59375 & 62073)

Reviewer's Comments:

The RLD is known to be sensitizing in some patients: the 01/2008 RLD product label states that at least 13.5% of the 133 adult subjects in an RLD sensitization study were confirmed to have been sensitized based on results of the challenge and/or rechallenge phases of the study. The product draft guidance indicates that enrollment for the sensitization challenge phase may be lower than the usual 200 subjects. The applicant's sample size of 100 is acceptable as it is already known the drug product is sensitizing and unnecessary exposure is to be avoided.

The FDA statistical reviewer recommended to exclude subject (b) (6) *from the irritation and sensitization analyses because Visit 10 irritation data was missing, indicating the subject test and reference patches were absent for 2 days in induction. DCR agreed with the statistician's recommendation.*

No adjustments to the applicant's adhesion per-protocol population were needed for the FDA adhesion analysis. All 100 subjects included in the applicant's adhesion per-protocol population were included in the FDA adhesion per-protocol population.

Demographics

Table 12. Demographics in the FDA's PPIRR (FPPIRR) Population in Irritation Study MPTP-12130

Characteristics	FPPIRR (N=92)
Age (years)	
Mean (STD)	27.3 (7.1)
Female n (%)	57 (62.0%)
Race n (%)	
White	86 (93.5%)
Other	6 (6.5%)

Table 13. Demographics in the FDA's PPSEN (FPPSEN) Population in Challenge (N=66) and Re-Challenge (N=31) Phase of Study MPTP-12130

Phase	Challenge	Re-Challenge
Characteristics	**FPPSEN (N=66)**	**FPPSEN (N=31)**
Age (years)		
Mean (STD)	27.5 (7.6)	29.0 (8.0)
Female n (%)	40 (60.6%)	19 (61.3%)
Race n (%)		
White	64 (97.0%)	30 (96.8%)
Other	2 (3.0%)	1 (3.2%)

Table 14. Demographics in the FDA's PPPA (FPPPA) Population in Adhesion Study MPTP-12130

Characteristics	FPPPA (N=100)
Age (years)	
Mean (STD)	27.2 (7.2)
Female n (%)	62 (62.0%)
Race n (%)	
White	93 (93.0%)
Other	7 (7%)

Reviewer's Comments:

The majority of study subjects were female (> 60%) and white (> 93%). The demographics of this study are acceptable for a typical skin irritation, sensitization, and adhesion study.

2.4.2.1.4 Results

Irritation Results

The applicant and FDA statistical analysis results are provided in Table 15. Table 16 provides the frequency of each irritation score at each evaluation time point.

Table 15. Irritation Analysis Results (MPTP-12130)

Applicant* (Applicant's PPIRR N=93)				FDA (FDA's PPIRR N=92)			
NI Hypothesis	**LSmean**	**95%UB of $U_T - 1.25U_R$**	**Pass or Fail NI**	**NI Hypothesis**	**LSmean (std error)**	**95%UB of $U_T - 1.25U$**	**Pass or Fail NI**
H_0 (Inferior): $\frac{U_T}{U_R} > 1.25$ H_1(Non-Inferior) $\frac{U_T}{U_R} \leq 1.25$	TEST: 1.874 RLD: 2.324	-0.94 (<0)	**Pass NI**	H_0 (Inferior): $\frac{U_T}{U_R} > 1.25$ H_1 (Non-Inferior): $\frac{U_T}{U_R} \leq 1.25$	TEST: 1.99 (0.12) RLD: 2.45 (0.12)	-0.96 (<0)	**Pass NI**

*Source: Table 14.6 on page 76 in the sponsor's study report MPTP-12130

Table 16. Frequency of Irritation Scores at Each Time Point for TEST and RLD in the FPPIRR Population (MPTP-12130)

Visit	TEST (N=92) n (%)									RLD (N=92) n (%)								
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Mean**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Mean**
2	23 (25)	62 (67.4)	6 (6.5)	0	0	0	0	1 (1.1)	0.88	12 (13)	72 (78.3)	7 (7.6)	0	0	0	0	1 (1.1)	1.01
3	5 (5.4)	84 (91.3)	2 (2.2)	0	0	0	0	1 (1.1)	1.03	2 (2.2)	77 (83.7)	12 (13.0)	0	0	0	0	1 (1.1)	1.17
4	1 (1.1)	85 (92.4)	5 (5.4)	0	0	0	0	1 (1.1)	1.11	3 (3.3)	71 (77.2)	17 (18.5)	0	0	0	0	1 (1.1)	1.22

Visit	TEST (N=92) n (%)									RLD (N=92) n (%)								
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Mean**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Mean**
5	0	80 (87.0)	6 (6.5)	0	4 (4.4)	0	0	2 (2.2)	1.33	1 (1.1)	54 (58.7)	30 (32.6)	0	5 (5.4)	0	0	2 (2.2)	1.61
6	0	58 (63.0)	15 (16.3)	0	15 (16.3)	0	0	4 (4.4)	1.91	0	34 (37.0)	33 (35.9)	1 (1.1)	20 (21.7)	0	0	4 (4.4)	2.29
7	0	41 (44.6)	22 (23.9)	0	23 (25.0)	0	0	6 (6.5)	2.38	0	22 (23.9)	32 (34.8)	0	29 (31.5)	0	2 (2.2)	7 (7.6)	2.86
8	0	22 (23.9)	37 (40.2)	0	25 (27.2)	0	1 (1.1)	7 (7.6)	2.73	1 (1.1)	9 (9.8)	30 (32.6)	1 (1.1)	31 (33.7)	7 (7.6)	4 (4.4)	9 (9.8)	3.46
9	0	18 (19.6)	35 (38.0)	0	28 (30.4)	3 (3.3)	1 (1.1)	7 (7.6)	2.93	1 (1.1)	4 (4.4)	25 (27.2)	0	34 (37.0)	13 (14.1)	5 (5.4)	10 (10.9)	3.86
10	0	20 (21.7)	30 (32.6)	0	28 (30.4)	5 (5.4)	1 (1.1)	8 (8.7)	3.03	0	8 (8.7)	19 (20.7)	0	34 (37.0)	14 (15.2)	4 (4.4)	13 (14.1)	3.99
All	29 (3.5)	470 (56.8)	158 (19.1)	0	123 (14.9)	8 (1.0)	3 (0.4)	37 (4.5)	1.93 (1.06)	20 (2.4)	351 (42.4)	205 (24.8)	2 (0.2)	153 (18.5)	34 (4.1)	15 (1.8)	48 (5.8)	2.39 (1.04)

Reviewer's Comment:
The test product is demonstrated to be no more irritating than the reference product by both the applicant's and FDA's statistical analyses.

Sensitization Results
Table 17 and Table 18 provide the applicant and FDA sensitization results of Study MPTP-12130.

Table 17. Frequency of Irritation Scores at Each Time Point during the Challenge (N=66) and Re-Challenge (N=31) Phase of Study MPTP-12130 in the FPPSEN Population

Challenge	TEST (N=66) n (%)										RLD (N=66) n (%)										
Hour	0	1	2	3	4	5	6	7	9	10	0	1	2	3	4	5	6	7	8	9	10
0.5 (n=66)	7 (10.6)	16 (24.2)	21 (31.8)	0	18 (27.3)	0	0	4 (6.1)	0	0	7 (10.6)	14 (21.2)	23 (34.9)	0	17 (25.8)	0	0	4 (6.1)	0	0	1 (1.5)
24 (n=66)	20 (30.3)	10 (15.2)	18 (27.3)	0	17 (25.8)	1 (1.5)	0	0	0	0	17 (25.8)	10 (15.2)	18 (27.3)	0	15 (22.7)	2 (3.0)	1 (1.5)	3 (4.6)	0	0	0
48 (n=66)	16 (24.2)	11 (16.7)	26 (39.4)	0	9 (13.6)	1 (1.5)	3 (4.5)	0	0	0	12 (18.2)	14 (21.2)	23 (34.9)	0	12 (18.2)	2 (3.0)	2 (3.0)	1 (1.5)	0	0	0
72 (n=66)	22 (33.3)	7 (10.6)	27 (40.9)	1 (1.5)	9 (13.6)	0	0	0	0	0	19 (28.8)	7 (10.6)	27 (40.9)	0	13 (19.7)	0	0	0	0	0	0
Total (n=66)	65 (24.6)	44 (16.7)	92 (34.9)	1 (0.4)	53 (20.1)	2 (0.8)	3 (1.1)	4 (1.5)	0	0	55 (20.8)	45 (17.1)	91 (34.5)	0	57 (21.6)	4 (1.5)	3 (1.1)	8 (3.0)	0	0	1 (0.4)
Re-Challenge	TEST (N=31) n (%)										RLD (N=31) n (%)										
Hour	0	1	2	3	4	5	6	7	9	10	0	1	2	3	4	5	6	7	8	9	10
0.5 (n=31)	0	4 (12.9)	4 (12.9)	0	17 (54.8)	0	0	6 (19.4)	0	0	0	2 (6.5)	5 (16.1)	0	16 (51.6)	0	0	8 (25.8)	0	0	0

24 (n=31)	1 (3.2)	1 (3.2)	4 (12.9)	0	19 (61.3)	2 (6.5)	1 (3.2)	2 (6.4)	0	1 (3.2)	1 (3.2)	0	5 (16.1)	0	17 (54.8)	2 (6.5)	1 (3.2)	3 (9.7)	1 (3.2)	0	1 (3.2)
48 (n=30)	1 (3.3)	1 (3.3)	13 (43.3)	0	10 (33.3)	1 (3.3)	0	2 (6.7)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	16 (53.3)	0	6 (20.0)	1 (3.3)	1 (3.3)	1 (3.3)	0	2 (6.7)	1 (3.3)
72 (n=31)	1 (3.2)	2 (6.5)	20 (64.5)	1 (3.2)	1 (3.2)	3 (9.7)	0	3 (9.7)	0	0	1 (3.2)	2 (6.5)	19 (61.3)	1 (3.2)	3 (9.7)	1 (3.2)	1 (3.2)	3 (9.7)	0	0	0
Total	3 (2.4)	8 (6.5)	41 (33.3)	1 (0.8)	47 (38.2)	6 (4.9)	1 (0.8)	13 (10.6)	1 (0.8)	2 (1.6)	3 (2.4)	5 (4.1)	45 (36.6)	1 (0.8)	42 (34.2)	4 (3.3)	3 (2.4)	15 (12.2)	1 (0.8)	2 (1.6)	2 (1.6)

Table 18. Frequency of Final Potential Sensitization Combining Challenge and Re-Challenge Phase of MPTP 12130 Among the 66 FPPSEN Subjects based on Sponsor's Study Report and FDA

Sponsor's Potential Sensitization based on Study Report				**FDA's Potential Sensitization**			
	Potential Sensitization				**Potential Sensitization**		
Treatment	**No**	**Yes**	**Total**	**Treatment**	**No**	**Yes**	**Total**
TEST	49 (74.2%)	17 (25.8%)	66 (100%)	**TEST**	48 (72.7%)	18 (27.3%)	66 (100%)
RLD	47 (71.2%)	19 (28.8%)	66 (100%)	**RLD**	57 (86.4%)	9 (13.6%)	66 (100%)

Total	96	36	132	**Total**	105	27	132

Reviewer's comments:

The applicant's determination of sensitization was based upon the product draft guidance criteria and the investigator's subjective opinion. FDA's clinical and statistical review teams' determination of sensitization was based upon the product draft guidance. Due to the applicant's subjective element of their sensitization determination, there were discrepancies in sensitization conclusions between the applicant and FDA:

Subjects (b) (6) (test, reference), (b) (6) (test), (b) (6) (test), (b) (6) (test), (b) (6) (test, reference), (b) (6) (test), (b) (6) (reference), (b) (6) (test, reference), (b) (6) (reference), (b) (6) (referen (b) (6) (reference), (b) (6) (reference), (b) (6) (reference), and (b) (6) (reference)

The applicant's explanations for these discrepancies in their 02/02/2016 ECD response were not clear. The subsequent 02/18/2016 ECD response did not clarify these discrepancies either. The applicant provided in their 02/18/2016 ECD response a post-hoc analysis using sensitization criteria based upon the 5 sensitization criteria in the product draft guidance. Three sensitization criteria were from the product guidance. One sensitization criterion was subject to the applicant's interpretation. One sensitization criterion modified from the product draft guidance.

- *Product draft guidance: "The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch." The applicant adhered to this criterion.*
- *Product draft guidance: "The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase." The applicant adhered to this criterion.*
- *Product draft guidance: "The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase." In the product draft guidance, "generally higher" is not clearly defined. Based on the sponsor's listing of potential sensitization (mptp-12130-statistical-1.pdf), the sponsor interpreted 'generally higher' as the average irritation score from the challenge/re-challenge phase being higher than the average irritation score from the induction phase. FDA has interpreted generally higher as the maximum irritation score from the challenge/rechallenge phase being higher than all irritation scores from the induction phase.*
- *Product draft guidance: "If a subject completed a Re-Challenge Phase, the above 3 criteria were met during* both *the Challenge Phase* and *the Re-Challenge Phase." Applicant's modified criterion for post hoc analysis: If the subject completed a Re-Challenge Phase, the above 3 criteria were met during* either *the Challenge Phase* or *the Re-Challenge Phase.*
- *Product draft guidance: "Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization." The applicant adhered to this criterion. Neither of the applicant's different sensitization criteria as listed above were deemed acceptable by the FDA's clinical and statistical review teams and the applicant's post-hoc analysis was not*

recognized by the FDA clinical review team. Per FDA Statistical Addendum Review dated 2/26/2016, "Post hoc analysis consists of choosing statistical methods and looking at the data - after the study has concluded – for patterns that are not specified a priori. The concern is that each time a pattern in the data is considered, a statistical test is effectively performed. This greatly inflates the total number of statistical tests and increases the likelihood that any finding is due to chance alone. A related concern is that once the data have been examined, analysis methods may then be chosen based on known properties of the methods that are more likely to give favorable results with the data values observed."

Adhesion Results

Table 19. Adhesion Analysis Results (MPTP-12130)

Applicant (N=100)*				**FDA (N=100)**			
NI Hypothesis	**LSmean**	**95%LB of** $U_T - 0.8U_R$	**Pass or Fail NI**	**NI Hypothesis**	**LSmean (std error)**	**95%UB of** $U_T - 1.25U$	**Pass or Fail NI**
H_0 (Inferior): $\frac{U_T}{U_R} < 0.8$ H_1(NonInferior) $\frac{U_T}{U_R} \geq 0.8$	TEST: 95.1 RLD: 91.2	22.1 (>0)	**Pass NI**	H_0 (Inferior): $\frac{U_T}{U_R} > 1.25$ H_1 (NonInferior): $\frac{U_T}{U_R} \leq 1.25$	TEST: 0.087 (0.025) RLD: 0.409 (0.042)	-0.5173 (<0)	**Pass NI**

*Source: Table 14.9 on page 78 in the sponsor's study report MPTP-12130.

Table 20. Frequency of Adhesion Scores at Each Time Point for TEST and RLD in the FPPPA Population (MPTP-12130)

Hr	TEST (N=100) n (%)						RLD (N=100) n (%)					
	Score 0	Score 1	Score 2	Score 3	Score 4	Mean	Score 0	Score 1	Score 2	Score 3	Score 4	Mean
1	95 (95)	5 (5)	0 (0)	0 (0)	0 (0)	0.05	82 (82)	16 (16)	2 (2)	0 (0)	0 (0)	0.20
3	90 (90)	10 (10)	0 (0)	0 (0)	0 (0)	0.10	68 (68)	30 (30)	2 (2)	0 (0)	0 (0)	0.34
5	87 (87)	13 (13)	0 (0)	0 (0)	0 (0)	0.13	57 (57)	41 (41)	2 (2)	0 (0)	0 (0)	0.45
7	86 (86)	14 (14)	0 (0)	0 (0)	0 (0)	0.14	46 (46)	51 (51)	3 (3)	0 (0)	0 (0)	0.57
9	85 (85)	15 (15)	0 (0)	0 (0)	0 (0)	0.15	42 (42)	55 (55)	2 (2)	1 (1)	0 (0)	0.62
All	443 (88.6)	57 (11.4)	0 (0)	0 (0)	0 (0)	0.11	295 (59.0)	193 (38.6)	11 (2.2)	1 (0.2)	0 (0)	0.44

Reviewer's Comments:

The adhesion study demonstrated that the test product adhesive performance is at least as good as that of the reference product by both the applicant's and FDA's statistical analyses.

2.4.3 Brief Statements of Skin Irritation, Sensitization, and Adhesion Conclusions

2.4.3.1 Irritation Conclusion

According to both the applicant's and FDA's analyses, Study MPTP-12130 (n=93) demonstrates that the irritation of the test product is non-inferior to the reference product.

2.4.3.2 Sensitization Conclusions

Among the 66 subjects of FDA's per-protocol population for sensitization (FPPSEN) in Study MPTP 12130, TEST has 13.7 more percentage point of subjects with potential sensitization than RLD (P_T=27.3%, P_R = 13.6%), with the one-sided 95% upper bound of 23.7% for the proportion difference between TEST and RLD: $P_T - P_R$.

Using the sponsor's interpretation of 'generally higher' (i.e., average irritation score):
Among the 66 subjects of FDA's per-protocol population for sensitization (FPPSEN) in Study MPTP 12130, TEST has 9.1 more percentage point of subjects with potential sensitization than RLD (P_T=50.0%, P_R = 40.9%), with the one-sided 95% upper bound of 18.5% for the proportion difference between TEST and RLD: $P_T - P_R$.

2.4.3.3 Adhesion Conclusions

The clinical data (Study MPTP-12130) demonstrate that the adhesive performance of Mylan's Methylphenidate patch is at least as good as that of the reference product, Daytrana®.

2.5 Comparative Review of Safety

2.5.1 Description of Adverse Events

2.5.1.1 Skin Irritation, Sensitization, and Adhesion Study (MPTP-12130)

This was an irritation evaluator blinded, multiple-dose, randomized application site, 2-treatment, 3-phase study of the human dermal safety of a formulation of Mylan's methylphenidate transdermal system, 10 mg/9 hours to Daytrana® patch, 10 mg/9 hours following administration of multiple transdermal doses of 10 mg/9 hours (1 × 10 mg/9 hours patch applied to both sides of the hip) in 100 healthy, adult subjects. Each subject applied both a test and reference patch simultaneously for a 2-3-day wear cycle per application for a total of 9 applications (21 days of Induction Phase), followed by a 15-day Rest phase of no application and subsequent 48-hr Challenge phase of one application.

Eight-five subjects experienced a total of 816 AEs over the course of the study. Adverse events were mild to moderate in intensity. No SAEs were reported.

No deaths, other serious adverse events, or other significant adverse events occurred over the course of the study. Twenty-one subjects were discontinued because of adverse events. Seventeen subjects were discontinued due to skin events, with all seventeen of these subjects having the skin events with both the test and reference products simultaneously.

Both the test and reference product exhibited comparable application site adverse events. The most frequently reported application site adverse events (AEs) were application site pruritus (Test 52%, RLD 56%).

For those AEs that could not be attributed to either test or reference product, the most frequently reported AE was insomnia which was reported by 13/100 (13.0%) subjects. There were 80 AEs that were unable to be attributed to a specific treatment. Of these AEs, there were 45 AEs (adverse drug reaction, aggression, anxiety, application site discoloration, blood pressure increased, chest pain [2], dizziness [2], dyspnea, eczema, euphoric mood, hypersensitivity, influenza, insomnia [20], nausea [2], palpitations [2], pruritus generalized, rash generalized, rash papular, restlessness [2], urticaria, and vomiting) considered probably related, 18 AEs (decreased appetite, diarrhea, dizziness, dry mouth, dyspnea [2], headache [10], nausea, and vomiting) considered possibly related, 5 AEs (abdominal pain, diarrhea, laryngitis, and vomiting [2]) considered unlikely related, and 12 AEs (chills, cyst, fatigue, gastroenteritis viral [2], hot flush, hypokalemia, nasopharyngitis, oropharyngeal pain, upper respiratory tract infection, urinary tract infection, and vomiting) considered unrelated/not related to the application of the test or reference product.

The pregnancy screen at the screening visit, each check-in, and study exit was negative for all female subjects over the course of the study with the exception of Subject (b) (6) Subject (b) (6) was discontinued by the Investigator after Day 18 activities due to skin evaluation. Subject (b) (6) completed exit procedures on (b) (6) and had an elevated serum β-HCG value of 5207.70 mIU/mL (reference range <5.00 mIU/mL). The elevated value was confirmed on (b) (6) with a value of 13063.00 mIU/mL. Subject (b) (6) underwent an elective termination of the pregnancy on (b) (6) Subject (b) (6) was included in the irritation and adhesion analyses and excluded from the sensitization analysis.

Reviewer's Comment:

- *This applicant recorded the application erythema, and application site irritation as AEs, whereas application erythema and application site irritation were usually recorded as irritation reaction instead of AEs in skin irritation and sensitization studies. That is one of the reason that more than eight hundred AEs were identified in the study.*
- *Both the test and reference product exhibited comparable application site adverse events. The most common application site adverse events (AEs) are application site pruritus (Test 52%, RLD 56%).*
- (b) (4)

Table 21. Adverse Events: Test Product

Treatment A: Adverse Events N = 100[a]										
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
General disorders and administration site conditions	Application site erythema	1 (1.00%) (b) (6)	0	59 (59.00%) (b) (6)	0	0	0	145	0	145
	Application site irritation	4 (4.00%) (b) (6)	0	35 (35.00%) (b) (6)	0	0	0	71	0	71

Table 21. Adverse Events: Test Product, continued

		Treatment A: Adverse Events N = 100[a]								
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
General disorders and administration site conditions	Application site pain	13 (13.00%) (b) (6)	0	0	0	0	0	14	0	14
	Application site pruritus	52 (52.00%) (b) (6)	0	0	0	0	0	84	0	84
	Application site swelling	2 (2.00%) (b) (6)	0	0	0	0	0	2	0	2
	Application site warmth	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
Skin and subcutaneous tissue disorders	Pruritus	0	3 (3.00%) (b) (6)	0	0	0	0	0	3	3

Table 21. Adverse Events: Test Product, continued

		Treatment A: Adverse Events N = 100[a]								
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
Skin and subcutaneous tissue disorders	Rash	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
Total Number of AEs reported		108	3	210	0	0	0	318	3	321
Total Number of Subjects Reporting at Least 1 AE by Intensity and Relationship		56	3	62	0	0	0			
Total Number of Subjects Reporting At Least One AE Over the Course of the Study								69	3	70[d]

[a] = Number of subjects dosed with Treatment

[b] = Total number of subjects reporting at least 1 incidence of respective AE
(%) percentage of subjects reporting at least 1 incidence of respective AE
Subject numbers of subjects reporting at least 1 incidence of respective AE
Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated AE experienced by that subject

[c] = Total number of reported AEs

[d] = There were 2 subjects who experienced both related and unrelated AEs

MedDRA Version 15.1; Treatment A: Methylphenidate Transdermal System, 10 mg/9 hours, (Lot No.: R6D0023)

Table 22. Adverse Events: Reference Product

		Treatment B: Adverse Events N = 100[a]								
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
General disorders and administration site conditions	Application site discharge	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
	Application site dryness	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
	Application site erythema	3 (3.00%) (b) (6)	0	61 (61.00%) (b) (6)	0	0	0	161	0	161

Table 22. Adverse Events: Reference Product, continued

		Treatment B: Adverse Events N = 100[a]								
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
General disorders and administration site conditions	Application site irritation	8 (8.00%) (b) (6)	0	59 (59.00%) (b) (6)	0	0	0	108	0	108
	Application site pain	19 (19.00%) (b) (6)	0	0	0	0	0	21	0	21

Table 22. Adverse Events: Reference Product, continued

		Treatment B: Adverse Events N = 100[a]								
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
General disorders and administration site conditions	Application site pruritus	56 (56.00%) (b) (6)	0	0	0	0	0	108	0	108
	Application site swelling	2 (2.00%) (b) (6)	0	0	0	0	0	2	0	2
	Application site warmth	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
Skin and subcutaneous tissue disorders	Pruritus	0	11 (b) (6)	0	0	0	0	0	11	11

Table 22. Adverse Events: Reference Product, continued

		Treatment B: Adverse Events N = 100[a]								
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
Skin and subcutaneous tissue disorders	Rash	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
Total Number of AEs reported		147	11	257	0	0	0	404	11	415
Total Number of Subjects Reporting at Least 1 AE by Intensity and Relationship		62	11	70	0	0	0			
Total Number of Subjects Reporting At Least 1 AE Over the Course of the Study								78	11	79[d]

[a] = Number of subjects dosed with Treatment

[b] = Total number of subjects reporting at least 1 incidence of respective AE
(%) percentage of subjects reporting at least 1 incidence of respective AE
Subject numbers of subjects reporting at least 1 incidence of respective AE
Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated AE experienced by that subject

[c] = Total number of reported AEs

[d] = There was 1 subjects who experienced both related and unrelated AEs

MedDRA Version 15.1; Reference Product (Treatment B): Daytrana® Patches 10 mg over 9 hours (Lot No.: 59375, Exp. Date: 03-2013 and Lot No.: 62073, Exp. Date: 09-2013)

Table 23. Adverse Events Unable to be Attributed to Either Test or Reference Product

Adverse Events Unable to be Attributed to Either Treatment A or Treatment B N = 100[a]										
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
Cardiac disorders	Palpitations	2 (2.00%) (b) (6)	0	0	0	0	0	2	0	2
Gastrointestinal disorders	Abdominal pain	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
	Diarrhoea	1 (1.00%) (b) (6)	1 (1.00%) (b) (6)	0	0	0	0	1	1	2
	Dry mouth	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
	Nausea	3 (3.00%) (b) (6)	0	0	0	0	0	3	0	3
	Vomiting	0	0	2 (2.00%) (b) (6)	2 (2.00%) (b) (6)	0	0	2	3	5
General disorders and administration site conditions	Adverse drug reaction	0	0	1 (1.00%) (b) (6)	0	0	0	1	0	1
	Application site discolouration	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
	Chest pain	1 (1.00%) (b) (6)	0	0	0	0	0	2	0	2

Table 23. Adverse Events Unable to be Attributed to Either Test or Reference Product, continued

Adverse Events Unable to be Attributed to Either Treatment A or Treatment B N = 100[a]										
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
General disorders and administration site conditions	Chills	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
	Cyst	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
	Fatigue	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
Immune system disorders	Hypersensitivity	0	0	1 (1.00%) (b) (6)	0	0	0	1	0	1
Infections and infestations	Gastroenteritis viral	0	2 (2.00%) (b) (6)	0	0	0	0	0	2	2
	Influenza	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
	Laryngitis	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
	Nasopharyngitis	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
	Upper respiratory tract infection	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
	Urinary tract infection	0	0	0	1 (1.00%) (b) (6)	0	0	0	1	1

Table 23. Adverse Events Unable to be Attributed to Either Test or Reference Product, continued

Adverse Events Unable to be Attributed to Either Treatment A or Treatment B N = 100[a]										
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
Investigations	Blood pressure increased	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
Metabolism and nutrition disorders	Decreased appetite	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
	Hypokalaemia	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
Nervous system disorders	Dizziness	2 (2.00%) (b) (6)	0	1 (1.00%) (b) (6)	0	0	0	3	0	3
	Headache	7 (7.00%) (b) (6)	0	0	0	0	0	10	0	10
Psychiatric disorders	Aggression	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
	Anxiety	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1
	Euphoric mood	1 (1.00%) (b) (6)	0	0	0	0	0	1	0	1

Table 23. Adverse Events Unable to be Attributed to Either Test or Reference Product, continued

Adverse Events Unable to be Attributed to Either Treatment A or Treatment B N = 100[a]										
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
Psychiatric disorders	Insomnia	13 (b) (6)	0	0	0	0	0	20	0	20
	Restlessness	1 (1.00%) (b) (6)	0	0	0	0	0	2	0	2
Respiratory, thoracic and mediastinal disorders	Dyspnoea	2 (2.00%) (b) (6)	0	1 (1.00%) (b) (6)	0	0	0	3	0	3
	Oropharyngeal pain	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
Skin and subcutaneous tissue disorders	Eczema	0	0	1 (1.00%) (b) (6)	0	0	0	1	0	1
	Pruritus generalised	0	0	1 (1.00%) (b) (6)	0	0	0	1	0	1
	Rash generalised	0	0	1 (1.00%) (b) (6)	0	0	0	1	0	1
	Rash papular	0	0	1 (1.00%) (b) (6)	0	0	0	1	0	1

Table 23. Adverse Events Unable to be Attributed to Either Test or Reference Product, continued

Adverse Events Unable to be Attributed to Either Treatment A or Treatment B N = 100[a]										
		Subjects Who Experienced Indicated AE at Least Once by Intensity and Relationship[b]						Total No. of AEs[c]		
		Mild		Moderate		Severe		Total		
System Organ Class	Preferred Term	Related	NR	Related	NR	Related	NR	Related	NR	Overall
Skin and subcutaneous tissue disorders	Urticaria	0	0	1 (1.00%) (b) (6)	0	0	0	1	0	1
Vascular disorders	Hot flush	0	1 (1.00%) (b) (6)	0	0	0	0	0	1	1
Total Number of AEs reported		52	13	11	4	0	0	63	17	80
Total Number of Subjects Reporting at Least 1 AE by Intensity and Relationship		20	9	8	3	0	0			
Total Number of Subjects Reporting At Least 1 AE Over the Course of the Study								25	10	32[d]

[a] = Number of subjects who received Treatments A and B

[b] = Total number of subjects reporting at least 1 incidence of respective AE
(%) percentage of subjects reporting at least 1 incidence of respective AE
Subject numbers of subjects reporting at least 1 incidence of respective AE
Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated AE experienced by that subject

[c] = Total number of reported AEs

[d] = There were 3 subjects who experienced both related and unrelated AEs

MedDRA Version 15.1; Test Product (Treatment A): Methylphenidate Transdermal System 10.4 mg Methylphenidate per 9.6 cm^2; Target: 10 mg/9 hrs (Lot No.: R6D0023; Mfg. Date: APR 2012) and Reference Product (Treatment B): Daytrana® Patches 10 mg over 9 hours (Lot No.: 59375, Exp. Date: 03-2013 and Lot No.: 62073, Exp. Date: 09-2013)

2.5.2 Brief Statement of Safety Conclusions

Both the test and reference product exhibited comparable application site reactions. The most common application site adverse event (AE) is application site pruritus (Test 52%, RLD 56%).

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Office of Study Integrity and Surveillance

Inspection is pending.

2.6.2 Office of Biostatistics

The FDA statistical review (by Wanjie Sun, Ph.D., Completed on 01/15/2016 (original review) & 02/26/2016 (addendum)) had the following conclusions:

Irritation

The non-inferiority of the test product, Methylphenidate Transdermal Systems 10mg/9 hours (3.3 mg/hr) manufactured by Mylan Technologies Inc. versus the reference product, Daytrana® Transdermal System, 3.3 mg/hr manufactured by Noven Pharms Inc.) was established in irritation based on the primary endpoint – mean irritation score across visits, among the 92 FPPIRR subjects in Study MPTP-12130.

Sensitization

In summary, among the 66 subjects of FPPSEN in Study MPTP 12130, TEST has 13.7 more percentage point of subjects with potential sensitization than RLD (P_T =27.3%, P_R = 13.6%), with the one-sided 95% upper bound of 23.7% for the proportion difference between TEST and RLD: $P_T - P_R$.

1) Post-hoc analyses are generally not acceptable. Post hoc analysis consists of choosing statistical methods and looking at the data - after the study has concluded – for patterns that are not specified a priori. The concern is that each time a pattern in the data is considered, a statistical test is effectively performed. This greatly inflates the total number of statistical tests and increases the likelihood that any finding is due to chance alone. A related concern is that once the data have been examined, analysis methods may then be chosen based on known properties of the methods that are more likely to give favorable results with the data values observed.

2) Although the FDA guidance did not explicitly interpret 'generally higher', it did clearly specify that "*If the subject completed a re-challenge phase, the above 3 criteria met during **both** the challenge **and** the re-challenge phases".* Based on the sponsor's listing of potential sensitization (mptp-12130-statistical-1.pdf), the sponsor used a criterion of "*3 criteria met during **either** the challenge **or** the re-challenge phases"*, which does not follow the FDA's guidance for methylphenidate.

3) The sponsor's post hoc statistical analysis tested whether the mean irritation score of the test product (TEST) is non-inferior to that of the reference listed drug (RLD) during the challenge phase and the re-challenge phase, respectively. However, in the FDA guidance, the primary endpoint is potential sensitization rather than the mean irritation score. NI tests of TEST vs RLD in the mean irritation score during the challenge and re-challenge phases do not address whether the TEST is no more sensitizing than the RLD. Therefore, the sponsor's statistical analysis is not appropriate by using a primary endpoint which does not follow the FDA guidance for methylphenidate.

Adhesion

The non-inferiority of the test product, Methylphenidate Transdermal Systems 10mg/9 hours (3.3 mg/hr) manufactured by Mylan Technologies Inc. versus the reference product, Daytrana® Transdermal System, 3.3 mg/hr manufactured by Noven Pharms Inc.) was established in adhesion based on the primary endpoint – mean adhesion score across visits, among the 100 FPPPA subjects in Study MPTP-12130.

Reviewer's Comment:
This reviewer agrees with the FDA Statisticians' conclusions.

2.7 Formulation

2.7.1 Product Design

2.7.1.1 RLD Product Design[5]

(b) (4)

2.7.1.2 Generic Product Design[6]

Reviewer's comments:

The applicant's generic patch design is different as the RLD by adding skin contact adhesive layer to the drug reservoir matrix. It could be a potential formulation issue to cause different sensitization reaction between the test product vs. RLD.

2.7.2 Components and Composition

2.7.2.1 RLD Components and Composition[7]

The RLD Components and Composition is provided below.

[6] \\cdsesub1\evsprod\anda206497\0000\m3\32-body-data\32p-drug-prod\mptp-td-p-mti\32p1-desc-comp\description-and-composition.pdf
[7] \\cdsesub1\evsprod\nda021514\0185\m3\32-body-data\32p-drug-prod\mts-transdermal-patch-all-strengths\32p1-desc-comp\specification-102298-release-r.pdf

Table 24. Qualitative Composition of Methylphenidate Transdermal System

Component	Trade Name	Function
Adhesive Containing Methylphenidate		
Methylphenidate (b) (4)		Active
Silicone Adhesive	(b) (4)	
Acrylic Adhesive		
(b) (4)		
Backing		
Polyester/ethylene vinyl acetate film laminate		
(b) (4)		
Protective Liner* **		
(b) (4)		
(b) (4)		

Table 25. Quantitative Composition of Methylphenidate Transdermal System

		Patch size (cm^2)					
Adhesive Containing Methylphenidate	per cm^2	(b) (4)	12.5	18.75	25	37.5	(b) (4)
Ingredient		Theoretical mg per stated cm^2*					
Methylphenidate (b) (4)							
Silicone Adhesive (b) (4)							
Acrylic Adhesive (b) (4)							
(b) (4)							
Total Weight							
(b) (4)							

2.7.2.2 Generic Components and Composition

Table 26. Generic Components and Composition

Components	Intermediate Laminate Composition		Finished Product mg/ system (area)			
	% w/w	g/m²	10 mg/ 9 hours (9.6 cm²)	15 mg/ 9 hours (14.4 cm²)	20 mg/ 9 hours (19.2 cm²)	30 mg/ 9 hours (28.8 cm²)
Solid Matrix Reservoir Layer						
Methylphenidate	(b) (4)					
Hydrophobic Colloidal Silica NF (b) (4)						
(b) (4) Mineral Oil NF (b) (4)						
Polyisobutylene Adhesive (b) (4)						
(b) (4)						
Solid Matrix Reservoir Subtotal	100.00%					(b) (4)
Skin Contact Adhesive Layer						
Hydrophobic Colloidal Silica NF (b) (4)						(b) (4)
(b) (4) Mineral Oil NF (b) (4)						
Polyisobutylene Adhesive (b) (4)						
(b) (4)						
Skin Contact Adhesive Subtotal	100.00%					(b) (4)
Backing, Release Liner, Printing Ink						
Ethylene-Vinyl Acetate (b) (4) Polyester Film (b) (4)						(b) (4)
(b) (4) Fluoropolymer-Coated Polyester Release Liner (b) (4)						
White Ink (b) (4)						

Reviewer's Comments:

The test product contains hydrophobic colloidal silica as the inactive ingredient which is not listed in the CDER's Inactive Ingredient Guidance (IIG) for FDA-Approved Drug Products. Based upon the DCR consult, the Division of Bioequivalence II determined the amount of hydrophobic colloidal silica was not a safety concern. The Division of Bioequivalence II deemed the applicant's test product formulation to be acceptable.

The test formulation is formulated using polyisobutylene adhesive (b) (4) *adhesive and mineral oil while the RLD uses a mixture of acrylic and silicone adhesives. Per chemistry*

reviewer, (b) (4) *This could be a potential issue to cause the sensitization reaction difference between the Test and RLD that we observed in the skin irritation, sensitization and adhesion study (Study MPTP012130).*

2.8 Conclusion and Recommendation

2.8.1 Conclusion

The clinical data (MPTP-12130) submitted to ANDA 206497 are adequate to support that the skin irritation potentials of Mylan's Methylphenidate Transdermal System are no worse than that of Daytrana®. The clinical data (MPTP-12130) do not demonstrate minimal potential of the test product to induce sensitization compared to the reference product. The clinical data (MPTP-12130) demonstrate that the adhesive performance of Mylan's Methylphenidate Transdermal System is at least as good as that of the RLD, Daytrana®.

2.8.2 Recommendations

DCR does not recommend approval of this application.

3 CLINICAL COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has completed its review and the following major deficiency have been identified for Skin irritation, Sensitization and Adhesion study (Study MPTP 12130):

> Study MPTP 12130 did not provide adequate data to ensure that the sensitization potential of the proposed generic methylphenidate transdermal system (Test) is no worse than that of the reference listed drug product (RLD).
>
> We do not agree with your numbers of subjects sensitized or potentially sensitized to each product. When we applied the four criteria described in the FDA product-specific bioequivalence guidance to your data,[8] of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the Test product and the RLD, respectively, with 100% more Test sites than reference sites showing potential sensitization.
>
> We noted that you interpreted the term *generally higher* in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we considered it reasonable and reevaluated your data using your interpretation. Using your interpretation of *generally higher*, 33 Test versus 27 RLD skin sites showed potential sensitization. The proportions are 50% for Test versus 40.9% for RLD, with 22% more Test sites than RLD sites showing sensitization.
>
> The point estimate for the proportion of skin sites showing potential sensitization was higher for the Test product compared with the RLD regardless of which interpretation of *generally higher* we used.
>
> We note that there are several formulation differences between your product and the RLD, which makes a difference in potential sensitization biologically plausible.

[8] Draft Guidance on Methylphenidate Film, Extended Release/Transdermal *Recommended Jul 2010* http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm220196.pdf

4 APPENDIX

Recommendation to FDA statistician from DCR (12/21/2015)
Methylphenidate Transdermal System, 10mg/9hrs, 15mg/9hrs, 20mg/9hrs, & 30mg/9hrs

On 12/15/2015, DCR recommended no subject adjustments. Following communication with the FDA statistical reviewer, DCR agrees with the FDA statistical reviewer to exclude subject (b) (6) from the irritation and sensitization analyses. DCR has no further recommended changes to the irritation PP population and sensitization PP population. DCR agrees with the applicant's adhesion PP population.

ANDA #	Study #	PP subject adjustment requested (yes/no)	Subject number	Reason for inclusion/exclusion	Comments
206497	MPTP-12130	yes; remove from irritation PP population and sensitization PP population	(b) (6)	Subject (b) (6) Visit 10 irritation data was missing, so the subject test and reference patches were absent for 2 days in induction.	This combined irritation, sensitization, and adhesion study is requested for statistics review.

DCR recommends not to perform detailed reviews on the following studies:

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
MPTP-11030 - Single-Dose Pilot Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fed BE	(b) (4)
MPTP-11007 - Comparative Evaluation of the Cumulative Irritation of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) following a 48 to 72 hour Wear in Healthy Adult Volunteers	Cumulative Irritation Study (n=32)	(b) (4)

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
MPTP-11125 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fasting Bioequivalence	Overlay is allowed
MPTP-12012 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fasting Bioequivalence	The applicant evaluated irritation. However, the study duration is only for 9 hours.
MPTP-12046 - Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Shire) in Healthy Adult Volunteers	Cumulative Irritation and Sensitization (n=100)	The sponsor noted data integrity issue and deficiencies in procedure by Novum Pharmaceutical Research Service. Due to data integrity issue, not recommended for the review.

DIVISION OF CLINICAL REVIEW FILING REVIEW DETERMINATION
FOR APPLICATION COMPLETENESS
(SKIN IRRITATION/SENSITIZATION/ADHESION STUDY)
AMENDMENT

ANDA#	206497
DRUG NAME	Methylphenidate Transdermal Extended Release Film, 10mg/9hr (1.1 mg/hr), 15mg/9hr (1.6 mg/hr), 20mg/9hr (2.2 mg/hr), & 30mg/9hr (3.3 mg/hr)
DOSAGE FORM	Film, Extended Release
APPLICANT NAME	Mylan Technologies, Inc.
REFERENCE LISTED DRUG (RLD)#	NDA 021514
DRUG NAME	Daytrana® Methylphenidate Transdermal Extended Release Film, 30mg/9hr (3.3 mg/hr)
DOSAGE FORM	Film, Extended Release
APPLICANT	Noven Pharms Inc.
APPROVAL DATE	4/6/2006
PRIMARY REVIEWER	Ying Fan, Ph. D. Clinical Reviewer Division of Clinical Review Office of Bioequivalence Office of Generic Drugs
SECONDARY REVIEWER	Carol Y. Kim, Pharm. D. Acting Team Leader, ANDA Team Division of Clinical Review Office of Bioequivalence Office of Generic Drugs
REQUESTED BY	Susan E. Polifko Division of Filing Review Office of Generic Drugs
REQUESTED DATE	9/1/2014
GOAL DATE FOR FILING REVIEW	10/1/2014

Summary of Findings by Division of Clinical Review (By Both DCR and Statistical Reviewers)	
Skin irritation/sensitization/adhesion study: Clinical Section ___ Complete _x_ Incomplete	[1] From DCR perspective, the application is acceptable to be received as an ANDA. Please see comments to be conveyed to the applicant for additional information requested for the review. DB II previously recommended acceptable for filing from their perspective.

RECOMMENDATION FROM DCR PERSPECTIVE:
X_ACCEPTABLE __NOT ACCEPTABLE

1 Any filing deficiencies to be communicated to the applicant will be listed under appropriate heading at the end of the review.

Reference ID: 3630655

Item Verified:	YES	NO	Comments
Response to "Refuse to File" deficiencies dated 5/15/2014	X		\\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf Page 1-11 Responses to comments # 1-7, 10-14 are acceptable for the review , however, responses to comments #8 and 9 **are not acceptable** for the review as shown below: 1. Adverse events in a SAS dataset (.xpt file) for Study MPTP-12130 was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\12130-ae.xpt 2. Concomitant medications in a SAS dataset (.xpt file) for Study MPTP-12130 was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\12130-cm.xpt 3. The frequency table for proportion of subjects with a meaningful degree of detachment for Study MPTP-12130 was provides as requested. \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf (page 3) 4. The frequency table for mean days until removed or moved due to a significant irritation during induction period for Study MPTP-12130 was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf (page 4) 5. The frequency table for combined irritation scores (irritation and other effect scores) during re-challenge Period for Study MPTP-12130 was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf (page 4) 6. Adhesion evaluation result (the summary of adhesion analysis) for Study MPTP-12130 demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the reference product is less than or equal to 0 as recommended in the draft guidance for this product was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf (page 5) 7. The description and composition of Study MPTP-12130 test product Lot R6D0023 was provided and indicated that it was consistent with that described in section "3.2.P.1 Description and Composition" as requested. \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf (page 6) 8. A list of subjects included in the evaluable population per treatment for adhesion analysis in a SAS .xpt file for Study MPTP-11030 was not provided (see Reviewer's Comments #1 below). 9. A list of subjects excluded from the evaluable population per treatment (if any) and reason for exclusion for adhesion analysis in a SAS .xpt file for Study MPTP-11030 was not provided (see Reviewer's Comments #1 below). 10. Adverse events in a SAS .xpt file for Study MPTP-11030 was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-ae.xpt 11. Concomitant medications in a SAS .xpt file for Study MPTP-11030 was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-cm.xpt 12. Adhesion scores in a SAS xpt file for Study MPTP-11030 was provided as requested.

Item Verified:	YES	NO	Comments
			\\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-adhe-r.xpt ***13.*** Adhesion evaluation result (the summary of adhesion analysis) for Study MPTP-11030 demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the RLD (30 mg/9 hours) is less than or equal to 0 as recommended in the draft guidance for this product was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf (page 8) 14. Table with proportion of subjects with meaningful degree of detachment for Study MPTP-11030 was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf (page 9) 15. The description and composition of Study MPTP-11030 test product Treatments A (Lot R6C0003) and B (Lot R6C0004) was provided as requested. \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf (page 11) ***Reviewer's Comments:*** *1. Per DCR review dated 2/14/2014 in DARRTS by Dr. Sunny Y. Tse, #8 and #9 of "Comments to be conveyed to the sponsor" were referred to Study MPTP-11030 (adhesion analysis). However, in the "refused to receive letter" dated 5/15/2014 in DARRTS by Timothy G. Jetton, #8 and #9 of "The following additional information is requested for the review" were referred to Study MPRP-12130, which was not consistent to the DCR filing review comments. As a result, the applicant did not submit the data set for Study MPRP-11030. Therefore, the data set for Study MPRP-11030 is requested for the review.* *2. The applicant indicated that two test formulations (lot R6C0003 and R6C0004) used in the Study MPTP-11030* (b) (4) *Any information from this study will be considered supportive.* *3. Per statistical filing review dated 9/16/2014, other datasets submitted for the Study MPTP-11030 (adhesion analysis) are acceptable for the statistical review.*

Comments to be conveyed to the applicant:

From Both DCR and STAT perspectives, comments to be conveyed to the applicant:	From DCR perspective, your application is acceptable to be received as an ANDA. The following additional information is requested for the review of the study (MPTP-11030): 1. A list of subjects included in the evaluable population per treatment for adhesion analysis in a SAS. xpt file for Study MPTP-11030 (adhesion analysis). **2.** A list of subjects excluded from the evaluable population per treatment (if any) and reason for exclusion for adhesion analysis in a SAS .xpt file for Study MPTP-11030 (adhesion analysis).

Attachment: Statistical Filing Review (in DARRTS 09/16/2014)

STATISTICAL FILLING REVIEW AMENDMENT

ANDA	**206497**
DRUG NAME	**Methylphenidate**
APPLICANT NAME	**Mylan Technologies Inc.**
REFERENCE LISTED DRUG (RLD)	**Daytrana® 10mg (releasing 10 mg/9 hours), Noven Pharmaceuticals Inc**
***Primary* REVIEWER**	**Guoying Sun**
***Secondary* REVIEWER**	**Stella Grosser**
DATE	9/12/2014

RECOMMENDATION TO DCR FROM A STATISTICAL PERSPECTIVE	
ACCEPTABLE	X
NOT ACCEPTABLE	

Reviewed by:

Guoying Sun, Ph.D.
Primary Reviewer Generic Team, DBVI/OB/OTS/CDER

Stella Grosser, Ph.D., Team Leader
Secondary Reviewer Generic Team, DBVI/OB/OTS/CDER

DBVI/OB Response to Sponsor's Resubmission after Refuse to Receive:

The adhesion data from study MPTP-11030 is acceptable.

As indicated in the original filing review, the data from study MPTP-12130 are acceptable for statistical review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YING FAN
09/19/2014

CAROL Y KIM
09/19/2014

DIVISION OF CLINICAL REVIEW CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA#	206497
DRUG NAME	Methylphenidate Transdermal System, 10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
DOSAGE FORM	Transdermal System
APPLICANT NAME	Mylan Technologies, Inc.
REFERENCE LISTED DRUG (RLD)	Daytrana® Transdermal System, 3.3 mg/hr, Noven Pharms Inc.
NDA	021514
PRIMARY REVIEWER	Sunny Tse, Ph.D. Division of Clinical Review Office of Generic Drugs
SECONDARY REVIEWER	Carol Y. Kim, PharmD. Division of Clinical Review Office of Generic Drugs
TERTIARY REVIEWER	John R. Peters, M.D. Director Division of Clinical Review Office of Generic Drugs
REQUESTED BY	Edward Washington Regulatory Support Team Office of Generic Drugs
REQUESTED DATE	12/23/2013

Summary of Findings by Division of Clinical Review	
Clinical Endpoint Study: Clinical Section: Complete ___ Incomplete	
Skin irritation/sensitization/adhesion study: Clinical Section: Complete X__Incomplete	**From DCR perspective, skin irritation/sensitization/adhesion data (study MPTP-12130) and adhesion data from the study (MPTP-11030) are not acceptable for the review. The final acceptability of the filing review of this product is deferred to the DB II). Please see comments to be conveyed to sponsor.**
Waiver request for BE study requirements: Clinical Section: ___ Complete Incomplete	

RECOMMENDATION: ____ACCEPTABLE _X_NOT ACCEPTABLE

Reference ID: 3454112

	Irritation/ Sensitization/ Adhesion (#MPTP-12130)		Adhesion from a PK study (#MPTP-11030)		
Item Verified:	**YES**	**NO**	**YES**	**NO**	**Comments**
Protocol	X		X		Protocol #MPTP-12130 & MPTP-11030
Summary of Study	X		X		
Clinical Site (s)	X		X		
Study Investigator (s)	X		X		
List of subjects included in Evaluable population per treatment (SAS .xpt)	X			X	MPTP-11030: The sponsor should provide a list of subjects included in the evaluable population per treatment in a SAS .xpt.
List of subjects excluded/ from Evaluable population per treatment (SAS .xpt)	X			X	MPTP-11030: The sponsor should provide a list of subjects excluded from the evaluable population per treatment in a SAS .xpt.
Reason for exclusion from Evaluable population per treatment (SAS .xpt)	X			X	MPTP-11030: The sponsor should provide reason for subject exclusion from the evaluable population in a SAS .xpt.
Reasons for discontinuation from the study if discontinued (SAS .xpt)	X			X	MPTP-11030: No subjects were discontinued.
Adverse Events (SAS .xpt)		X		X	MPTP-12130 & MPTP-11030: The sponsor should provide adverse events included in a SAS .xpt file. It is available only in .pdf file.
Concomitant Medications		X		X	MPTP-12130 & MPTP-11030:

Reference ID: 3454112

(SAS .xpt)					The sponsor should provide concomitant medications included in a SAS .xpt file.
Individual subject's scores/data per visit (SAS .xpt)	X			X	MPTP-11030: The sponsor should provide individual subjects' adhesion scores/data per visit in a SAS .xpt file.
Pre-screening of Patients	X		X		
IRB Approval	X		X		
Consent Forms	X		X		
Randomization Schedule	X		X		
Protocol Deviations	X		X		
Case Report Forms	X		X		
Primary data in SAS .xpt file	X			X	MPTP-12130: See statistical filing review for details MPTP-11030: The sponsor should provide adhesion data in SAS .xpt file
Study Results	X		X		
Clinical Raw Data/ Medical Records	X		X		
Composition	X		X		
Financial Disclosure	X		X		
BioStudy Lot Numbers	X		X		
Date of Manufacture	X		X		
Exp. Date of RLD	X		X		
Statistical Reports	X		X		
Summary results provided by the firm indicate no worse skin irritation,	X			X	MPTP-12130: See comments below for details. MPTP-11030:

adhesion, and sensitization properties of the test product compared to that of the RLD					The sponsor should provide summary results indicating no worse adhesion of the test products compared to that of the RLD
Waiver requests for other strengths / supporting data	X		X		10 mg/9 hrs (1.1 mg/hr), 15 mg/9 hrs (1.6 mg/hr), and 20 mg/9 hrs (2.2 mg/hr) The final acceptability of the waiver requests of this product is deferred to the DB II.

Comments NOT to be conveyed to the sponsor

The draft guidance of this product is available on the website as follows:

Drug Product	Posted Date	Website
Methylphenidate Film, Extended Release/Transdermal	7/2010	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UC220196.pdf

Sponsor's ANDA 206497 included the following studies:

STUDY NUMBER AND TITLE	STUDY SUB TYPE	DOSAGE	Comments
MPTP-11030 - Single-Dose Pilot Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fed BE		The sponsor should provide adhesion scores in a SAS dataset for DCR statistical review.
MPTP-12130- Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Noven) in Healthy Adult Volunteers	Cumulative Irritation/sensitization/ and adhesion study (n=100)		
MPTP-11007 - Comparative Evaluation of the Cumulative Irritation of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) following a 48 to 72 hour Wear in Healthy Adult Volunteers	Cumulative Irritation Study (n=32)	29 mm^2 die-cut of each treatment worn every 48-72 hours for 21 consecutive days	Adhesion data cannot be evaluated due to patch reinforcement.
MPTP-11125 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult	Fasting Bioequivalence	1 × 30 mg/9 hours patch worn for 9 hours	

Volunteers			
MPTP-12012 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fasting Bioequivalence	1 × 30 mg/9 hours patch worn for 9 hours	
MPTP-12046 - Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Shire) in Healthy Adult Volunteers	Cumulative Irritation and Sensitization (n=100)	Nine applications of a 1 ×10 mg/9 hours patch of each treatment worn simultaneously; changed every 48-72 hours over a 21 day period; after rest phase, 1 × 10 mg/9 hours patch worn for 48 hours	The sponsor noted data integrity issue and deficiencies in procedure by Novum Pharmaceutical Research Service. Due to data integrity issue, not recommended for the review.

Reviewer's Comment: *Per 1/19/14 DB II filing review, the sponsor's data are complete and acceptable for the review from DB II perspective.*

1. **Skin irritation/sensitization/adhesion study MPTP-12130 is not acceptable for the review due to missing dataset.**

Key elements	Sponsor's study design	Comments
Study number	MPTP-12130	
During Induction		
Study drugs	**Test:** Methylphenidate Transdermal System, 10 mg/9 hours (Mylan Technologies Inc.) **Reference:** Daytrana®, 10 mg/9 hours (Manufactured for: Noven Therapeutics, LLC)	
Patch size	**Test:** 9.6 cm^2 **Reference:** 12.5cm^2	
Patch application frequency	Total of 9 applications 3 times per week; For example on Monday, Wednesday, and Friday (e.g., Days 1, 3, 5, 8, 10, 12, 15, 17, and 19) to the same sites	
Application location	Skin on the hip	
Simultaneous application on the same subject or parallel	Both test and reference products were applied simultaneously to each subject at different sites on the hip.	
Application duration	48-72 hours for 21 days	
Overlay or reinforcement tape used	Yes, except for the first 9 hours	(b) (4) Soft Cloth Surgical Tape (b) (4) was applied to 2 edges of each dermal patch at the time of every application except for the first 9 hours of the first application.
Irritation score evaluation time points	On Days 3, 8, 10, 12, 15, 17, 19, 21	
Rest period (days)	15 days	
During challenge		
Study drugs	**Test:** Methylphenidate Transdermal System, 10 mg/9 hours (Mylan Technologies Inc.) **Reference:** Daytrana®, 10 mg/9 hours (Manufactured for: Noven Therapeutics, LLC)	
Patch size	**Test:** 9.6 cm^2 **Reference:** 12.5cm^2	
Application location	a clean, dry area of the skin on	

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	the hip (naïve site) according to the randomization scheme	
Removal time	48 hours (± 30 minutes) after application	
Sensitization score evaluation time points	0.5, 24, 48, and 72 hours after the expected time of patch removal.	
Re-challenge	4 to 8 weeks after the conclusion of the Challenge Phase Procedures.	
Statistical analysis Mean Frequency tables per application time point. Mean days until patch was removed Sensitization response frequency table	Mean: yes Frequency tables per application time point: yes Sensitization response frequency table: yes	The statistical analysis did not include mean days until patch was moved due to a significant irritation. The sponsor should provide this information.
Meet FDA non-inferiority limit?	Yes	
Adhesion Evaluation		
Key elements	Sponsor's study design	Comments
Application duration	48-72 hours	
Overlay or reinforcement tape used	Yes, except for the first 9 hours	(b) (4) Soft Cloth Surgical Tape (b) (4) was applied to 2 edges of each dermal patch at the time of every application except for the first 9 hours of the first application.
Adhesion evaluation time points	1, 3, 5, 7, and 9 hours (± 10 minutes) after patch application	
Statistical analysis Mean Frequency tables per evaluation time point. Proportion of subjects with meaningful degree of detachment.	Mean: yes Frequency tables per evaluation time point: yes Proportion of subjects with meaningful degree of detachment: no	
Meet FDA non-inferiority limit?	Not provided	The sponsor used alternate method.

Reviewer's Comment:

The sponsor's study MPTP-12130 is consistent with the FDA guidance.

2. **Adhesion data from study MPTP-11030 are not acceptable for the review due to missing dataset**.

Study number	MPTP-11030; Single-Dose Pilot Bioequivalence Study	
Key elements	Study design	Comments
Products:	**2 different test Formulations: 30 mg/9 hr (3.3 mg/hr) (**28.8 cm^2) **Reference: 30 mg/9 hr (3.3 mg/hr) (**37.5 cm^2)	
Patch applied	A single 30 mg/9 hr transdermal system was applied per study period.	
Application location	• A clean, dry area of the skin on the hip • The next patch application occurred on a naïve site contralateral to the previous patch location (e.g., 1st patch placed on left hip area, 2nd patch placed on right hip area, and the 3rd patch placed on a different portion of the left hip).	
Application frequency	• The patches were removed 9 hours ± 10 minutes after application. • Following a washout period of at least 2 days, all subjects returned to the clinical facility to be dosed with one of the alternative treatments as per the randomization	
Patch reinforcement or overlay use	none	
Statistical analysis Mean Frequency tables per evaluation time point. Proportion of subjects with meaningful degree of detachment.	Mean: yes Frequency tables per evaluation time point: yes Proportion of subjects with meaningful degree of detachment: no	The sponsor needs to provide table with proportion of subjects with meaningful degree of detachment
Meet FDA non-inferiority limit?	Not provided	Sponsor needs to provide the result using the statistical method recommended in the draft guidance for this product.

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Summary of the sponsor's statistical analyses results are shown below.

MPTP-11030
Mean Adhesion Results for Transdermal Patch:

Arithmetic Mean (%CV) A = Mylan	Arithmetic Mean (%CV) B = Mylan	Arithmetic Mean (%CV) C = Daytrana®
87.46 (16.2)	95.92 (10.98)	94.13 (4.02)

Least-Squares Mean			
Treatment A Mylan	Treatment C Daytrana®	μ_1-0.8μ_2[1]	90% Confidence Interval[2]
87.28	94.13	11.98	7.16% – 16.79%
Treatment B Mylan	**Treatment C Daytrana®**	**μ_1-0.8μ_2[1]**	**90% Confidence Interval[2]**
96.10	94.13	20.80	15.99% – 25.61%

1 Estimated as Mylan least-squares mean – 0.8 x Daytrana® least-squares mean.
2 Lower 90% confidence interval ≥ 0 indicates Mylan is non-inferior to Exelon®.

Reviewer's Comments:
Study MPTP-11030 is a pilot PK study. Adhesion performance can be evaluated.

According to the sponsor's analysis, Treatments A (Lot R6C0003) and B (Lot R6C0004) appear to demonstrate non-inferior adhesion performance compared with Treatment C Daytrana®. However, the sponsor should provide adhesion result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the RLD (30 mg/9 hours) is less than or equal to 0 as recommended in the Draft Guidance for this product.

MPTP-12046
Study MPTP-12046
Study MPTP-12046 had deficiencies in procedure by Novum Pharmaceuticals Research Service. The study was repeated as Study MPTP-12130 employing a different clinical research organization, PRACS Institute.[1]

Reviewer's Comment: *Due to a significant data integrity issues, the sponsor noted that data from this study (MPTP-12046) are not acceptable. This reviewer concurs with the sponsor's decision.*

1 ANDA 206497 in EDR[0000 (1) 12/13/2013 ORIG-1 /Multiple Categories/Subcategories Module 2.5 – Clinical Overview, page 3/5]

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MPTP-12130

Cumulative Irritation Results: (n =93)

Least-Squares Mean Cumulative Irritation			
Treatment A Mylan	**Treatment B Daytrana®**	**μ_1-1.25μ_2[1]**	**90% Confidence Interval[2]**
1.874	2.324	-1.031	-1.127– -0.936

[1] Estimated as Mylan least-squares mean – 1.25 x Daytrana® least-squares mean.

[2] Upper 90% confidence interval < 0 indicates Mylan is non-inferior to Daytrana®.

APPEARS THIS WAY ON ORIGINAL

Table 14.5 Frequency of Irritation Scores* Observed In Ninety-three Healthy Adult Subjects Following Repeat Application of Methylphenidate Transdermal System 10 mg/9 hours and Daytrana® 10 mg Every 48-72 Hours for 9 Applications Over 21 Days

Day (Days elapsed from 1st patch application)	Treatment A Methylphenidate Transdermal System 10 mg/9 hours (Mylan)									Treatment B Daytrana® 10 mg (Noven)								
Score	0	1	2	3	4	5	6	7	Total	0	1	2	3	4	5	6	7	Total
Day 3	23	63	6	0	0	0	0	1	93	12	73	7	0	0	0	0	1	93
Day 5	5	85	2	0	0	0	0	1	93	2	78	12	0	0	0	0	1	93
Day 8	1	86	5	0	0	0	0	1	93	3	72	17	0	0	0	0	1	93
Day 10	0	81	6	0	4	0	0	2	93	1	55	30	0	5	0	0	2	93
Day 12	0	59	15	0	15	0	0	4	93	0	35	33	1	20	0	0	4	93
Day 15	0	42	22	0	25	0	0	4	93	0	23	33	0	29	0	2	6	93
Day 17	0	23	37	0	28	0	1	4	93	1	9	31	1	34	6	5	6	93
Day 19	0	19	35	0	31	3	1	4	93	1	4	26	0	38	12	6	6	93
Day 21	0	21	30	0	32	5	1	4	93	0	8	20	0	41	12	6	6	93
Total	29	479	158	0	135	8	3	25	837	20	357	209	2	167	30	19	33	837

*Scores represent the sum of the Dermal Response and Other Effects Scores. ^Irritation scores were recorded every 48-72 hrs. For frequency of scores for each patch wear, see Appendix 16.2.6.1 of this report.

SKIN IRRITATION EVALUATION SCORING SYSTEM

Dermal Response

Scale	Irritation	Scale	Irritation
0	No evidence of irritation	4	Definite edema
1	Minimal erythema, barely perceptible	5	Erythema, edema, and papules
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	6	Vesicular eruption
3	Erythema and papules	7	Strong reaction spreading beyond test (i.e., application) site

Other Effects

A (0)	Slighty glazed appearance
B (1)	Marked glazed appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudates covering all or part of the patch site
H (3)	Small petechial erosions and/or scabs

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Mean Adhesion Results for Transdermal Patch: (n = 100)

Arithmetic Mean (%CV)	Arithmetic Mean (%CV)
Treatment A Mylan	**Treatment B Daytrana®**
95.1 (3.4%)	91.2 (7.0%)

Least-Squares Mean			
Treatment A Mylan	**Treatment B Daytrana®**	**μ_1-0.8μ_2[1]**	**90% Confidence Interval[2]**
95.1	91.2	22.1	21.2% – 23.0%

1 Estimated as Mylan least-squares mean – 0.8 x Daytrana® least-squares mean.
2 Lower 90% confidence interval ≥ 0 indicates Mylan is non-inferior to Daytrana®.

Sensitization Results: (n =66)

Treatment	Sensitization		
	Yes	No	Total
Methylphenidate Transdermal System 10 mg/9 hours (Mylan)	17	49	66
Daytrana® 10 mg (Noven)	19	47	66
Total	36	96	132

Reviewer's Comment

According to the sponsor's analysis of the study MPTP-12130 for mean irritation, mean adhesion, and sensitization results indicate that Mylan's test product is non-inferior to the reference product. However, the sponsor should provide adhesion evaluation result using the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the reference product as recommended in the Draft Guidance for this product.

Formulation[2]

3.2.P.1 Description and Composition;

Mylan Technologies, Inc. (St. Albans, VT USA)

Table 3.2.P.1/1: Qualitative and Quantitative Unit Composition, Pharmaceutical Function, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Methylphenidate Transdermal Systems

Component	10 mg/ 9 hours (9.6 cm^2)	15 mg/ 9 hours (14.4 cm^2)	20 mg/ 9 hours (19.2 cm^2)	30 mg/ 9 hours (28.8 cm^2)	% w/w	Pharmaceutical Function	Maximum Level[1] Listed in FDA *Inactive Ingredient Database for Approved Drug Products*	Quality Standards
Active Ingredient								
Methylphenidate	(b) (4)						(b) (4)	(b) (4)
Inactive Ingredients - Solid Matrix Reservoir and Skin Contact Adhesive Layers								
Hydrophobic Colloidal Silica	(b) (4)						(b) (4)	
Mineral Oil	(b) (4)							
Polyisobutylene Adhesive	(b) (4)							
Total:	(b) (4)							
Total Matrix Weight								

2 ANDA 206497 in EDR[0000 (1) 12/13/2013 ORIG-1 /Multiple Categories/Subcategories Module 3.2.P.1 – Description and Composition of the Drug Product, page 2/6]

3.2.P.1 Description and Composition;

Mylan Technologies, Inc. (St. Albans, VT USA)

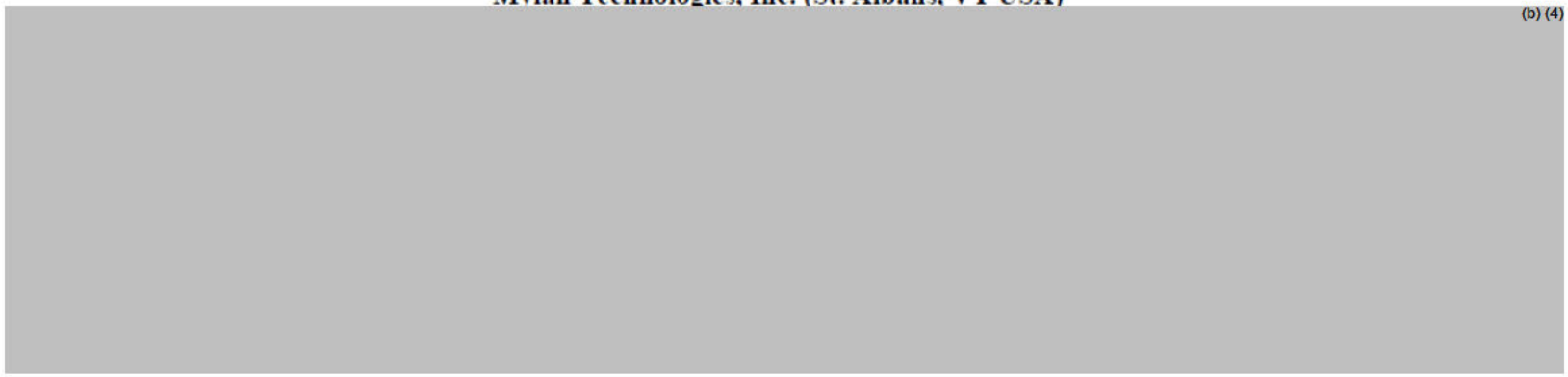
Component	10 mg/ 9 hours (9.6 cm^2)	15 mg/ 9 hours (14.4 cm^2)	20 mg/ 9 hours (19.2 cm^2)	30 mg/ 9 hours (28.8 cm^2)	% w/w	Pharmaceutical Function	Maximum Level[1] Listed in FDA *Inactive Ingredient Database for Approved Drug Products*	Quality Standards
Inactive Ingredients – Backing Film, Release Liner, Printing Ink								
Ethylene-Vinyl Acetate / Polyester (b) (4)	(b) (4)							(b) (4)
(b) (4) Fluoropolymer-Coated Polyester Release Liner (b) (4)								
White Ink (b) (4)								
Total Drug Product Weight (excluding Release Liner)								

[1] FDA's electronic Inactive Ingredient Database for Approved Drug Products (Database Last Updated October 24, 2013) for transdermal products. The proposed inactive ingredient levels do not affect the safety of the proposed drug product, and the requirements outlined in 21 CFR 314.94(a) (9) (ii) have been satisfied.
[2] Hydrophobic colloidal silica is not currently listed in the Inactive Ingredients Database. Colloidal Silicone Dioxide is listed in the Inactive Ingredients Database with a maximum potency of 49 mg. Mylan has conducted a safety assessment of hydrophobic colloidal silica and has concluded that the proposed level does not present a safety concern.

(b) (4)

3.2.P.1 Description and Composition;

Mylan Technologies, Inc. (St. Albans, VT USA)



Placebo formulation was not used in pivotal Study MPTP-12130.

Reviewer's Comments:

With the exception of hydrophobic colloidal silica, the formulation inactive ingredients were below the IID limit.

The sponsor provided data to support the use of hydrophobic colloidal silica at a maximum of (b) (4) *without change to the safety and efficacy of the test product.*[3]

The test product does not require Q1 and Q2 sameness.

3 ANDA 206497 in EDR[0000 (1) 12/13/2013 ORIG-1 /Multiple Categories/Subcategories Module 3.2.P.1 – Description and Composition of the Drug Product, page 3/6]

Comments to be conveyed to the sponsor:

From DCR perspective, your data from a skin irritation/sensitization/adhesion study (MPTP-12130) and the adhesion study (MPTP-11030) are not acceptable for receiving your ANDA. The submission is incomplete. Data requested below are the combined requests of the DCR and the statistical reviewers.

The following additional information is requested for the review:

For the Study MPTP-12130:

1. Adverse events in a SAS dataset (.xpt file)

2. Concomitant medications in a SAS dataset (.xpt file)

3. The frequency table for proportion of subjects with a meaningful degree of detachment. See below for an example.

		Adhesion score				
Product	N	100 (100% adhesion), N (%)	95 N (%)	85 N (%)	75 N (%)	<75, N (%)
A						
B						

4. The frequency table for mean days until removed or moved due to a significant irritation during induction period. See below for an example.

Irritation data			
Product	Combined irritation score (dermal response + other effects) > 3	Patches removed due to unacceptable degree of irritation	Mean days until patch was removed due to unacceptable degree or irritation
A			
B			

5. The frequency table for combined irritation scores (irritation and other effect scores) during re-challenge Period

6. Adhesion evaluation result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the reference product is less than or equal to 0 as recommended in the draft guidance for this product

7. The description and composition of Study MPTP-12130 test product Lot R6D0023. It is unclear whether the formulation provided in section "3.2.P.1 Description and Composition" is for this lot or not.

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For the study MPTP-11030 (adhesion analysis):

8. A list of subjects included in the evaluable population per treatment for adhesion analysis in a SAS .xpt file

9. A list of subjects excluded from the evaluable population per treatment (if any) and reason for exclusion for adhesion analysis in a SAS .xpt file

10. Adverse events in a SAS .xpt file

11. Concomitant medications in a SAS .xpt file

12. Adhesion scores in a SAS xpt file

13. Adhesion evaluation result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the RLD (30 mg/9 hours) is less than or equal to 0 as recommended in the draft guidance for this product

10. Table with proportion of subjects with meaningful degree of detachment (see comment #3 above for an example)

14. The description and composition of Study MPTP-11030 test product Treatments A (Lot R6C0003) and B (Lot R6C0004). It is unclear whether the formulation provided in section "3.2.P.1 Description and Composition" is for this lot or not.

Attachment: Statistical Filing Review

STATISTICAL REVIEW CHECKLIST FOR GENERIC ANDA (Patch Study)
FOR APPLICATION COMPLETENESS AT FILLING

ANDA#	**206497**
DRUG NAME	**Methylphenidate**
DOSAGE FORM	**Transdermal System, 10 mg/9 hours**
APPLICANT NAME	**Mylan Technologies Inc.**
REFERENCE LISTED DRUG (RLD)	**Daytrana® 10mg (releasing 10 mg/9 hours), Noven Pharmaceuticals Inc**
PRIMARY REVIEWER	**Guoying Sun**
SECONDARY REVIEWER	**Stella Grosser**
DATE	

	Summary of Findings by Statistical Review Team
X	**Acceptable**
	Not Acceptable

RECOMMENDATION: **_X_ COMPLETE** **___INCOMPLETE**

Reviewed by:

Guoying Sun -S Digitally signed by Guoying Sun -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Guoying Sun -S, 0.9.2342.19200300.100.1.1=2000486690 Date: 2014.01.17 11:48:40 -05'00' Date: ___1/17/2014_____

Guoying Sun, Ph. D.
Statistical Reviewer

Stella C. Grosser Digitally signed by Stella C. Grosser DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stella C. Grosser, 0.9.2342.19200300.100.1.1=1300146679 Date: 2014.01.17 15:10:10 -05'00' Date: ___1/17/2014_____

Stella Grosser. Ph. D.
Acting Division Deputy Director, Office of Biostatistics

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Item Verified:	YES	NO	Comments
Protocol	X		
Study report	X		
Statistical Methods Interim Analysis Plan	X		
Clinical Site (s)	X		
List of subjects included in PP/ (M)ITT populations per treatments	X		
List of subjects excluded/ from PP/ (M)ITT per treatments	X		
Reasons for discontinuation from the study if discontinued	X		
Individual subject's scores/data per visit	X		
Analysis data define File	X		
Demographic data in SAS .xpt file		X	In summary SAS .xpt file, variables age, gender and race are included
Primary analysis data (Summary data) in SAS .xpt file	X		
Clinical Raw Data in SAS .xpt file	X		
Clinical LOCF data in SAS .xpt file	X		
Statistical study Reports	X		
Defined endpoints	X		
Summary results provided by the firm indicate studies pass non-inferiority criteria	X		

Reference ID: 3454112

Additional Comments regarding the ANDA:

Comments <u>not</u> to be conveyed to the sponsor

FDA guidance for this product is available:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf

Location of data files:
\\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\

Study MPTP-12130 includes irritation, sensitization and adhesion studies:

This was an irritation evaluator blinded, multiple-dose, randomized application site, 2-treatment, 3-phase, 1-period study of the human dermal safety of a formulation of Mylan's methylphenidate transdermal system, 10 mg/9 hours to Daytrana® patch, 10 mg/9 hours following administration of multiple transdermal doses of 10 mg/9 hours (1 × 10 mg/9 hours patch applied to both sides of the hip) in 100 healthy, adult subjects.

Ninety-three subjects completed the Irritation (induction) phase of the study. Sixty-six subjects completed the Challenge phase, and 31 subjects completed the Re-challenge phase. One hundred (100) subjects had valid adhesion scores and were included in the statistical analysis of adhesion.

Irritation Study:

Statistical Analysis – Cumulative Dermal Irritation
The source data for the analysis of skin irritation was the actual patch irritation responses recorded following visual evaluation of the test site during the study period. The actual patch test scores were consistent with the definitions given in the grading scale and was the sum of the dermal response and the other effects scores (e.g. dermal response of 2 + other effects of B (l) =actual score of 3). The number of irritation scores that included an Other Effects Score for each treatment is presented in a listing
The objective of the cumulative irritation assessment was to evaluate the irritation of Mylan's Methylphenidate Transdermal System 10 mg/9 hours as compared with Daytrana® after repeated applications to the same skin site for twenty-one consecutive days. The primary assessment parameter was the mean cumulative irritation, which was defined for each subject as the sum of all 9 individual irritation scores obtained at 0.5 hours after patch removal divided by 9. Subjects must have had 7 valid irritation scores recorded to be included in the analysis. For any missing score, the previous score was carried forward.

The study was designed to evaluate the test product, Mylan's Methylphenidate Transdermal System 10 mg/9 hours versus Daytrana® for cumulative dermal irritation. These mean scores were evaluated by Analysis of Variance using Proc GLM of SAS 9.1 (or higher) with a statistical model incorporating

terms for sequence, subject-nested- within-sequence, treatment, and patch application site. A one-sided hypothesis test was to be used to determine if the response of the Mylan's Methylphenidate Transdermal System, 10 mg/9 hr was equivalent to or better than the Noven's Daytrana® 10 mg (for the reference product). For the mean irritation scores, the null and alternative hypotheses are:

$$H_0: \mu_1 - 1.25\mu_2 > 0$$
$$H_1: \mu_1 - 1.25\mu_2 \leq 0$$

where μ_1 is the mean response for the test product and μ_2 is the mean response for the reference product. The null hypothesis H_0 will be rejected when the upper limit of the 90% confidence interval (that is the 95% upper confidence bound) for the quantity $\mu_1 - 1.25\mu_2 \leq 0$.

Table 14.6 Statistical Comparison of the Cumulative Irritation Scores following Nine Applications of Methylphenidate Transdermal System, 10 mg/9 hrs and Daytrana® 10 mg to Ninety-three Healthy adult volunteers for 48-72 hours over a period of 21 days

Least-Squares Mean Cumulative Irritation		**μ_1-1.25μ_2[1]**	**90% Confidence Interval[2]**
Treatment A Mylan	**Treatment B Daytrana®**		
1.874	2.324	-1.031	-1.127– -0.936

[1] Estimated as Mylan least-squares mean – 1.25 x Daytrana® least-squares mean.
[2] Upper 90% confidence interval < 0 indicates Mylan is non-inferior to Daytrana®.

Comments: Irritation SAS data set was available for statistical analysis.

Sensitization:

There were seventeen (17) and nineteen (19) subjects that had contact sensitization reactions to Mylan's Methylphenidate Transdermal System and Noven's Daytrana®, respectively (Table 14.7).

Table 14.7 Frequency Of Sensitization Following Nine Applications Of Mylan's Methylphenidate Transdermal System And Noven's Daytrana For 48-72 Hours Over A Period Of 21 Days Followed by a 15-Day Rest Period To Healthy Adult Male And Female Volunteers

Treatment	Sensitization		
	Yes	No	Total
Methylphenidate Transdermal System 10 mg/9 hours (Mylan)	17	49	66
Daytrana® 10 mg (Noven)	19	47	66
Total	36	96	132

Comments: Sensitization SAS data set was available for statistical analysis.

Reference ID: 3454112

Adhesion Study:

. Statistical Analysis – Adhesion

Transdermal adhesion was assessed at 1, 3, 5, 7, and 9 hours (± 10 minutes) after patch application according to the criteria found in Appendix 16.1.1. - MPTP-12130 Protocol, Appendix II *Adhesion Evaluations*.

The objective of adhesion assessment was to evaluate the adhesion of Mylan's Methylphenidate Transdermal System 10 mg/9 hours as compared with Daytrana® 10 mg under normal conditions. The assessment parameter was the mean adhesion score, which was defined for each subject as the sum of adhesion scores divided by 5. For any missing score, the previous score was carried forward. If the first score was missing, the following score was carried back. If the last score is missing, the previous score was carried forward. The study was designed to evaluate the test product, Mylan's Methylphenidate Transdermal System 10 mg/9 hours versus Daytrana® for adhesion. A one-sided hypothesis test was used to determine if the adhesion score (based upon a 12- point scale, where a lower score indicates less adhesion to the skin) of Mylan's Methylphenidate Transdermal System, 10 mg/9 hr was equivalent to or better than the Daytrana® Transdermal System, 10 mg/9 hr (for the reference product). For the mean adhesion scores, the null and alternative hypotheses were:

H_0: $\mu_1/\mu_2 < 0.8$

H_1: $\mu_1/\mu_2 \geq 0.8$; which (assuming $\mu_2 > 0$) can be written as:

H_0: $\mu_1 - 0.8\mu_2 < 0$

H_1: $\mu_1 - 0.8\mu_2 \geq 0$,

Where μ_1 is the mean adhesion score for the test product and μ_2 is the mean adhesion score for the reference product. The null hypothesis H_0 would be rejected when the upper limit of the 90% confidence interval (that is the 95% lower confidence bound) for the quantity $\mu_1 - 0.8\mu_2$ is ≥ 0.

Rating Scale for Assessing Patch Adhesion				
Adhesion	Score		Adhesion	Score
100%	100		>40% to 50%	45
>90% to <100%	95		>30% to 40%	35
>80% to 90%	85		>20% to 30%	25
>70% to 80%	75		>10% to 20%	15
>60% to 70%	65		>0% to 10%	5
>50% to 60%	55		Fall off	0

Table 14.9 Statistical Comparison of the Adhesion of Methylphenidate Transdermal System, 10 mg/9 hrs and Daytrana® 10 mg following a Nine Hour Wear Period in 100 Healthy adult volunteers

Least-Squares Mean		**$\mu_1 - 0.8\mu_2$[1]**	**90% Confidence Interval[2]**
Treatment A Mylan	**Treatment B Daytrana®**		
95.1	91.2	22.1	21.2% – 23.0%

1 Estimated as Mylan least-squares mean – 0.8 x Daytrana® least-squares mean.
2 Lower 90% confidence interval ≥ 0 indicates Mylan is non-inferior to Daytrana®.

Reference ID: 3454112

Comments:

In sponsor's analysis, the mean adhesion score was calculated as the sum of the adhesion scores at hour 1, 3, 5, 7 and 9 divided by 5. They used hypothesis:

$$H_0: \mu_1 - 0.8\mu_2 < 0$$
$$H_1: \mu_1 - 0.8\mu_2 \geq 0$$

Instead of

$$H_0: \mu_1 - 1.25 < 0$$
$$H_1: \mu_1 - 1.25\mu_2 \geq 0,$$

because the adhesion score was assessed based on 100% rating scale. We need to convert to 0-4 rating scale based on FDA guidance before conducting analyses.

The LOCF score for adhesion is the same as the raw data. There is no missing data.

Reference ID: 3454112

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUNNY Y TSE
02/13/2014

CAROL Y KIM
02/14/2014

JOHN R PETERS
02/14/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

CHEMISTRY REVIEWS

OPQ QUALITY ENDORSEMENT CHECKLIST (See Reference Guide for details):

ANDA# 206497 Methylphenidate Transdermal system

Function	**Performed By (Initial and Date)**	**Check appropriate box**
Is the final review signed and archived in the current IT platform?	RBPM JN 2/22/22	☒ Yes ☐ No
DMF adequate and review up to date?	RBPM JN 2/22/22	☒ Yes ☐ No *(see comments)
Are consults complete and adequate?	RBPM JN 2/22/22	☐ Yes *(see comments) ☐ No ☒ N/A
Are all facility inspections acceptable?	RBPM JN 2/22/22	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	RBPM JN 2/22/22	☐ Yes ☐ No ☒ N/A
Final recommended dissolution method/specification acknowledged by Firm?	ATL MC 02/22/2022	☒ Yes ☐ No ☐ N/A
Are there comparability protocols provided? If yes, how many?	ATL MC 02/22/2022	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	ATL MC 02/22/2022	☐ Yes ☐ No *(see comments) ☒ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	ATL MC 02/22/2022	☒ Yes ☐ No *(see comments) ☐ N/A

Comments
ANDA 206497 is approvable from Quality perspective.

Division	Name	Date
DIMRP III / Branch 7	Meenal Chavan	02/22/2022

Meenal Chavan

Digitally signed by Meenal Chavan
Date: 2/22/2022 03:55:10PM
GUID: 584022f900ac6ecb6c4a62a5577ae496

Jennifer Nguyen

Digitally signed by Jennifer Nguyen
Date: 2/25/2022 04:24:28PM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

Recommendation:
ANDA:
☒ **Approval**
☐ **Information Request – Minor**
(_____days for applicant to response)
☐ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 206497

Amendment Review

Drug Name/Dosage Form	Methylphenidate Transdermal System
Strength	10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr
Reviewer(s)	Cedar Boakye
Applicant	Mylan Technologies, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Response to IR	02/18/2022
Response to CR Letter (SD# 0025)	16-DEC-2021
Labeling Amendment (SD# 0024)	01-JUL-2021
Response to IR (SD# 0023)	01-APR-2021
Response to CR Letter (SD# 0022)	25-FEB-2021

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	Comments
(b) (4)	II		(b) (4)	Adequate	04/15/2021	Reviewer: Roger Farr
	IV			N/A	N/A	(b) (4)
	IV			Adequate	08/12/2013	Adequate for different application (NDA)
	IV			Adequate	02/02/2018	Reviewed by Suneela Prodduturi
11404	III	Mylan Technologies Inc.	(b) (4)	N/A		
(b) (4)	III		(b) (4)	N/A		
	III			N/A		

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling*	Adequate	07/23/2021	Julie Neshiewat
Bioequivalence	Dissolution: Adequate Bioequivalence: Adequate DCR: Adequate	01/11/2018 04/17/2016 02/07/2018	Yoriko Harigaya Yoriko Harigaya Sunny Tse
EA	Acceptable		Suneela Prodduturi
Radiopharmaceutical	N/A		
Samples Requested	Samples Received by DPQR and found acceptable for physical description	03/21/2016	Suneela Prodduturi
Pharm/Tox Consult	Levels of colloidal silica are acceptable	02/24/2016	Honggang Wang
Pharm/Tox Consult	(b) (4) Adequate	06/28/2021	Wei Ding

FACILITIES:

Overall Inspection Recommendation: Approve on 18-APR-2021

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
	(b) (4)		Approve
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Contract testing facility - Microbiological Testing of the Finished Dosage Form	(b) (4)		Approve
Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Release and Stability Testing of Finished Dosage Form	Mylan Technologies Inc	FEI: 1220747 DUNS:063790265	Approve

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Meenal Chavan

Digitally signed by Meenal Chavan
Date: 2/22/2022 08:51:03AM
GUID: 584022f900ac6ecb6c4a62a5577ae496

Cedar Boakye

Digitally signed by Cedar Boakye
Date: 2/22/2022 09:51:11AM
GUID: 56814ecf00099832273fd394ea7b8783

Recommendation:

ANDA:

☐ **Approval**

☐ **Information Request – Minor**

(_____days for applicant to response)

☐ **Complete Response - Minor**

☒ **Complete Response – Major**

ANDA 206497

Amendment Review

Drug Name/Dosage Form	Methylphenidate Transdermal System
Strength	10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr
Reviewer(s)	Suneela Prodduturi
Applicant	Mylan Technologies, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission- Complete Response Amendment	07/27/2017
Information Request Response- Dissolution	10/19/2017

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS2	DATE REVIEW COMPLETED	Comments
(b) (4)	II		(b) (4)	Adequate	07/31/2017	ONE annual report pending review
	IV			N/A		(b) (4)
	IV			Adequate	08/12/2013	Adequate for different application (NDA)
	IV			Adequate	02/02/2018	Reviewed by Suneela Prodduturi
11404	III	Mylan Technologies	(b) (4)	N/A		
(b) (4)	III		(b) (4)	N/A		
	III			N/A		

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling*	Inadequate-Minor	01/22/2018	Julie Neshiewat
Bioequivalence	Dissolution: Adequate Bioequivalence: Adequate DCR: Adequate	01/11/2018 04/17/2016 02/07/2018	Yoriko Harigaya Yoriko Harigaya Sunny Tse
EA	Acceptable		Suneela Prodduturi
Radiopharmaceutical	N/A		
Samples Requested	Samples Received by DPQR and found acceptable for physical description	03/21/2016	Suneela Prodduturi
Pharm/Tox Consult	Levels of colloidal silica are acceptable	02/24/2016	Honggang Wang

FACILITIES:

Overall Inspection Recommendation: Approve on 09/27/2017

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
	(b) (4)		Approve
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
	(b) (4)		Approve
	Mylan Technologies Inc	FEI: 1220747 DUNS:063790265	Approve

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2.3.P DRUG PRODUCT

P.1 *Description and Composition of the Drug Product (NO CHANGE from previous review)*

Methylphenidate Transdermal System Composition and Function

Component	10 mg/ 9 hours (9.6 cm^2)	15 mg/ 9 hours (14.4 cm^2)	20 mg/ 9 hours (19.2 cm^2)	30 mg/ 9 hours (28.8 cm^2)	% w/w	Pharmaceutical Function
Active Ingredient						
Methylphenidate	(b) (4)					Active
Inactive Ingredients: Solid Matrix Reservoir and Skin Contact Adhesive Layers						
Hydrophobic Colloidal Silica NF (b) (4)	(b) (4)					
(b) (4) Mineral Oil NF (b) (4)						
Polyisobutylene Adhesive (b) (4) (b) (4)						
(b) (4)						
Total Matrix Weight	(b) (4)				*100.00%*	
Inactive Ingredients: Backing Film, Release Liner, Printing Ink						
Ethylene-Vinyl Acetate (b) (4) / Polyester Film (b) (4)	(b) (4)					
(b) (4) Fluoropolymer-Coated Polyester Release Liner (b) (4)						
White Ink (b) (4)						
Total Drug Product Weight (excluding Release Liner)	(b) (4)				*100.00%*	

(b) (4)

Compositional break down of reservoir and skin contact layer

Components	Intermediate Laminate Composition		Finished Product mg/ system (area)			
	% w/w	g/m²	10 mg/ 9 hours (9.6 cm²)	15 mg/ 9 hours (14.4 cm²)	20 mg/ 9 hours (19.2 cm²)	30 mg/ 9 hours (28.8 cm²)
Solid Matrix Reservoir Layer						
Methylphenidate	(b) (4)					
Hydrophobic Colloidal Silica NF (b) (4)						
(b) (4) Mineral Oil NF (b) (4)						
Polyisobutylene Adhesive (b) (4)						
(b) (4)						
Solid Matrix Reservoir Subtotal	100.00%	(b) (4)				
Skin Contact Adhesive Layer						
Hydrophobic Colloidal Silica NF (b) (4)	(b) (4)					
(b) (4) Mineral Oil NF (b) (4)						
Polyisobutylene Adhesive (b) (4)						
(b) (4)						
Skin Contact Adhesive Subtotal	100.00%	(b) (4)				

***Reviewer's Assessment (R02)**: Adequate (NO CHANGE from previous review)*

P.2 Pharmaceutical Development

Deficiency # 4 (CR01 dated 27-JUL-2016):

(b) (4)

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Suneela Prodduturi

Digitally signed by Suneela Prodduturi
Date: 2/09/2018 09:05:12PM
GUID: 537252370005b3496a077614fa0f6d80

Robert Berendt

Digitally signed by Robert Berendt
Date: 2/09/2018 04:22:20PM
GUID: 508da7380002b309c612f7e27bdf5995

Recommendation:
ANDA:
☐ **Approval**
☐ **Information Request**
(_____days for applicant to response)
☒ **Complete Response-MINOR**
☐ **Complete Response-MAJOR**

ANDA 206497

Methylphenidate Transdermal System

10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr

Mylan Technologies, Inc.

CR #1

Suneela Prodduturi, Ph.D.
OPQ/OLDP/DMRP/Branch I

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 206497

2. REVIEW #: 1

3. REVIEW DATE: 01/07/2016

4. REVIEWER: Suneela Prodduturi, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Information request (samples request)	02/24/2016
Resubmission after Refuse to Receive; Quality/Response to Information Request	06/19/2014
New/ANDA; Form 3674; User Fee/Coversheet	12/13/2013
Form 3674; Correspondence	12/13/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies, Inc.
Address:	110 Lake Street, St. Albans, VT 05478
Representative:	Jeffrey Lloyd, Vice President, Quality
Telephone:	(b) (4)
Fax:	(802) 527-8155
Email:	jeffrey.lloyd@mylan.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Methylphenidate Transdermal System

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

RLD: Daytrana® (Methylphenidate Transdermal System)
NDA # 021514
Noven Pharmaceuticals, Inc. for Shire US, Inc
1.1 mg/hr over 9 hours, 1.6 mg/hour over 9 hours, 2.2 mg/hr over 9 hours, 3.3 mg/hr over 9 hours

10. PHARMACOL. CATEGORY:

Treatment of Attention Deficit Disorder (ADHD)

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY:

10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _X_ Rx __ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:
α-phenyl-2-piperdineacetic acid methyl ester

Other Non-Proprietary Name(s) (e.g. National Name, United States Adopted Name (USAN), Japanese Accepted Name (JAN), British Approved Name (BAN)):

Methyl phenidylacetate

Methyl α-phenyl-α-(2-piperidyl)acetate

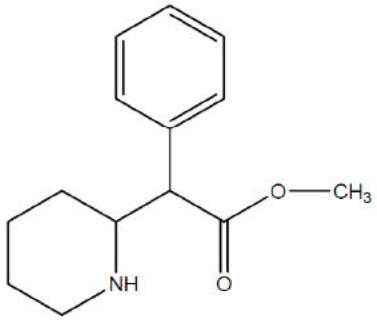
Methylphenidan

Methyl α-phenyl-α-2-piperidinylacetate

Methylphenidyl acetate

Chemical Abstracts Service (CAS) Registry Number:
113-45-1

Chemical Structure:



Molecular Formula:
$C_{14}H_{19}NO_2$

Molecular Weight:
233.31

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[2]	DATE REVIEW COMPLETED	Comments
(b) (4)	II		(b) (4)	PENDING (see comments)	08/15/2013	Adequate for a different NDA, pending annual reports review. TWO annual reports and administrative change information pending review
	IV			N/A		(b) (4)
	IV			Adequate	08/12/2013	Adequate for different appilication (NDA)
	IV				12/07/2009 SAMAAN, NASHED I	Pending review of annual reports and Quality information
11404	III	Mylan Technologies	(b) (4)	N/A		
(b) (4)	III		(b) (4)	N/A		
	III			N/A		

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		Suneela Prodduturi
Labeling*	Pending		
Bioequivalence	Dissolution: Inadequate Bioequivalence: Adequate DCR: Inadequate	10/01/2015 04/17/2016 03/28/2016	Yoriko Harigaya Yoriko Harigaya Sunny Tse
EA	Acceptable		Suneela Prodduturi
Radiopharmaceutical	N/A		
Samples Requested	Samples Received by DPQR and found acceptable for physical description	03/21/2016	Suneela Prodduturi
Pharm/Tox Consult	Levels of colloidal silica are acceptable	02/24/2016	Honggang Wang

*** Notes to Chemist-will be verified after the completion of the review**

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Overall Recommendation: Approve as of 12/03/2015

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
Drug substance manufacturer DMF #	(b) (4)		Approve
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
	(b) (4)		
	Mylan Technologies Inc	FEI: 1220747 DUNS:063790265	Approve

Chemistry Review for ANDA 206497

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 206497 is not approvable from a CMC perspective. This ANDA has not provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities has issued an "Approvable" overall recommendation on all the manufacturing facilities.

The labels have adequate CMC information as required.

Not approvable.

- CMC has minor deficiencies. Biopharmaceutics is Inadequate.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

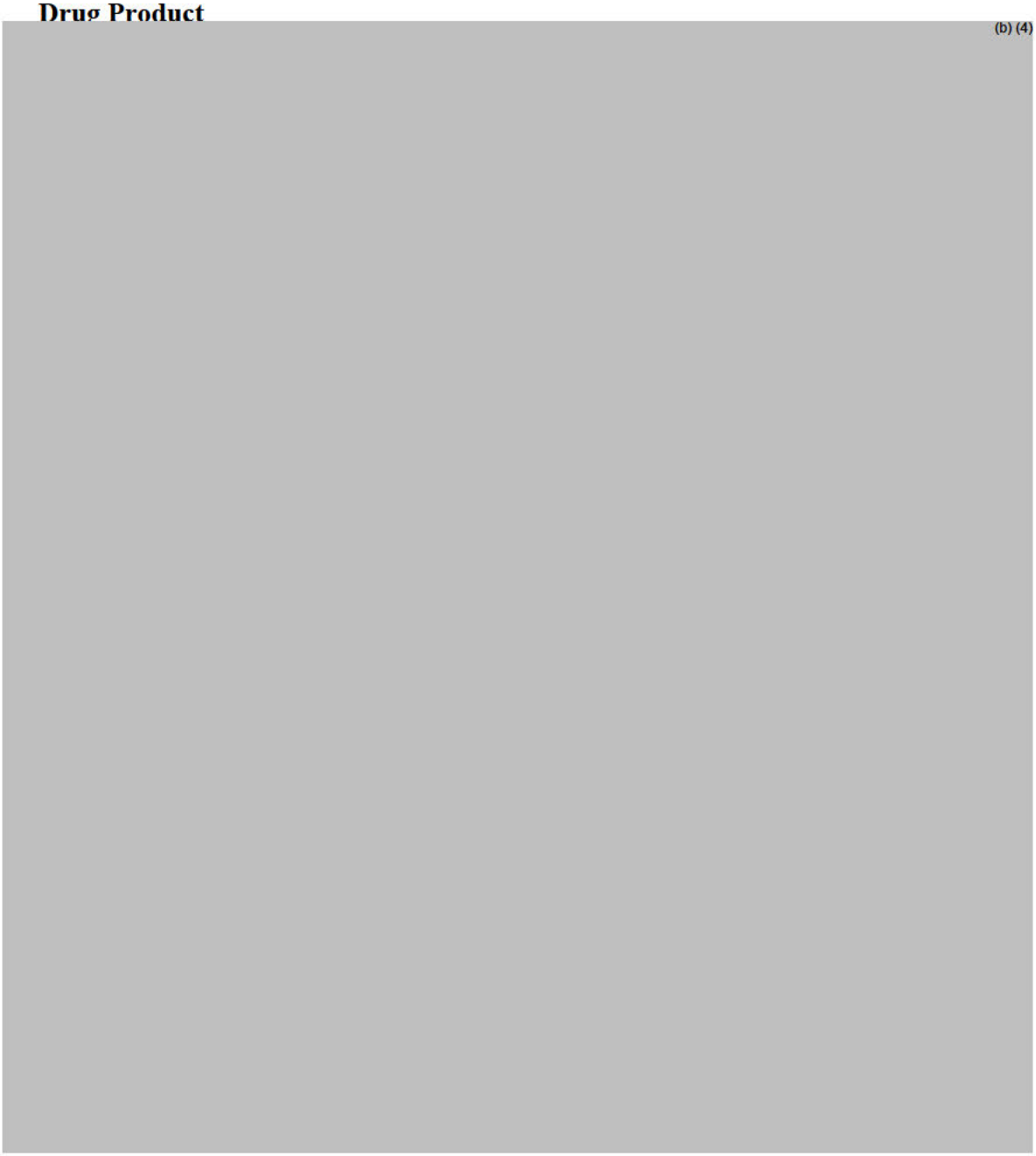
A. Description of the Drug Product(s) and Drug Substance(s)

I. Drug Substance

(b) (4)

II. Drug Product

(b) (4)



B. Description of How the Drug Product is intended to be used.

Indications and Usage

- Methylphenidate transdermal system is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). (1)
- Children (ages 6 to 12): the efficacy of methylphenidate transdermal system in ADHD was established in two 7-week controlled trials in children (1)

- Adolescents (ages 13 to 17): the efficacy of methylphenidate transdermal system in ADHD was established in one 7-week, controlled study in adolescents (1)

Dosage and Administration

- The recommended starting dose for patients new to or converting from another formulation of methylphenidate is 10 mg. (2)
- Methylphenidate transdermal system should be applied to the hip area (using alternating sites) 2 hours before an effect is needed and should be removed 9 hours after application. Methylphenidate transdermal system may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. (2)
- Dosage should be titrated to effect. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient. (2)
- Patients should be advised to follow the full instructions for patch use provided in the Medication Guide. (17)

How Supplied/Storage and Handling

(b) (4)

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Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	None
Non-Proprietary Name of Drug Product	Methylphenidate Transdermal System
Non-Proprietary Name of Drug Substance	Methylphenidate
Company Name	Mylan Technologies, Inc.
Dosage Form	Transdermal System
Strength(s)	10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr
Route of Administration	Transdermal
Proposed Indication(s)	Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

(b) (4)

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(b) (4)

[redacted]

A APPENDICES

A.1 Facilities and Equipment (biotech only)

N/A

A.2 Adventitious Agents Safety Evaluation

None

A.3 Novel Excipients

None

A.4 Nanotechnology Product Information

N/A

R REGIONAL INFORMATION

R.1 ***Executed Batch Records***

Provided

R.2 ***Comparability Protocols***

N/A

R.3 ***Methods Validation Package***

Provided

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification:
Provided

Exclusivity:
Provided

Debarment Certification:
Provided

cGMP Statement:
Provided

Reprocessing Statement:
Present in section 3.2.P.3.3.

Letters of Authorization:
Provided in section 1.4.1.

Request for Bio-waiver:
Provided in section 1.12.15 for lower strength of 1 mg/24 hours and higher strengths of 10 mg/9 hrs (1.1 mg/hr), 15 mg/9 hrs (1.6 mg/hr) and 20 mg/9 hrs (2.2 mg/hr).

Citizen Petition and/or Control Request Linked to the Application:
None

Environmental Impact Considerations/Categorical Exclusions:
Provided in section 1.12.14.

Appendix D: Labeling Section.

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain:

ii) Are the storage conditions acceptable? ☒ Yes, with a comment ☐ No
If "No," explain.

The RLD states to "**Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F)** [see USP Controlled Room Temperature]. Do not store patches unpouched. Do not store patches in refrigerators or freezers".
The proposed product states to "**Store at 20° to 25°C (68° to 77°F).** [See USP Controlled Room Temperature]. Do not store (b) (4) unpouched. Do not store (b) (4) in refrigerators or freezers".

c) DOSAGE AND ADMINISTRATION:

Adequate

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances: N/A.

e) For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

Issue communicated to Labeling Reviewer (using GDRP, emails and meetings):None

Overall Reviewer's Assessment and Signature: Inadequate
Suneela Prodduturi, 01/07/2016, 04/18/2016, 04/22/2016

Secondary Review Comments and Concurrence:

ANDA 206497 is not recommended for approval from a CMC perspective. This ANDA has not provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities has issued an "Approvable" overall recommendation on all the manufacturing facilities.

The labels have adequate CMC information as required.

Caroline Strasinger 04/21/2016

III. List of Deficiencies to be communicated in COMPLETE RESPONSE

ANDA: 206497 APPLICANT: Mylan Technologies, Inc.

(b) (4)

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A. Reviewer's Signature

B. Endorsement Block

Chemist /Date: Suneela Prodduturi, 01/07/2016, 4/18/2016, 04/22/2016
Chemistry Secondary Reviewer/Date: Caroline Strasinger 04/21/2016
Supervisory Chemist/Date:
Project Manager/Date:

TYPE OF LETTER: Complete Response

PRODUCT NAME: Methylphenidate Transdermal System
10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr

ANDA: 206497 **APPLICANT:** Mylan Technologies, Inc.

Sample and Information Request:

1. Provide updated stability data for all submission batches.

2. To aid in review of the ANDA 206497, provide the following transdermal drug delivery system (TDDS) samples:

   - 5 samples of the smallest size TDDS from the most recently manufactured batch (< 12 months preferred).
   - 5 samples of the smallest size TDDS nearing the end of shelf-life (~ 24 months)
   - 5 samples of the largest size TDDS from the most recently manufactured batch (< 12 months preferred).
   - 5 samples of the largest size TDDS nearing the end of shelf-life (~ 24 months)
   - 5 samples of all remaining submission batches not represented by the above samples requested.
   - 5 samples for the largest and smallest size of the RLD

   Include with the samples a table containing the batch/lot numbers, date of manufacture and the mean value (± standard deviation) for release liner peel, probe tack, shear and adhesion to steel tests associated with the sample lots provided above. Include values from the date of release and all applicable stability time points. The transdermal systems may be sent to the attention of:

Xiaoming Xu,
Food and Drug Administration
Division of Product Quality Research
10903 New Hampshire Ave
WO64, RM1028
Silver Spring, MD 20993
Tel: (301) 796-5035
DEA license: RX0466311 (Exp. 05/31/16)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

PHARMACOLOGY/TOXICOLOGY REVIEWS

PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Pharmacology/Toxicology Review (DPTR)
Office of Safety and Clinical Evaluation (OSCE), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Product:	Methylphenidate Transdermal System, 10 mg/9 hrs (1.1 mg/hr), 15 mg/9 hrs (1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr)
DMF#/ANDA#: **Applicant:**	ANDA 206497 Mylan Technologies Inc
RLD#/Approval Date: **Sponsor:**	NDA 021514 (DAYTRANA®; methylphenidate transdermal system), Approved 04/06/2006 Noven Pharmaceuticals Inc
Pharmacology-Toxicology Primary Reviewer:	Wei Ding, PhD, DABT Pharmacologist
Pharmacology-Toxicology Secondary Reviewer:	Richard Houghtling, PhD Lead Pharmacologist, Team Leader
Tertiary Reviewer:	Sruthi King, PhD Deputy Director
To:	Cedar Boakye, PhD Division of Immediate Release Products (DIMRP) Office of Lifecycle Drug Products (OLDP) Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To evaluate if the toxicity information provided supports the safety of the (b) (4)
Impurity Chemical Name:	(b) (4)
Date of Submission:	The ANDA application originally submitted at 12/13/2013
Date Consult Received:	04/15/2021
Date of Completion:	06/28/2021
Conclusion:	OGD Pharm/Tox concludes that the (b) (4) does not raise a safety concern at the proposed specification limit of (b) (4) See Section 2 for Internal Recommendations.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1. Executive Summary:

This Pharmacology/Toxicology review addresses a consult request from Office of Pharmaceutical Quality (OPQ) to evaluate a (b) (4) in the drug product and determine if the toxicity assessment submitted supports the safety of the transdermal system for this generic methylphenidate transdermal system under ANDA 206497.

Mylan Technologies Inc submitted ANDA 206497 for methylphenidate transdermal system on 12/13/2013. The reference listed drug (RLD) is Daytrana® (methylphenidate transdermal system), under NDA 021514, sponsored by Noven Pharmaceuticals Inc. The maximum daily dose (MDD) is 30 mg/day.

(b) (4)

(b) (4) Justification stated no additional toxicity data were identified.

DPTR reviewed the applicant's justification and used a surrogate approach based on publicly available data and on prior Pharmacology/Toxicology reviews of (b) (4) is acceptable from a Pharmacology/Toxicology perspective.

2. Internal Recommendation:

Pharmacology/Toxicology concludes that the maximum daily exposure (MDE) of the (b) (4) in methylphenidate transdermal system (b) (4) does not raise a safety concern and is acceptable.

3. Comments to be conveyed by RPM to the ANDA applicant as written:

None.

4. Regulatory Background:

ANDA 206497 was submitted at 12/13/2013, for methylphenidate transdermal system by Mylan Technologies Inc.[1] The reference listed drug (RLD) is Daytrana® (methylphenidate transdermal system), under NDA 021514, sponsored by Noven Pharmaceuticals Inc. Daytrana® is a CNS

[1] ANDA 206497 docuBridge section 1.2 Cover Letter at: ANDA206497 (206497 - 0023 - (24) - 2021-04-01 - ORIG-1 /Multiple Categories/Subcategories) - Cover Letter - 0000 - Original ANDA - 20131213

stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The maximum daily dose (MDD) is 30 mg/day. ANDA 206497 is prioritized as a First Generic.

A stimulated use (b) (4) study was performed by using artificial sweat as the extraction solvent with aged methylphenidate TDS patches from three separate lots (aged between 18 and 76 months, stored at ambient temperature). (b) (4)
(b) (4)

The applicant subsequently submitted the toxicology review of this (b) (4) on 02/25/2021.[3] In this regard, Division of Immediate Release Products (DIMRP)/OPQ consulted DIPTR to evaluate the submitted report.[4]

4.1 Orange Book Information:

The RLD (Daytrana®, NDA 21514) is the only approved methylphenidate transdermal system on market.

Source: Search on 5/12/2021 by Wei Ding of the Orange Book at site:
https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

5. Labeling:

The current product label for Daytrana® (methylphenidate transdermal system) was approved on 10/22/2019.[5] The RLD labeling contains a boxed warning:

WARNING: DRUG DEPENDENCE
See full prescribing information for complete boxed warning

Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior.

5.1. Indications and Usage:

Daytrana® is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

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[2] ANDA 206497 docuBridge section 3.2.P.2 Extractables and Leachables Risk Assessments at: ANDA206497 (206497 - 0023 - (24) - 2021-04-01 - ORIG-1 /Multiple Categories/Subcategories) - Extractables and Leachables Risk Assessment

[3] ANDA 206497 docuBridge section 3.2.P.2 Toxicological Review of Extractable/Leachables Program at: ANDA206497 (206497 - 0023 - (24) - 2021-04-01 - ORIG-1 /Multiple Categories/Subcategories) - Toxicological Review of Extractables/Leachables Program

[4] ANDA 206497 PharmTox Consult-1,4,7-trioxacyclotridecane-8,13-dione-4-13-2021.pdf at: https://panorama.fda.gov/internal/document/preview?versionID=6076ea9a0086dce691a20fb51ec5f09f&ID=6076ea9a0086dce511af650873ad576a

[5] RLD (Daytrana®, NDA 21514) label at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021514s030lbl.pdf

The efficacy of Daytrana in ADHD was established in two 7-week controlled trials in children (age 6-12) and one 7-week controlled study in adolescents (age 13-17).

(b) (4)

6. Discussion:

6.1 Applicant's justification:

6.1.1. Applicant's AET:[6]

Applicant calculated analytical evaluation threshold using a safety concern threshold of 1.5 mcg/day based on Agency recommendation communicated in the Complete Response Letter (dated 02/25/2021). Applicant states that MDD is achieved using one TDS per day for a period of 9 hrs. (b) (4)

(b) (4)

The quality team was contacted, and the team confirmed that the analytical methods and AET calculations as reported for the extractables and leachables study are adequate from their perspective.

[6] ANDA 206497 docuBridge section 3.2.P.2 Toxicological Review of Extractable/Leachables Program at: ANDA206497 (206497 - 0023 - (24) - 2021-04-01 - ORIG-1 /Multiple Categories/Subcategories) - Toxicological Review of Extractables/Leachables Program

[7] The quality team was contacted, and the team confirmed that the analytical methods and AET calculations as reported for the extractables and leachables study are adequate from their perspective.

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Wei Ding

Digitally signed by Wei Ding
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Richard Houghtling

Digitally signed by Richard Houghtling
Date: 6/28/2021 12:48:06PM
GUID: 508da6e7000271ba077f3f44d91a4ab1

Sruthi King

Digitally signed by Sruthi King
Date: 6/28/2021 04:56:31PM
GUID: 502d1b1300002b0559e552d5f6aa4cc2

Pharmacology Toxicology Consult

Consult#	11561
From:	The Office of Generic Drugs (OGD)
Consult for:	Hydrophobic Colloidal Silica (b) (4)
Date requested:	November 25, 2015
Desired Completion Date:	January 25, 2016
Application Type and #:	ANDA# 206497
Drug:	Methylphenidate
Indication:	ADHD
Sponsor:	Mylan Technologies
Reviewer:	Shiny V. Mathew, Ph.D.
Division:	Psychiatry Products, HFD-130

Table of Contents

1. Reason for the Consult:

The Office of Generic Drugs (OGD) consulted the Division of Psychiatry Products (DPP) regarding the levels of hydrophobic colloidal silica (b) (4) found in Mylan's Methylphenidate Transdermal System. OGD indicated that this excipient is not listed in the CDER Inactive Ingredient Guide (IIG) database for FDA approved drug products and they are requesting pharmacology/toxicology input on whether the levels found in the firm's formulation (b) (4) pose any safety concerns.

2. Division's Conclusions and Recommendations:

Based on an informal ONDQA chemistry consult, this Reviewer understands that hydrophobic colloidal silica is a derivative of hydrophilic silicon dioxide (silica). (b) (4) does not alter its toxicological profile. The Sponsor of this ANDA, Mylan Technologies, submitted a limited data summary on (b) (4) leading to the conclusion that toxicities derived from systemic exposure are not overly concerning. However, no long-term local toxicity data with the excipient were provided by the Sponsor. Based on its chemical properties, (b) (4) is considered to be minimally absorbed through the skin.

The Inactive Ingredient Guide (IIG) database lists up to (b) (4) present in Mylan's methylphenidate transdermal system should be covered by the previous approval of (b) (4) (b) (4) Moreover, a clinical study comparing irritation and sensitization potential for Mylan's methylphenidate and Noven's Daytrana® patch (the reference product) showed no significant differences. (b) (4) (b) (4) (b) (4) in Mylan's Methylphenidate Transdermal System is considered acceptable from a Pharmacology/Toxicology perspective.

3. Background Information

The following is a schematic diagram of Mylan's methylphenidate transdermal system as submitted in the consult.

Schematic Cross-Section of Test Product Methylphenidate Transdermal System.

(b) (4)

The ingredient in question, hydrophobic colloidal silica NF (b) (4) is present in the second layer (b) (4) The third layer is the skin contact adhesive, which also contains this compound. The total amount of hydrophobic colloidal silica at the highest dose of methylphenidate patch (28.8 cm^2) is (b) (4) See the excerpted table below for details provided in the consult.

Ingredient	30 mg/ 9 hours ($28.8\ cm^2$)	% w/w	Amount based on MDD	Maximum amount/day based on MDD of approved drug product
Hydrophobic Colloidal Silica NF (b) (4) (b) (4)	(b) (4)			

4. Information Submitted by the Sponsor:

In OGD's consult, the following information was included from the Sponsor: a 30-page pdf file titled (b) (4) (Hydrophobic colloidal Silicon Dioxide) Safety assessment."

(b) (4)

(b) (4)

In Mylan's Methylphenidate Transdermal Systems (10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9 hrs and 30 mg/9 hrs), the hydrophobic colloidal silica levels are (b) (4) At the highest dose, the maximum daily exposure is (b) (4) based on skin exposure.

According to the Sponsor, there are 103 products listed containing silica/silicon dioxide in FDA's Current IIG Database. Regarding dermal application, there is a single listing for silicon dioxide (topical gel, 0.25%) (b) (4) and controlled release transdermal film containing 49 mg).

The following table was extracted from the IIG Database (from the external FDA website) to indicate the relevant levels:

Table. IIG Database search results for: "silicon" (transdermal products):

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency
SILICON DIOXIDE	TRANSDERMAL	FILM, CONTROLLED RELEASE	7631869	ETJ7Z6XBU4	49MG

(b) (4)

The Sponsor's submission provides a tabular summary of ADME and toxicology data for silicon dioxide including acute, chronic, reproductive, and genotoxicity studies. ADME studies are conducted via inhalation, subcutaneous, oral, and IP routes. There were no

data provided for the dermal route but due to the lack of lipid solubility and absorption through the skin, subsequent bioavailability is anticipated to be low.

They also conclude that data available from mice, rats, and rabbits via oral, inhalation, dermal, intratracheal, intraperitoneal and intravenous exposures demonstrated very low order of acute toxicity for silica. In chronic toxicity studies, doses of up to 24,200 mg/kg/day for 14 days, 1,500 mg/kg/day for a month, 8,980 mg/kg/day for six months and 2,500 mg/kg/day for 21 months did not have any significant toxic effects. In mice, the NOAEL was 7,500 mg/kg/day after a 21 month oral exposure to silicon dioxide. They also conclude that 2-year carcinogenicty studies in both mice and rats did not show any tumorigenic potential and silica was not mutagenic or clastogenic. In addition, silica did not have any severe adverse findings in reproductive and developmental toxicity studies. The Sponsor noted that that there was a decrease in fertility index and number of implants following oral dosing of 5,000 mg/kg/day for 5 days in a single study.

Even though there were a variety of studies described in the Sponsor's document for the effect of hydrophilic silica, fewer studies were described for the effect of hydrophobic silica. Below is a list of toxicity studies excerpted from the Sponsor's submission. The list is edited to include only those studies using hydrophobic colloidal silica (b) (4) which is used in Mylan's Methylphenidate transdermal systems.

Single Dose Toxicity studies

Species	Route	Doses	Results	Reference
Rat	Oral	(b) (4) Doses not provided	LD_{50} > 5000 mg/kg	(b) (4)
Rat	Oral	Not provided	LD_{50} > 7900 mg/kg	
Rat	Inhalation	(b) (4) 4 hours using maximum obtainable concentration	$LC_0 \geq 0.477$ mg/L	

Repeat Dose Studies

Species	Route	Duration	Doses	Results	Reference
Rat Wistar Male/Female	Oral Diet	8 weeks	(b) (4) 500, 1000 and *2000 mg/kg/day *High dose increased to 4000 mg/kg/day (wks 3-4), 8000 mg/kg/day (wks 5-6), and then 16000 mg/kg/day (wks 7-8)	At 16000 mg/kg/day there was decreased food intake and bodyweight, cachexia, hemorrhagic changes in mucous membranes of eye and nose, and atrophic changes in liver epithelial cells. At the mid dose, slight changes in liver epithelial cells in two female animals. NOEL = 500 mg/kg/day	(b) (4)

Carcinogenicity

Species	Route	Doses	Results	Reference
Rat Wistar Male/Female	Oral Diet	(b) (4) 100 mg/kg/day 24 months	No malignant tumors observed. No differences in the type and/or number of benign tumors compared to controls. No other organ lesions were reported.	(b) (4)

Genetic Toxicology

Study	Concentrations	Species/Strain	Result	References
In vitro				
Bacterial Mutation	(b) (4) 0.0158-1.58 mg/plate	*Salmonella typhimurium* TA98, TA100 and TA1537 ± S9	Negative	(b) (4)
Bacterial Mutation	(b) (4) 0.0158-1.58 mg/plate	*Escherichia coli* WP2 *uvr*A ± S9	Negative	

Reproductive and Developmental Toxicology

Species/Strain	Study	Dose/Route	Results	References
Rat Wistar Male/Female	Peri-/Post-natal	(b) (4) 100 mg/kg/day Oral diet 2 years	No effects on F1 and F2 animals including clinical symptoms, behavior, developmental changes and litter size. Also, there wre no pathological changes in F0 animals. NOAEL ≥ 100 mg/kg/day	(b) (4)

Special Studies

Species	Test Type	Route	Dose	Summary	Reference
Rabbit	Irritation	Skin Semi-occlusive	(b) (4) Undiluted	Not irritating	(b) (4)
Rabbit	Irritation	Ocular	(b) (4) Unknown dose(s)	Not irritating	
Rabbit	Irritation	Ocular	(b) (4) 0.1 mL (50%) in olive oil	Slightly irritating	

In addition, the Sponsor concludes, and this Reviewer would agree based on its chemical properties, that dermally applied hydrophobic colloidal silica (non-nanoparticle) is minimally absorbed. Moreover, a clinical study comparing irritation and sensitization potential for Mylan's methylphenidate and Noven's Daytrana® patch showed no significant differences. Therefore, they conclude that a level of not more than (b) (4) of hydrophobic colloidal silica does not present any safety concern. Overall, the Sponsor believes that there is enough nonclinical data to demonstrate a wide safety margin for the hydrophobic colloidal silica (b) (4)

5. Reviewer's Evaluation:

The Reviewer's evaluation described here is based on the Sponsor's submission and additional information gathered by this Reviewer:

The Sponsor's tabular summary from the submission included a number of toxicity studies that have been completed. However, only a few of those pertain to this particular product, (b) (4) (these excerpts are presented in section titled "Information submitted by the Sponsor"). Based on this tabular summary no chronic toxicity studies have been conducted with (b) (4)

An oral dietary carcinogencity study was conducted in Wistar Han rats at a dose of 100 mg/kg/day for 24 months but there is no evidence that this product has been tested in carcinogenicity study in a second species. In the rat carcinogenicity study, no malignant or benign tumors were reported. Ames test conducted with (b) (4)

was negative but did not contain all bacterial strains recommended by the guidance on genotoxicity testing (ICH-S2-R1). Strains included in the study were Salmonella typhimurium TA98, TA100, and TA1537 and Escherichia Coli WP2 uvrA in the presence or absence of S9 but missing TA 1535 from the standard battery. No chromosomal aberration assay or *in vivo* micronucleus assay were done with this excipient.

There were no Fertility (Segment I) or Embryofetal (Segment II) studies performed with this formulation. A peri/postnatal (Segment III) oral dietary study was conducted in Wistar Han rats for 2 years and found no effects in F1 or F2 generation. A rabbit ocular irritation study was done with (b) (4) and the compound was found to be slightly irritating. The Sponsor also conducted a clinical irritation and sensitization study and found that cumulative irritation scores and frequency of sensitization for Mylan's methylphenidate transdermal system is similar to that for Daytrana® patch.

The major issue to be resolved is whether (b) (4) should be considered a new excipient based on its chemical properties. In order to better understand the difference between hydrophobic colloidal silica and silicon dioxide, this Reviewer conducted an informal consult with the Chemistry Reviewer, Mariappan Chelliah, Ph.D., assigned to DPP in the OND. It was clarified that (b) (4) is a particular grade of hydrophobic colloidal silica (SiO_2) (b) (4) It is not exactly the same as silicon dioxide but rather a derivative due to surface modification. Dr. Chelliah also provided the following link: *www.medicinecomplete.com* which gives a summary statement on safety indicating that toxicological properties of hydrophobic colloidal silica is the same as hydrophilic silica types because the modified silica surface does not increase its toxicity (Lewinson J *et al. 1994)*. Furthermore, based on its chemical properties, the Chemist also agreed with the Sponsor's claim that the excipient would not be significantly absorbed through the skin. Therefore, (b) (4) is not very different from an already approved excipient (silicon dioxide) and therefore should not be considered a "new excipient".

Considering the amounts listed in the IIG of 49 mg for silicon dioxide and assuming that the amounts are for the biggest patch size of the approved product, these levels correspond to (b) (4) Therefore, current level of skin exposure from Mylan's methylphenidate patch containing (b) (4) of hydrophobic colloidal silica is within previously approved limits for silicon dioxide.

6. Conclusions:

This consult from OGD requests an assessment of the safety of hydrophobic colloidal silica NF (b) (4) levels present in Mylan's Methylphenidate

Transdermal patch. Hydrophobic colloidal silica contains silicon dioxide content of (b) (4) . Based on an informal ONDQA Chemistry consult, silicon dioxide and hydrophobic colloidal silica are not different in chemistry or toxicological profile. Furthermore, due to its chemical properties, it can be considered to be minimally absorbed through the skin. Mylan's summary of studies available for silicon dioxide and hydrophobic colloidal silica indicate no concerning toxicity from systemic exposure. Local toxicity concerns are alleviated based on the IIG database listing for other approved transdermal products containing up to (b) (4) of silicon dioxide (i.e. presumed level of 49 mg in the largest patch). Therefore, a dose of (b) (4) of hydrophobic silicon dioxide (b) (4) planned for Mylan's Methylphenidate should be covered by the previous approval.

7. References:

Lewinson J *et al.* Characterization and toxicological behavior of synthetic amorphous hydrophobic silica. *Regul Toxicol Pharmacol* 1994; 20(1): 37–57

8. Signatures:

Shiny V. Mathew, Ph.D., Pharmacologist *{see appended electronic signature page}*

Shiny V. Mathew -A
Digitally signed by Shiny V. Mathew -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300435414, cn=Shiny V. Mathew -A
Date: 2016.01.25 11:24:35 -05'00'

Ikram Elayan, Ph.D., Supervisor on Detail *{see appended electronic signature page}*

Ikram M. Elayan -A
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Date: 2016.01.25 11:34:27 -05'00'

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	206497	
Drug Product Name	Methylphenidate Transdermal System (TDS)	
Strength(s)	10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr	
Applicant Name	Mylan Technologies, Inc., a Viatris Company[1]	
Applicant Address	110 Lake Street, St. Albans, VT 05478	
Contact Name and Mailing Address	Bradley Davis, Head of Regulatory Science (BD) OR Wayne Talton, Head of Global Regulatory Affairs (WT) 3711 Collins Ferry Road, Morgantown, WV 26505	
Contact Telephone Number	(b) (6)	
Contact Fax Number; Email	(304) 285-6407; Email: brad.davis@viatris.com; wayne.talton@viatris.com	
Original Submission Date(s) and Submission Date of Amendments Previously Reviewed	December 13, 2013	
Submission Date(s) of Amendment(s) Under Review	December 16, 2021	
Primary Assessor	Yoriko Harigaya, Pharm.D.	
Secondary Assessor	Parthapratim Chandaroy, Ph.D.	
Tertiary Assessor	N/A	
Study Number(s)	MPTP-12012	
Study Type(s)	Pivotal PK Endpoint	
Strength(s)	30 mg/9 hr	
Clinical Site	Kendle International Inc a subsidiary of INC Research LLC	
Clinical Site Address	763 Chestnut Ridge Road, Morgantown WV 26505 Tel: 304-599-1197 Fax: 304-599-1254	
Analytical Site	Mylan Pharmaceuticals Inc.	
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd., Morgantown, WV 26505 Tel: 304-598-5430 Fax: 304-285-6478	
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**
Waiver/Deem Bioequivalent	☒ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☐ **N/A**	
QC Dissolution[2]	☐ **Pending** ☒ **Adequate** ☐ **Inadequate** ☐ **N/A**	

[1] In November 2020, Mylan merged with Upjohn, Pfizer's off-patent medicine division, to form Viatris.
[2] There is no assigned OPQ Biopharmaceutics Review. Dissolution data is being assessed by DB only.

Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☐ Minor/IR ☒ N/A (Review is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: Nov 2019[3] RLD Number: NDA 021514 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	**Pharmacokinetic (PK) Study**	**30 mg/9 hr**	☒ Adequate ☐ Inadequate
1, 23, 26	**Waiver**	**10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr**	☒ Adequate ☐ Inadequate

1 EXECUTIVE SUMMARY

This is an amendment review of ANDA 206497, Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr submitted on December 16, 2021.

In the original ANDA dated December 13, 2013, the applicant submitted PK endpoint bioequivalence (BE) study on its test product, Methylphenidate Transdermal System, 30 mg/9 hr, comparing to the corresponding reference listed drug (RLD), as well as reference standard (RS), Noven Pharmaceuticals Inc.'s Daytrana® (methylphenidate transdermal film), 30 mg/9 hr, NDA 021514[4], approved on April 6, 2006. The applicant's PK endpoint BE study was considered adequate[5]. The non-bio strengths: 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr of the test product were deemed bioequivalent to the corresponding reference strengths based on criteria set forth in 21 CFR § 320.24 (b) (6).

Based on the Office of Pharmaceutical Quality (OPQ) Drug Product (DP) review[6], there is significant downward trend in the stability results for assay and in vitro release tests

[3] Draft PSG https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021514.pdf
[4] Orange Book keyword search "021514" accessed on 02/15/2022 https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021514#21355
[5] GDRP, ANDA206497-ORIG-1-RESCIND, Bioequivalence Primary Review, A206497N000DB_N12132013 final final.doc, dated 04/19/2016
[6] GDRP, ANDA206497-ORIG-1-AMEND-15, Drug Product Review, A206497N000CHEMR02.pdf, dated 02/09/2018

(IVRT) and significant upward trend in the stability results for the specified impurities (ritalinic acid and erythro isomer) and total impurities for both the accelerated conditions (ACC) and controlled room temperature (CRT) stability studies.

In the amendment submitted on February 25, 2021, the applicant stated that investigation was performed for the significant downward trend in the IVRT for the stability data, but the root cause was not determined. Briefly, in their investigation, the applicant noted that

(b) (4)

Based on the results, OPQ recommended[7] that the applicant provides their root cause analyses for all the quality issues identified in the stability data and provide their mitigation strategy for each quality issue to ensure that the quality of all future manufactured batches is maintained. The applicant was also requested to submit all stability data for Agency's review.

(b) (4)

[7] GDRP, ANDA206497-ORIG-1-AMEND-23, Drug Product Review, A206497 Drug Product R03- IQ (1).pdf, dated 08/30/2021

[8] SUPAC-MR guidance, Guidance for Industry: *Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (Sep 1997)* https://www.fda.gov/media/70956/download

[9] The SUPAC-MR guidance is for oral products, which are usually far less complex than a TDS product. SUPAC only applies to post-approval changes, not changes to a premarket application. However, previously, OPQ agreed that the spirit of the SUPAC-MR guidance is relevant to TDS (b) (4) (b) (4)

[10] The lowest (10 mg/9 hr) and the highest (30 mg/9 hr) strengths can act as bracketing strengths for the two middle strengths since all four original strengths were (b) (4). To date, the applicant manufactured two new batches #4001578 (30 mg/9 hrs strength) and #4001579 (10 mg/9 hrs strength) (b) (4). The new batches for the middle strengths, 15 mg/9 hr and 20 mg/9 hr, have not been manufactured.

The request for waiver of BE requirements for all strengths of the new test product and Overall Review Result status of the current DB review is now **adequate**.

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[11] GDRP, ANDA206497-ORIG-1-AMDND-26, Drug Product Quality Review, A206497 Drug Product R04-AQ.docx, In Progress as of 02/17/2022

3 REVIEW OF THE AMENDMENT

3.1 Deficiency Comment Sent to the Applicant

[redacted] your original test batches are considered inadequate to support the bio-waiver request. Therefore, please provide comparative in vitro release test (IVRT) data for your new test product, Methylphenidate Transdermal System, 10 mg/9 hr and 30 mg/9 hr, [redacted] with adequate sampling time points (e.g., such as the IVRT sampling times used in your original submission, 0.5, 1.5, 2, 3, 4 and 6 hours) using the FDA recommended dissolution method per the Draft Product Specific Guidance on Methylphenidate Transdermal Film (revised November 2019).

3.1.1 Applicant's Response for Deficiency

Mylan has performed in vitro release testing comparing Mylan's Methylphenidate Transdermal System [redacted] to Daytrana® (reference product) using fully-validated STM-0819. This test method is consistent with the FDA recommended dissolution method that is specified in the Draft Product Specific Guidance on Methylphenidate Transdermal Film (revised November 2019). Per the Agency's request, the 10 mg/9 hr and 30 mg/9 hr strengths of the Mylan and the reference product were tested using the suggested sampling times from the original submission (0.5, 1.5, 2, 3, 4, and 6 hours) at n=12 dosage units. The Bioequivalence Summary Table 5 in Section 2.7 was updated to include the new data and the corresponding Dissolution Profiles Comparison Study is also provided in Section 2.7.

The similarity factor, f_2, between Mylan's Methylphenidate Transdermal System, 10 mg/9 hr (1.1 mg/hr) and the 30 mg/9 hr (3.3 mg/hr) patch strengths was calculated as 80.0, which supports the bio-waiver request.

The updated Bio-waiver Request is provided in Section 1.12.15.

The following additional supporting documents are provided:

- Finished Product Certificates of Analysis for Lots 4001578 and 4001579 provided in Section 3.2.P.5.4
- Certificates of Analysis for Daytrana® Lots 89551 and 90456 provided in Section 3.2.P.5.4

3.1.2 Assessor's Comments on Applicant's Response

The applicant submitted the IVRT comparing the new test products 10 mg/9 hr (lot # 4001579) and 30 mg/9 hr (lot # 4001578) (b) (4) 10 mg/9 hr (lot # 89551) and 30 mg/9 hr (lot # 90456) using the FDA recommended method (900 mL of 0.01N HCl, USP Apparatus VI-Cylinder at 50 rpm, 32°C ± 0.5°C) with the FDA recommended six sampling time points (i.e., 0.5 hr, 1.5 hr, 2 hr, 3 hr, 4 hr and 6 hr). The applicant also submitted the IVRT conducted in October 2013 using the old test products reviewed, previously[12].

The assessor summarized the product formation of bio-strength, 30 mg/9 hr, in the table below.

	New Test	Old Test	New Reference
Batch/Lot No.	4001578	R6D00014	90456
Manufacture Date	9/10/2020	3/1/2012	N/A
Expiration Date	N/A	N/A	Jun-22
Strength	30 mg/9 hr	30 mg/9 hr	30 mg/9 hr
Batch Size	(b) (4)		
Production Batch Size			
Potency	102.60%	98.80%	100.80%
Content Uniformity (mean, %CV)	102.7% ± 0.5%	98.8% ± 1.4%	N/A

*EDR, ANDA206497, SDN23, Module 3.2.P.3.2. Batch Formula, dated 02/25/2021

The f2 values were calculated and listed in the tables below.

F2 values in FDA-Recommended Dissolution Medium

30 mg/9 hr vs 10 mg/9 hr	**Test**	**New**	**Old**
		79.96	70.36
	Reference	**New**	**Old**
		91.61	91.61

30 mg/9 hr		Reference 30 mg/9 hr	F2 value
Test	**Lot #**		
Old Bio-Batch	R6D0014	Old Lot # 66085	71.09
		New Lot # 90456	73.64
N	4001578	Old Lot # 66085	66.94
		New Lot # 90456	69.67

10 mg/9 hr		Reference 10 mg/9 hr	F2 value
Test	**Lot #**		

[12] GDRP, ANDA206497-ORIG-1-RESCIND, Bioequivalence Primary Review, A206497N000DB_N12132013.doc, dated 04/19/2016

Old	R6D0023	Old Lot # 64166	77.20
		New Lot # 89551	82.89
N	4001579	Old Lot # 64166	79.68
		New Lot # 89551	75 94

Note: In these figures, 30 mg/9 hr and 10 mg/9 hr strengths are indicated as 3.3 mg/hr and 1.1 mg/hr, respectively.

Using the FDA-recommended method, the f2 values for the new test 30 mg/9 hr vs. the new test 10 mg/9 hr was greater than 50, which indicates that the IVRT profiles of the new test 10 mg/9 hr strength is **comparable** to the bio-strength 30 mg/9 hr of the new test product in the QC medium. Also, the f2 values of the reference products vs. the new test products for both 30 mg/9 hr and 10 mg/9 hr strengths were greater than 50. The results indicate that IVRT profiles between the new test product and the reference product are **comparable** for both 30 mg/9 hr and 10 mg/9 hr strengths.

The new batches for the middle strengths, 15 mg/9 hr and 20 mg/9 hr, have not been evaluated in the QC medium. However, this is acceptable as the lowest (10 mg/9 hr) and the highest (30 mg/9 hr) strengths can act as bracketing strengths for the two middle strengths, as all four original strengths were (b) (4) .

The results suggest that the IVRT profiles of the new test 30 mg/9 hr and 10 mg/9 hr strengths using the FDA-recommended method are **adequate** to support bio-waiver of the 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr strengths of the new test product.

Briefly, the applicant also conducted drug release studies in multi-pH media with three sampling time points (i.e., 0.5 hr, 1.5 hr and 4 hr) on the new test 30 mg/9 hr lot # 400062 and the reference 30 mg/9 hr lot # R616056. (b) (4) The results suggest that pH differences in the dissolution media have no or minimal impact on IVRT profiles of the new test product 30 mg/9 hr strength. Moreover, for the TDS product, multi-pH media dissolution studies, generally recommended for modified release oral products, would not be relevant. The original IVRT conducted in May 2013 using the FDA-recommended method with three sampling time ranges (i.e., 0-0.5 hr, 0.5-2 hr, 2-6 hr) was also submitted. These results from multi-pH media and original IVRT are provided in the Section 3.2.1 as additional submissions for information purpose.

(b) (4)

3.2 Summary of In Vitro Drug Release Data

Comparative Drug Release Summaries – Mylan 2020 Exhibit Batches vs. Daytrana®

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Applicant's Proposed Specifications	0.5 hrs – (b) (4)	1.5 hrs – (b) (4) (b) (4) 3 hrs – (b) (4) 4 hrs – (b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						0.5 hr	**1.5 hr**	**2 hr**	**3 hr**	**4hr**	**6hr**	
N/A	10/19/21	New Test Methylphenidate Transdermal System Lot 4001579 MFG: September 2020	1.1 mg/hr	12	Mean % of Label Claim	34	58	66	76	83	89	2.7
					RSD%	2.2	1.2	1.2	0.9	0.6	0.8	
					Range % of Label Claim	(b) (4)						
N/A	10/21/21	Daytrana® Lot 89551 Expiry: January 2022	1.1 mg/hr	12	Mean % of Label Claim	31	54	62	74	81	89	
					RSD%	1.9	1.1	1.1	0.7	0.9	0.7	
					Range % of Label Claim	(b) (4)						

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Applicant's Proposed Specifications	0.5 hrs (b) (4) 1.5 hrs – (b) (4) (b) (4) 3 hrs (b) (4) 4 hrs – (b) (4)	
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						0.5 hr	**1.5 hr**	**2 hr**	**3 hr**	**4hr**	**6hr**	
N/A	10/19/21	New Test Methylphenidate Transdermal System Lot 4001578 MFG: September 2020	3.3 mg/hr	12	Mean % of Label Claim	34	59	68	79	86	92	2.7
					RSD%	1.3	0.8	1.2	1.1	0.8	0.8	
					Range % of Label Claim	(b) (4)						
N/A	10/21/21	Daytrana® Lot 90456 Expiry: June 2022	3.3 mg/hr	12	Mean % of Label Claim	31	55	63	74	82	91	
					RSD%	0.0	0.9	0.8	0.7	0.6	0.6	
					Range % of Label Claim	(b) (4)						

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Applicant's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						0.5 hr	**1.5 hr**	**2 hr**	**3 hr**	**4 hr**	**6 hr**	
N/A	10/31/13	Old Test Methylphenidate Transdermal System Lot R6D0023 April 2012	1.1 mg/hr	12	Mean µg/hr/cm^2	32	56	63	74	80	85	3.2.P.5.4
					RSD%	1.6	1.8	1.4	1.5	1.6	1.7	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 64166 January 2014	1.1 mg/hr	12	Mean µg/hr/cm^2	31	55	63	75	82	91	
					RSD%	1.3	1.0	0.9	1.0	1.1	1.4	
					Range µg/hr/cm^2	(b) (4)						

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Applicant's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						0.5 hr	**1.5 hr**	**2 hr**	**3 hr**	**4 hr**	**6 hr**	
N/A	10/31/13	Old Test Methylphenidate Transdermal System Lot R6D0014 March 2012	3.3 mg/hr	12	Mean µg/hr/cm^2	34	59	67	78	84	90	3.2.P.5.4
					RSD%	0.8	0.9	0.8	0.8	0.7	0.7	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 66085 March 2014	3.3 mg/hr	12	Mean µg/hr/cm^2	31	54	62	74	82	89	
					RSD%	1.7	0.8	0.9	0.8	0.8	0.6	
					Range µg/hr/cm^2	(b) (4)						

Dissolution Conditions	Apparatus:	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Applicant's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/29/13 – 10/30/13	Old Test Methylphenidate Transdermal System Lot R6D0035 November 2012	1.6 mg/hr	12	Mean µg/hr/cm²	35	61	69	80	86	91	3.2.P.5.4
					RSD%	1.1	0.7	0.9	0.7	0.8	0.9	
					Range µg/hr/cm²	(b) (4)						
N/A	10/28/13	Daytrana® Lot 65474 February 2014	1.6 mg/hr	12	Mean µg/hr/cm²	30	54	62	73	80	89	
					RSD%	1.6	1.2	1.0	1.7	1.1	1.5	
					Range µg/hr/cm²	(b) (4)						

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Applicant's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						0.5 hr	**1.5 hr**	**2 hr**	**3 hr**	**4 hr**	**6 hr**	
N/A	10/30/13	Old Test Methylphenidate Transdermal System Lot R6D0036 November 2012	2.2 mg/hr	12	Mean µg/hr/cm^2	37	64	72	83	90	96	3.2.P.5.4
					RSD%	1.1	0.8	0.5	0.6	1.0	0.9	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/29/13	Daytrana® Lot 64925 January 2014	2.2 mg/hr	12	Mean µg/hr/cm^2	30	52	60	71	78	87	
					RSD%	1.7	1.0	0.6	1.0	0.7	0.7	
					Range µg/hr/cm^2	(b) (4)						

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Dissolution Conditions		**Apparatus:**	Apparatus VI - Cylinder						
		Speed of Rotation:	50 rpm						
		Medium:	0.01N Hydrochloric Acid						
		Volume:	900 mL						
		Temperature:	32°C ± 0.5°C						
Applicant's Proposed Specifications			(b) (4)						
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)		Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478							
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**			**Study Report Location**
						0-0.5 hr	**0.5-2 hr**	**2-6 hr**	
N/A	10/31/13	Methylphenidate Transdermal System Lot R6D0023 April 2012	1.1 mg/hr	12	Mean µg/hr/cm^2	702	224	59	3.2.P.5.4
					RSD%	1.7	1.4	3.9	
					Range µg/hr/cm^2	(b) (4)			
					% Claim	32	63	85	
N/A	10/28/13	Daytrana® Lot 64166 January 2014	1.1 mg/hr	12	Mean µg/hr/cm^2	1371	470	153	
					RSD%	1.0	0.9	2.9	
					Range µg/hr/cm^2	(b) (4)			
					% Claim	31	63	91	

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Applicant's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**			**Study Report Location**
						0-0.5 hr	**0.5-2 hr**	**2-6 hr**	
N/A	10/29/13 - 10/30/13	Methylphenidate Transdermal System Lot R6D0035 November 2012	1.6 mg/hr	12	Mean µg/hr/cm^2	767	245	60	3.2.P.5.4
					RSD%	0.6	1.3	3.2	
					Range µg/hr/cm^2	(b) (4)			
					% Claim	35	69	91	
N/A	10/28/13	Daytrana® Lot 65474 February 2014	1.6 mg/hr	12	Mean µg/hr/cm^2	1339	458	149	
					RSD%	0.9	1.2	2.8	
					Range µg/hr/cm^2	(b) (4)			
					% Claim	30	62	89	

Dissolution Conditions		**Apparatus:**	Apparatus VI - Cylinder						
		Speed of Rotation:	50 rpm						
		Medium:	0.01N Hydrochloric Acid						
		Volume:	900 mL						
		Temperature:	32°C ± 0.5°C						
Applicant's Proposed Specifications			(b) (4)						
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)			Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478						
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**			**Study Report Location**
						0-0.5 hr	**0.5-2 hr**	**2-6 hr**	
N/A	10/30/13	Methylphenidate Transdermal System Lot R6D0036 November 2012	2.2 mg/hr	12	Mean µg/hr/cm^2	791	253	64	3.2.P.5.4
					RSD%	0.5	0.6	2.1	
					Range µg/hr/cm^2	(b) (4)			
					% Claim	37	72	96	
N/A	10/29/13	Daytrana® Lot 64925 January 2014	2.2 mg/hr	12	Mean µg/hr/cm^2	1302	445	148	
					RSD%	0.6	0.7	0.9	
					Range µg/hr/cm^2	(b) (4)			
					% Claim	30	60	87	

Dissolution Conditions		**Apparatus:**	Apparatus VI - Cylinder						
		Speed of Rotation:	50 rpm						
		Medium:	0.01N Hydrochloric Acid						
		Volume:	900 mL						
		Temperature:	32°C ± 0.5°C						
Applicant's Proposed Specifications			(b) (4)						
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)		Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478							
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**			**Study Report Location**
						0-0.5 hr	**0.5-2 hr**	**2-6 hr**	
N/A	10/31/13	Methylphenidate Transdermal System Lot R6D0014 March 2012	3.3 mg/hr	12	Mean µg/hr/cm^2	736	237	62	3.2.P.5.4
					RSD%	0.8	0.8	1.0	
					Range µg/hr/cm^2	(b) (4)			
					% Claim	34	67	90	
N/A	10/28/13	Daytrana® Lot 66085 March 2014	3.3 mg/hr	12	Mean µg/hr/cm^2	1348	464	148	
					RSD%	1.2	1.5	1.5	
					Range µg/hr/cm^2	(b) (4)			
					% Claim	31	62	89	

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Dissolution Conditions									
	Apparatus:	Apparatus VI - Cylinder							
	Speed of Rotation:	50 rpm							
	Medium:	0.01N Hydrochloric Acid							
	Volume:	900 mL							
	Temperature:	32°C ± 0.5°C							
Applicant's Proposed Specifications	0.5 hrs - (b) (4) 1.5 hrs – (b) (4) 4 hrs – (b) (4)								
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478								
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Manufacture Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**			**Study Report Location**
						0.5 hr	**1.5 hr**	**4 hr**	
N/A	05/08/17	**New Test** Methylphenidate Transdermal System Lot 4000462 February 2017	3.3 mg/hr	12	Mean % of Label Claim	35	61	87	2.7
					RSD%	1.6	1.7	1.8	
					Range % of Label Claim	(b) (4)			
N/A	05/08/17	**New Test** Methylphenidate Transdermal System Lot R616056 September 2016	3.3 mg/hr	12	Mean % of Label Claim	36	63	89	
					RSD%	0.8	0.7	0.8	
					Range % of Label Claim	(b) (4)			

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BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA:	206497
APPLICANT:	Mylan Technologies, Inc., a Viatris Company
DRUG PRODUCT:	Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

The Division of Bioequivalence (DB) II has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Hongling Zhang, Ph.D.
Acting Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Completed Assignment for 206497 ID: 47476

Reviewer: Harigaya, Yoriko **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

ID	Letter Date	Productivity Category	Sub Category	Sc re	Subt al
47476	12/16/2021	BIO	ANDA Amendment [1]	1	1
47476	12/16/2021	Parallel	Minor Amendment (Original or Supplement) [1]	1	1
47476	12/16/2021	Parallel	Pre-Screening [0.25]	0 25	0.25
				Total:	2.25

DIVISION OF BIOEQUIVALENCE ADDENDUM REVIEW

ANDA No.	206497	
Drug Product Name	Methylphenidate Transdermal System (TDS)	
Strength(s)	10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr	
Applicant Name	Mylan Technologies, Inc., a Viatris Company[1]	
Applicant Address	110 Lake Street, St. Albans, VT 05478	
Contact Name and Mailing Address	Bradley Davis, Head of Regulatory Science or Wayne Talton, Head of Global Regulatory Affairs 781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504-4310	
Contact Telephone Number	(b) (6)	
Contact Fax Number; Email	(304) 285-6407; brad.davis@viatris.com; wayne.talton@viatris.com	
Original Submission Date(s) and Submission Date of Amendments Previously Reviewed	December 13, 2013	
Submission Date(s) of Amendment(s) Under Review	February 25, 2021	
Primary Assessor	Yoriko Harigaya, Pharm.D.	
Secondary Assessor	Parthapratim Chandaroy, Ph.D.	
Tertiary Assessor	N/A	
Study Number(s)	MPTP-12012	
Study Type(s)	Pivotal PK Endpoint	
Strength(s)	30 mg/9 hr	
Clinical Site	Kendle International Inc a subsidiary of INC Research LLC	
Clinical Site Address	763 Chestnut Ridge Road, Morgantown WV 26505 Tel: 304-599-1197 Fax: 304-599-1254	
Analytical Site	Mylan Pharmaceuticals Inc.	
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd., Morgantown, WV 26505 Tel: 304-598-5430 Fax: 304-285-6478	
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent)	**Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A	

[1] In November 2020, Mylan merged with Upjohn, Pfizer's off-patent medicine division, to form Viatris.

Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☒ Minor/IR ☐ N/A (Review is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: Nov 2019 RLD Number: NDA 021514 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	**Pharmacokinetic (PK) Study**	**30 mg/9 hr**	☒ Adequate ☐ Inadequate
1, 23	**Waiver**	**10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr**	☐ Adequate ☒ Inadequate

1 EXECUTIVE SUMMARY

This is an addendum to the bioequivalence (BE) assessment dated 04/19/2016[2]. The purpose of this addendum is to review the new test product batch of Methylphenidate Transdermal System [redacted] (b) (4) by Mylan Technologies, Inc., a Viatris Company (Mylan).

In the original ANDA dated December 13, 2013, the applicant submitted PK endpoint bioequivalence (BE) study on its test product, Methylphenidate Transdermal System, 30 mg/9 hr, comparing to the corresponding reference listed drug (RLD), as well as reference standard (RS), Noven Pharmaceuticals Inc.'s Daytrana® (methylphenidate transdermal film), 30 mg/9 hr, NDA 021514[3], approved on April 6, 2006. The BE study was designed as randomized, open label, two treatment, three period, single dose, partially-replicate, crossover study in healthy male and female subjects. The applicant's PK endpoint BE study was considered adequate[2]. The non-bio strengths: 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr of the test product were deemed bioequivalent[2] to the corresponding reference strengths based on criteria set forth in 21 CFR § 320.24 (b) (6).

[2] GDRP, ANDA206497-ORIG-1-RESCIND, Bioequivalence Primary Review, A206497N000DB_N12132013.doc, dated 04/19/2016

[3] Orange Book keyword search "021514" accessed on 09/15/2021 https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021514#21355

Based on the Office of Pharmaceutical Quality (OPQ) Drug Product (DP) review[4], there is significant downward trend in the stability results for assay and in vitro release tests (IVRT) and significant upward trend in the stability results for the specified impurities (ritalinic acid and erythro isomer) and total impurities for both the accelerated conditions (ACC) and controlled room temperature (CRT) stability studies.

In the current amendment submitted on February 25, 2021, the applicant states that investigation was performed for the significant downward trend in the IVRT for the stability data, but the root cause was not determined. Briefly, in their investigation, the (b) (4)

Based on the results, the OPQ recommends[5] that the applicant provides their root cause analyses for all the quality issues identified in the stability data and provide their mitigation strategy for each quality issue to ensure that the quality of all future manufactured batches is maintained. The applicant is also requested to submit all stability data for Agency's review.

The DBII review team contacted the OPQ review team by Email[6] to clarify the level of (b) (4) The OPQ review team responded that the (b) (4) according to the Scale-Up and Post-approval Changes Modified Release Solid Oral Dosage (SUPAC-MR) guidance[7,8]. (b) (4)

[4] GDRP, ANDA206497-ORIG-1-AMEND-15, Drug Product Review, A206497N000CHEMR02.pdf, dated 02/09/2018

[5] GDRP, ANDA206497-ORIG-1-AMEND-23, Drug Product Review, A206497 Drug Product R03- IQ (1).pdf, dated 08/30/2021

[6] Email communication with OPQ regarding ANDA 206497 ORIG-1-AMEND-23.pdf is archived at \\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\Email Communications

[7] SUPAC-MR guidance, Guidance for Industry: *Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (Sep 1997)* *https://www.fda.gov/media/70956/download*

[8] The SUPAC-MR guidance is for oral products, which are usually far less complex than a TDS product. SUPAC only applies to post-approval changes, not changes to a premarket application. However, previously, OPQ agreed that the spirit of the SUPAC-MR guidance is relevant to TDS (b) (4) (b) (4)

(b) (4)

Additionally, the Guidance[9] for Transdermal and Topical Delivery Systems-Product Development and Quality Considerations (November 2019) says, "*changes to TDS after the conduct of pivotal clinical studies should be avoided when possible because of the sensitivity of TDS to small changes in formulation and manufacturing process*" and also indicates "*moderate-risk changes may warrant additional developmental studies and stability data on commercial scale batches to demonstrate that they will not result in an adverse impact on the quality of the product*."

Overall, the applicant is requested to conduct IVRT testing in compendial release requirements for the new test batches manufactured (b) (4)

To date, the applicant manufactured two new batches #4001578 (30 mg/9 hrs strength) and #4001579 (10 mg/9 hrs strength) (b) (4) The new batches for the middle strengths, 15 mg/9 hr and 20 mg/9 hr, have not been manufactured. However, this is acceptable as the lowest (10 mg/9 hrs) and the highest (30 mg/9 hrs) strengths can act as bracketing strengths for the two middle strengths since all four original strengths (b) (4) Therefore, the applicant will be requested to conduct IVRT testing on the two strengths (b) (4)

Overall, the application is inadequate at this point due to pending new IVRT studies. The request for waiver of BE requirements for all strengths of the new test product and Overall Review Result status of the current DB review is **inadequate**. The letter to the applicant in this review supersedes the letter in previous BE review.

[9] Guidance for Industry: Transdermal and Topical Delivery Systems-Product Development and Quality Considerations (November 2019) https://www fda.gov/media/132674/download

[10] "All dosing strengths of Mylan's Methylphenidate Transdermal Systems and Daytrana® (b) (4) The only differences between dosing strengths are the area." \\CDSESUB1\evsprod\anda206497\0000\m3\32-body-data\32p-drug-prod\mptp-td-p-mti\32p2-pharm-dev\pharmaceutical-development.pdf (page 107 of 160)

NOTE to the RPM: The deficiency letter in the current review document supersedes the letter of the BE review dated 04/19/2016 for the current ANDA in GDRP (A206497N000DB_N12132013).

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:	206497
APPLICANT:	Mylan Technologies, Inc., a Viatris Company
DRUG PRODUCT:	Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

The Division of Bioequivalence (DB) II has completed its review and has identified the following deficiency:

(b) (4) your original test batches are considered inadequate to support the bio-waiver request. Therefore, please provide comparative in vitro release test (IVRT) data for your new test product, Methylphenidate Transdermal System, 10 mg/9 hr and 30 mg/9 hr, (b) (4) strengths with adequate sampling time points (e.g., such as the IVRT sampling times used in your original submission, 0.5, 1.5, 2, 3, 4 and 6 hours) using the FDA recommended dissolution method per the Draft Product Specific Guidance on Methylphenidate Transdermal Film (revised Nov. 2019).

Sincerely yours,

Hongling Zhang, Ph.D.
Acting Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Completed Assignment for 206497 ID: 46161

Reviewer: Harigaya, Yoriko **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

D	*Letter Date*	*Productivity Category*	*Sub Category*	*Sc re*	*Sub a l*		
46161	2/24/2021	BIO	Addendum [1]	1	1	Edit	Delete
46 1	2/24/ 21	Par lel	Addend m (not for Clarific ion or Error Correction) [1]	1	1	Edit	Delete
				Total	2		

DIVISION OF BIOEQUIVALENCE DRUG RELEASE AMENDMENT REVIEW

ANDA No.	206497
Drug Product Name	Methylphenidate Transdermal System
Strength	10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr
Applicant Name	Mylan Technologies, Inc.
Applicant Address	110 Lake Street, St. Albans, VT 05478
Applicant's Point of Contact	Bradley Davis, Head of Regulatory Science or Wayne Talton, Head of Global Regulatory Affairs 781 Chestnut Ridge Road, P.O. Box 4310 Morgantown, WV 26504-4310
Contact's Telephone Number	(b) (6)
Contact's Fax Number	(304) 285-6407
Contact's Email Address	brad.davis@mylanlabs.com; wayne.talton@mylan.com
Original Submission Date(s)	December 13, 2013
Submission Date(s) of Amendment(s) Under Review	October 19, 2017
Primary Reviewer	Yoriko Harigaya, Pharm.D.
Secondary Reviewer	Parthapratim Chandaroy, Ph.D.
Tertiary Reviewer	N/A
Drug release Method	**ADEQUATE**
OVERALL REVIEW RESULT	**ADEQUATE**
COMMUNICATION	☐ **Major** ☐ **Minor/IR** ☒ **N/A (Review is Adequate)**

1. Executive Summary

This is a drug release review of the data submitted in the amendment dated October 19, 2017.

In the original ANDA submission dated December 13, 2013, Mylan Technologies, Inc. conducted acceptable drug release testing for its Methylphenidate Transdermal System 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr using the FDA-recommended method [900 mL of 0.01 N HCl, USP Apparatus VI (Cylinder) at 50 rpm][1]. However, the applicant's proposed specifications were not acceptable. Based on the submitted drug release testing data, the Division of Bioequivalence (DB) recommended the following specifications for the test product: (b) (4) in 0.5 hr; (b) (4) in 1.5 hr; (b) (4) in 4 hr.

[1] GDRP, ANDA-206497-ORIG-1-RESCIND, Biopharmaceutics Primary Review, A206497N000DB_D12132013.doc, dated 3/31/2016

In the amendment dated July 27, 2017, the applicant did not accept the FDA-recommended specification at 4 hr and proposed [(b) (4)] in 4 hr due to the slight downward trend observed on stability data at 6 months of the test product. Per DB practice, the drug release method and specifications are established based on the drug release data on 12 units of the fresh (not stored) lot of the test product that has been used in acceptable bioequivalence. Therefore, the applicant's proposal to change FDA-recommended drug release specification for the test product, based on stability data, was not acceptable.

In the current amendment, dated October 19, 2017, the applicant accepts the following Agency's proposed method and specifications.

Medium	0.01 N HCl
Volume	900 mL
USP Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications*	[(b) (4)] in 0.5 hr in 1.5 hr **in 4 hr**

*percent of labeled content

The drug release testing is now **adequate**.

2. Table of Contents

3. Review of the Amendment

3.1 Deficiency Comment

Your proposal to change the FDA-recommended drug release specification of [(b) (4)] in 4 hr to [(b) (4)] in 4 hr is not acceptable. Per the DB policy, the drug release specifications are established based on the drug release data obtained from fresh (not stored) lots. Accordingly, the FDA-recommended specification of [(b) (4)] at 4 hr was based on release rate for all four strengths of the fresh test product lot at 4 hr. The DB does not revise specifications based on stability data. Therefore, as communicated previously, please acknowledge your acceptance of the following FDA-recommended drug release method and specifications for your test product:

Medium	0.01 N HCl
Volume	900mL
Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications*	(b) (4) in 0.5 hr in 1.5 hr in 4 hr

* percent of labeled content

Alternatively, you may submit additional comparative drug release data on 12 dosage units each of all strengths of the test product from three fresh production lots, and unexpired reference lots, for the Agency to determine if any revision of drug release specification is warranted.

3.2 Applicant's Response to the Deficiency Comment

Mylan acknowledges and accepts the FDA-recommended dissolution method and specifications.

The following documents have been revised to reflect the FDA-recommended drug release specifications:

- Finished Product Specifications; 10 mg/9 hr (1.1 mg/hr), 15 mg/9 hr (1.6 mg/hr), 20 mg/9 hr (2.2 mg/hr), and 30 mg/9 hr (3.3 mg/hr) (provided in Section 3.2.P.5.1)
- Certificate of Analysis for Lots R6D0014, R6D0023, R6D0035, R6D0036, R616056, and 4000462 (provided in Section 3.2.P.5.4)
- Justification of Specifications (provided in Section 3.2.P.5.6)

3.3 Reviewer's Comment

The applicant was requested to acknowledge the following FDA-recommended drug release method and specifications of its test product.

FDA-Recommended Method and Specifications

Medium	0.01 N HCl
Volume	900 mL
USP Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specification	(b) (4) in 0.5 hr in 1.5 hr **in 4 hr**

In the current amendment, dated October 19, 2017, the applicant accepts the above Agency's recommended method and specifications. The reviewer confirmed that applicant amended the specification ranges in the Certificate of Analyses for lots #R6D0014 (30 mg/hr), #R6D0023 (10 mg/hr), #R6D0035 (15 mg/hr), #R6D0036 (20 mg/hr), #R61656 (30 mg/hr) and #4000462 (30 mg/hr) accordingly.

The drug release testing is now **adequate**.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 206497

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

The Division of Bioequivalence (DB) has completed its review of the dissolution testing portion of your submission and has no further questions at this time.

We acknowledge that you will conduct the dissolution testing of your test product using the following dissolution method and specifications:

Medium	0.01 N HCl
Volume	900 mL
Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications*	(b) (4) in 0.5 hr in 1.5 hr in 4 hr

*percent of labeled content

Sincerely yours,

Ethan M. Stier, Ph.D., R.Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Completed Assignment for 206497 ID: 33541

Reviewer: Harigaya, Yoriko **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
33541	10/19/2017	BIO	Dissolution Amendment [1]	1	1
33541	10/19/2017	Parallel	Dissolution Amendment [1]	1	1
				Total:	2

DIVISION OF BIOEQUIVALENCE DRUG RELEASE AMENDMENT REVIEW

ANDA No.	206497
Drug Product Name	Methylphenidate Transdermal System
Strength	10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr
Applicant Name	Mylan Technologies, Inc.
Applicant Address	110 Lake Street, St. Albans, VT 05478
Applicant's Point of Contact	Bradley Davis, Head of Regulatory Science 781 Chestnut Ridge Road, P.O. Box 4310 Morgantown, WV 26504-4310
Contact's Telephone Number	(b) (6)
Contact's Fax Number	(304) 285-6407
Contact's Email Address	brad.davis@mylanlabs.com
Original Submission Date(s)	December 13, 2013
Submission Date(s) of Amendment(s) Under Review	July 27, 2017
Primary Reviewer	Yoriko Harigaya, Pharm.D.
Secondary Reviewer	Parthapratim Chandaroy, Ph.D.
Tertiary Reviewer	N/A
Drug release Method	**ADEQUATE**
OVERALL REVIEW RESULT	**INADEQUATE**
COMMUNICATION	☐ **Major** ☒ **Minor/IR** ☐ **N/A (Review is Adequate)**

1. Executive Summary

This is a drug release review of the data submitted in the amendment dated July 27, 2017.

In the original ANDA submission dated December 13, 2013, Mylan Technologies, Inc. conducted acceptable drug release testing for its Methylphenidate Transdermal System 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr using the FDA-recommended method [900 mL of 0.01 N HCl, USP Apparatus VI (Cylinder) at 50 rpm][1]. However, the firm's proposed specifications were not acceptable. Based on the submitted drug release testing data, the DB recommended the following specifications for the test product: (b) (4) in 0.5 hr; (b) (4) in 1.5 hr; (b) (4) in 4 hr.

In the current amendment dated July 27, 2017, the firm did not accept the FDA-recommended specification at 4 hr and proposed (b) (4) in 4 hr due to the slight downward trend observed on stability data at 6 months of the test product. Per Division

[1] GDRP, ANDA-206497-ORIG-1-RESCIND, Biopharmaceutics Primary Review, A206497N000DB_D12132013.doc, dated 3/31/2016

of Bioequivalence (DB) practice, the drug release method and specifications are established based on the drug release data on 12 units of the fresh (not stored) lot of the test product that has been used in acceptable bioequivalence testing. Therefore, the firm's proposal to change FDA-recommended drug release specification for the test product is not acceptable.

The firm will be requested to acknowledge the following drug release method and specifications of its test product.

Medium	0.01 N HCl
Volume	900 mL
USP Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specification	(b) (4) n 0.5 hr in 1.5 hr **in 4 hr**

Alternatively, the DB may consider revision of drug release method and specifications based on data from three fresh production lots. The firm may submit additional drug release data on 12 dosage units each of all strengths of the test product from three fresh production lots, for the Agency to determine if any revision of the drug release specification is warranted.

The drug release testing is **inadequate**.

2. Table of Contents

3. Review of the Amendment

3.1 Deficiency Comment

The dissolution testing on your test product, Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, using the FDA recommended dissolution method is incomplete. Your proposed specifications of (b) (4) (b) (4) (b) (4) are not acceptable. Based on the data submitted, the Office of Bioequivalence recommends following method and specifications.

Medium	**0.01 N HCl**
Volume	900 mL
Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications*	(b) (4) in 0.5 hr in 1.5 hr in 4 hr

*percent of labeled content

With your response, please indicate if you accept the above FDA recommended method and specifications.

For your future applications, please provide specifications in percent of labeled content expressed in ranges per the USP General Chapter <724> Transdermal Delivery Systems – General Drug Release Standards, and its Acceptance Table.

3.2 Firm's Response to the Deficiency Comment

Mylan acknowledges and accepts the FDA-recommended dissolution method and the specification ranges for the 0.5 hr and 1.5 hr sampling times. A minor shift in the specification range for the 4 hr sampling time is proposed, as listed in the summary table below.

Parameters	**Current Mylan Method/Specifications**	**FDA-Recommended Method/Specifications**	**Proposed Mylan Method/Specifications**
Method			
Medium	0.01N HCl	0.01N HCl	0.01N HCl
Volume	900 mL	900 mL	900 mL
Apparatus	App. VI (Cylinder)	App. VI (Cylinder)	App. VI (Cylinder)
Speed	50 rpm	50 rpm	50 rpm
Temperature	32°C ± 0.5°C	32°C ± 0.5°C	32°C ± 0.5°C
Specifications			
0.5 hrs	(b) (4)		

1.5 hrs	(b) (4)
2 hrs	
4 hrs	
6 hrs	

Mylan's request for a minor shift in the specification range for the 4 hr sampling time is due to the very limited data that Mylan has at this timepoint, the slight downward trend observed on stability for this test, and the measured result of a recently manufactured scale-up batch, lot R616066 (10 mg/9 hr), where the % drug release at 4 hours was nearly at the FDA-recommended lower limit of (b) (4) after storage at 40°C/75% RH for 6 months. This data is provided below.

Lot No.	Storage Conditions	Sampling Time (hrs)	Drug Release (% of claim)	Proposed Mylan Specifications
R616066	6 Months 40°C/75% RH	0.5		(b) (4)
		1.5		
		4		

Based on even this very limited data, Mylan would be at significant risk of failing the FDA-Recommended limit. The mean % Release at the 4 hr sampling time is at the low end of the FDA-recommended specification range of (b) (4) The alternative specification range proposed by Mylan, (b) (4) better fits the data, allowing for the slight decrease in % Release expected during product shelf life, yet still maintains the same FDA-recommended ± 10% window for acceptance criteria.

With only extremely limited data at the 4 hour sampling time, Mylan attempted to estimate an acceptance range at 4 hours based on data that Mylan has acquired at 2 hours and 6 hours. However, this requires the interpolation of the data in a region of the dissolution profile that is non-linear where assumptions of the curve-fitting would need to be made. This made the estimate of % drug released at 4 hours using historic data unreliable, adding even more risk to establishing an acceptance range at this sampling time.

The following documents have been revised to reflect the FDA-recommended drug release method and Mylan proposed specifications:

- Drug Product Specifications; 10 mg/9 hr (1.1 mg/hr), 15 mg/9 hr (1.6 mg/hr), 20 mg/9 hr (2.2 mg/hr), and 30 mg/9 hr (3.3 mg/hr) (provided in Section 3.2.P.5.1)
- Drug Release from Methylphenidate Transdermal Systems, STM-0819 (provided in Section 3.2.P.5.2).
- Certificate of Analysis for Lots R6D0014, R6D0023, R6D0035, and R6D0036 (provided in Section 3.2.P.5.4)
- Justification of Specifications (provided in Section 3.2.P.5.6)
- Stability Protocol (provided in Section 3.2.P.8.2)

3.3 Reviewer's Comment

As per the external drug release database, the following drug release method is recommended for Methylphenidate Transdermal System.

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Methylphenidate	Transdermal Patch	VI (Cylinder)	50	0.01 N HCl at 32°C	900	0.5, 1.5, 3, 4 hours and until at least 80% released	04/15/2008

FDA-Recommended Method and Specifications

Medium	0.01 N HCl
Volume	900 mL
USP Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specification	(b) (4) n 0.5 hr in 1.5 hr **in 4 hr**

The above specifications are recommended based on the USP General Chapter <724> (Transdermal Delivery Systems) Drug Release - General Drug Release Standards for Apparatus 6 and its Acceptance Table listed below.

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range.

The firm accepted the FDA-recommended specifications at 0.5 hr and 1.5 hr time points. However, the firm did not accept the above FDA-recommended specifications at 4 hr and proposed (b) (4) **in 4 hr**, since a slight downward trend was observed in stability data at 6 months for their product. The **mean % release at 4 hr sampling time was** (b) (4) **at 6 months** which is at the low end of the FDA-recommended specification range of (b) (4)

Stability Data at 6 Months

Lot No.	Storage Conditions	Sampling Time (hrs)	Drug Release (% of claim)	Proposed Mylan Specifications
R616066	6 Months 40°C/75% RH	0.5		(b) (4)
		1.5		
		4		

However, the drug release method and specifications are established based on the drug release data on 12 units of the fresh (not stored) lot of the test product that has been used in acceptable bioequivalence studies. Accordingly, the FDA-recommended specification of (b) (4) at 4 hr was based on release rate for all four strengths of the test product at 4 hr. The DB does not revise specifications based on stability data. Therefore, the firm's proposed specification of (b) (4) in 4 hr, based on stability data, is not acceptable.

The firm will be requested to acknowledge the above FDA-recommended drug release method and specifications of its test product.

Alternatively, the firm may submit additional drug release data, on 12 dosage units each of all strengths of the test product from three fresh production lots, for the Agency to determine if any revision of the drug release specification is warranted.

The drug release testing is **incomplete**.

4. Summary of In Vitro Drug Release Data

In May 2013, the firm conducted drug release tests using the FDA-recommended method with three sampling time ranges (i.e., 0-0.5 hr, 0.5-2 hr, 2-6 hr). In October 2013, the firm re-conducted the drug release tests for all strengths using the FDA-recommended method with six sampling time points as follows:

10 mg/9 hr (1.1 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)		Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/31/13	Methylphenidate Transdermal System Lot R6D0023 April 2012	1.1 mg/hr	12	Mean µg/hr/cm^2	32	56	63	74	80	85	3.2.P.5.4
					RSD%	1.6	1.8	1.4	1.5	1.6	1.7	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 64166 January 2014	1.1 mg/hr	12	Mean µg/hr/cm^2	31	55	63	75	82	91	
					RSD%	1.3	1.0	0.9	1.0	1.1	1.4	
					Range µg/hr/cm^2	(b) (4)						

15 mg/9 hr (1.6 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	(b) (4)	
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/29/13 – 10/30/13	Methylphenidate Transdermal System Lot R6D0035 November 2012	1.6 mg/hr	12	Mean µg/hr/cm^2	35	61	69	80	86	91	3.2.P.5.4
					RSD%	1.1	0.7	0.9	0.7	0.8	0.9	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 65474 February 2014	1.6 mg/hr	12	Mean µg/hr/cm^2	30	54	62	73	80	89	
					RSD%	1.6	1.2	1.0	1.7	1.1	1.5	
					Range µg/hr/cm^2	(b) (4)						

20 mg/9 hr (2.2 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)		Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/30/13	Methylphenidate Transdermal System Lot R6D0036 November 2012	2.2 mg/hr	12	Mean µg/hr/cm^2	37	64	72	83	90	96	3.2.P.5.4
					RSD%	1.1	0.8	0.5	0.6	1.0	0.9	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/29/13	Daytrana® Lot 64925 January 2014	2.2 mg/hr	12	Mean µg/hr/cm^2	30	52	60	71	78	87	
					RSD%	1.7	1.0	0.6	1.0	0.7	0.7	
					Range µg/hr/cm^2	(b) (4)						

30 mg/9 hr (3.3 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)		Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/31/13	Methylphenidate Transdermal System Lot R6D0014 March 2012	3.3 mg/hr	12	Mean µg/hr/cm^2	34	59	67	78	84	90	3.2.P.5.4
					RSD%	0.8	0.9	0.8	0.8	0.7	0.7	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 66085 March 2014	3.3 mg/hr	12	Mean µg/hr/cm^2	31	54	62	74	82	89	
					RSD%	1.7	0.8	0.9	0.8	0.8	0.6	
					Range µg/hr/cm^2	(b) (4)						

Reviewer's Note: The test lot of the bio-strength (3.3 mg/hr: 30 mg/9 hr) used in the drug release testing is the same as that used in the PK bioequivalence study. The expiration date of the reference lot (#58415) used in the PK bioequivalence study was 2/2013. Thus, the new reference lot (#66085) was used for the drug release testing conducted in 10/2013.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 206497

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

The Division of Bioequivalence (DB) has completed its review of the drug release testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Your proposal to change the FDA-recommended drug release specification of (b) (4) in 4 hr to (b) (4) in 4 hr is not acceptable. Per the DB policy, the drug release specifications are established based on the drug release data obtained from fresh (not stored) lots. Accordingly, the FDA-recommended specification of (b) (4) at 4 hr was based on release rate for all four strengths of the fresh test product lot at 4 hr. The DB does not revise specifications based on stability data. Therefore, as communicated previously, please acknowledge your acceptance of the following FDA-recommended drug release method and specifications for your test product:

Medium	0.01 N HCl
Volume	900 mL
Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications*	(b) (4) n 0.5 hr in 1.5 hr in 4 hr

*percent of labeled content

Alternatively, you may submit additional comparative drug release data on 12 dosage units each of all strengths of the test product from three fresh production lots, and unexpired reference lots, for the Agency to determine if any revision of drug release specification is warranted.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Completed Assignment for 206497 ID: 32220

Reviewer: Harigaya, Yoriko **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*		
32220	7/27/2017	BIO	Dissolution Amendment [1]	1	1	Edit	Delete
32220	7/27/2017	Parallel	Dissolution Amendment [1]	1	1	Edit	Delete
				Total:	2		

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	206497
Drug Product Name	Methylphenidate Transdermal System (TDS)
Strengths	10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr
Applicant Name	Mylan Technologies, Inc.
Address	110 Lake Street, St. Albans, VT 05478
Applicant's Point of Contact Name and the mailing address	Joseph J. Sobecki, Vice President, Regulatory Affairs 781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504-4310
Telephone Number	(b) (6)
Fax Number	(304) 285-6407
Email Address	Joseph.Sobecki@mylan.com
Original Submission Date	December 13, 2013
Submission Date of Amendment Under Review	N/A
Reviewer	Yoriko Harigaya, Pharm.D.

Study Number (s)	MPTP-11030	MPTP-11125	MPTP-12012
Study Type (s)	Failed (A), Passed (B) Pilot PK Endpoint	Failed Pilot PK Endpoint	Pivotal PK Endpoint
Strength (s)	30 mg/9 hours	30 mg/9 hours	30 mg/9 hours
Clinical Site	Celerion, Inc.		Kendle International Inc a subsidiary of INC Research LLC
Clinical Site Address	2420 West Baseline Road, Tempe, AZ 85283, Tel: 602-437-0097 ext 67162 Fax: 602-437-3386		763 Chestnut Ridge Road Morgantown WV 26505 Tel: 304-599-1197 Fax: 304-599-1254
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd., Morgantown, WV 26505 Tel:304-598-5430 Fax:304-285-6478		
Study Number (s)	MPTP-11007	MPTP-12046	MPTP-12130
Study Type (s)	Irritation and Sensitization (b) (4)	[Lack of GCP] Irritation, Sensitization and Adhesion	Irritation, Sensitization and Adhesion
Strength (s)	30 mg/9 hours x 3; cut to a diameter of 29 mm prior to application; The total methylphenidate content of all three patches combined was 28.8 mg	10 mg/9 hours x 2 (test, ref); both side of the hip	10 mg/9 hours x 2 (test, ref); both side of the hip

Clinical Site	Celerion, Inc.	Novum Pharmaceutical Research Services	PRACS Institute
Clinical Site Address	2420 West Baseline Road Tempe, AZ 85283, Tel: 602-437-0097 ext 67162 Fax: 602-437-3386	(b) (6) 5900 Penn Avenue Pittsburgh, PA 15206, Tel: 412-363-3300 Fax: 412-362-5783 (b) (6) 3760 Pecos McLeod Las Vegas, NV 89121, Tel: 702-435-3739 Fax: 702-435-7249	4801 Amber Valley parkway Fargo, ND 58104 Tel: 701-239-4750 Fax: 701-239-4955

OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete** ☐ **Not Applicable** **The results of OSIS inspection will not alter the outcome of the study.**	**Year 3 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**	
OVERALL REVIEW RESULT	**ADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**No**		
COMMUNICATION	☐ **ECD** ☐ **IR** ☒ **NOT APPLICABLE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Pharmacokinetic (PK) Study**	**30 mg/9 hr**	**ADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of pharmacokinetic (PK) endpoint bioequivalence (BE) study comparing test product, Methylphenidate Transdermal System, 30 mg/9 hr to the corresponding reference product, Daytrana® (methylphenidate Transdermal Film), 30 mg/9 hr.

The original submission, dated December 13, 2013, was "refuse to receive" due to insufficient information[1]. However, Division of Filing Review (DFR) later concluded that the original "refuse to receive" action was erroneously issued because of Division of Clinical Review (DCR)'s characterization of the issues with Mylan's ANDA 206497 as major deficiencies, which was based on an evaluation of the sufficiency of the information in the ANDA for *review*

[1] GDRP, ANDA206497, Filing Primary Review, A206497N000DFR_Memo.pdf dated on 8/27/2015

purposes, not for *filing* purposes. Thus, the receipt date for this ANDA was restored to the original December 13, 2013 date.

The PK endpoint BE study was designed as randomized, open label, two treatment, three period, single dose, partially-replicate, crossover study in healthy subjects. The results of pharmacokinetic (PK) statistical analysis of the BE study, as calculated by the reviewer, are summarized in the tables below.

Summary of Statistical Analysis - Reference-Scaled Data – PK BE Study

Methylphenidate Transdermal System, Dose: 1 × 30 mg/9 hr (9 hours) Bioequivalence Study, Study No. MPTP-12012, N=37 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Parameter (units)	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**S2wr**	**Swr**	**Criteria Bound**	**Method Used**	**Outcome**
	Analyte: methylphenidate							
AUC0-t (ng*hr/ml)	0.93	87.02	100.85	0.042	0.205	-0.011453	Unscaled	PASS*
AUC∞ (ng*hr/ml)	0.92	86.47	98.67	0.036	0.192	-0.004097	Unscaled	PASS*
Cmax (ng/mL)	0.93	84.52	102.01	0.056	0.237	-0.013167	Unscaled	PASS*

*Scaled data is not applicable due to Swr < 0.294. Please see the unscaled data below.

Summary of Statistical Analysis - Unscaled Data – PK BE Study

Methylphenidate Transdermal System, Dose: 1 × 30 mg/9 hr (9 hours) Bioequivalence Study, Study No. MPTP-12012, N=37 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Analyte: methylphenidate					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/ml)	122.32	130.57	0.94	87 02	100 85
AUC∞ (ng*hr/ml)	128.20	138.79	0.92	86 47	98 67
Cmax (ng/mL)	14.64	15.77	0.93	84 52	102 01

In the PK endpoint BE study, the methylphenidate AUC0-t, AUC∞ and Cmax of the test and reference products were comparable.

In recent times, the Office of Generic Drugs (OGD) revised BE guidance for multiphasic methylphenidate modified-release oral products[2], recommending additional partial AUCs (AUC_{0-3}, AUC_{3-7}, and $AUC_{7-12/t}$ for the fasting studies and AUC_{0-4}, AUC_{4-8}, and $AUC_{8-12/t}$ for the fed study). The DB requested the Office of Research and Standards (ORS) to evaluate the

[2] In 11/2014 Methylphenidate Extended-Release Tablets (Concerta, http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm320007.pdf); in 3/2015 Methylphenidate Extended-Release Capsules (http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf) and in 1/2016 Methylphenidate Extended-Release Capsules (http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320005.pdf)

necessity of partial AUCs and other PK parameters such as T_{lag} for Methylphenidate Transdermal Films (see Section 4.4.1). Per the ORS recommendation, the product specific BE guidance for Methylphenidate Extended-release Film (transdermal product; posted in 7/2010) may be revised to include partial AUC_{2-9}.. For the current application, the reviewer evaluated partial AUC_{2-9} and found the test and reference products comparable (see Section 4.1.1.4).

The firm also submitted two pilot PK endpoint BE studies (#MPTP-11030 and #MPTP-11125) comparing the test formulation, Methylphenidate TDS, 30 mg/9 hr (lot #R6C0003, #R6C0004 and #R6C00016) to the corresponding reference product, Daytrana® (methylphenidate Transdermal Film), 30 mg/9 hr, lot #50893. The pilot PK BE studies were designed as single-dose, two-way crossover studies in healthy subjects (please see section 4.6 for further details).

The firm has conducted acceptable comparative dissolution testing on all strengths using the USP dissolution method. The dissolution was reviewed in separate documents [GDRP, ANDA206497, Biopharmaceutics Quality Review, A206497N000DB_D12132013.doc]. Please refer to the review for further details.

The formulations for the 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr strengths are proportionally similar to that of the 30 mg/9 hr strength of the test product which underwent BE testing. The Division of Bioequivalence (DB) deems the 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr strengths of the test product Methylphenidate Transdermal System bioequivalent to the corresponding reference strengths based on criteria set forth in 21 CFR § 320.24 (b) (6).

The Office of Study Integrity and Surveillance (OSIS) inspection status for the pivotal BE study #MPTP-12012 of the current ANDA 206497 is adequate (please see section 4.7).

The application is **adequate** from the bioequivalence perspective.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Methylphenidate Transdermal System, 30 mg/9 hr
Reference Product[3]	Daytrana® (Methylphenidate Transdermal Film), 30 mg/9 hr is the RLD
RLD Manufacturer[4],[5]	Noven Pharmaceuticals facility in Miami, Florida (distributed by Noven Pharms Inc.)
NDA No.	021514
RLD Approval Date	April 6, 2006
Indication[5]	Daytrana is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

3.2 PK/PD Information[5]

Bioavailability	The amount of methylphenidate (MPH) absorbed systemically is a function of both wear time and patch size. On single dosing with Daytrana to children or adolescents, there was a delay of, on average,

[3] Electronic Orange Book (http://www.accessdata fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021514&TABLE1=OB_Rx), accessed on 02/29/2016
[4] DARRTS, NDA021514, REV-QUALITY-03(General Review) dated on 12/19/2005
[5] Label for Daytrana® from drugs@fda.gov. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021514s023lbl.pdf Approved on 08/14/2015.

2 hours before *d*-methylphenidate was detectable in the circulation. On repeat dosing, low concentrations (1.2-3.0 ng/mL in children and 0.5-1.7ng/mL in adolescents, on average across the dose range) were observed earlier in the profile, due to carry-over effect. Following the application of Daytrana once daily with a 9 hour wear time, the mean pharmacokinetic parameters of *d*-methylphenidate in children and adolescents with ADHD after 4 weeks of therapy are summarized in the following Table.

Mean Plasma *d*-Methylphenidate Pharmacokinetic Parameters After Repeated 9-Hour Applications of Daytrana or Oral ER-MPH for up to 28 days to Pediatric ADHD Patients (Aged 6 – 17 years)

Parameter	Daytrana[1] 12.5 cm^2 (N=12)	Daytrana[2] 37.5 cm^2 (N=10)	Oral ER-MPH[3] 18 mg	Oral ER-MPH[3] 54 mg
Children				
C_{ssmax} (ng/mL)	15.7 ± 9.39	42.9 ± 22.4	8.37 ± 4.14	26.1 ± 11.2
C_{ssmin} (ng/mL)`	1.04 ± 1.17	1.96 ± 1.73	0.708 ± 1.08	1.19 ± 1.54
AUC_{ss} (ng·hr/mL)	163 ± 101	447 ± 230	97.7 ± 67.0	317 ± 160
t_{lag} (h)[4]	0 (0 – 2.0)	0 (0 – 1.0)	0	0
Adolescents				
C_{ssmax} (ng/mL)	8.32 ± 4.60	16.5 ± 6.94	5.23 ± 1.72	18.0 ± 6.97
C_{ssmin} (ng/mL)`	0.544 ± 0.383	1.02 ± 0.629	0.360 ± 0.478	1.50 ± 0.937
AUC_{ss} (ng·hr/mL)	85.7 ± 50.0	167 ± 66.0	59.7 ± 19.1	216 ± 80.8
t_{lag} (h)[4]	0 (0 – 2.0)	0 (0 – 2.0)	0	0

[1]Dose maintained fixed for 28 days;
[2]Dose escalated at 7 day intervals from 12.5 cm^2 through 18.75 cm^2 and 25 cm^2 to 37.5 cm^2;
[3]Dose escalated at 7 day intervals from 18 mg through 27 mg and 36 mg to 54 mg;
[4]Median (minimum – maximum); t_{lag} = Last Sampling Time Prior to Time of First Quantifiable Plasma Concentration

Following administration of Daytrana 12.5 cm^2 to pediatric and adolescent ADHD patients daily for 7 days, there were 13% and 14% increases, respectively, in steady state area under the plasma concentration-time curve (AUCss) relative to that anticipated on the basis of single dose pharmacokinetics (AUC0-∞); after 28 days administration, these increments increased to 64% and 76%, respectively. Cmax increased by nearly 69% and 100% within 4 weeks of daily administration of the starting dose in children and adolescents, respectively.

The observed exposures with Daytrana could not be explained by drug accumulation predicted from observed single dose pharmacokinetics and there was no evidence that clearance or rate of elimination changed between single and repeat dosing. Neither were they explainable by differences in dosing patterns between treatments, age, race, or gender. This

suggests that transdermal absorption of methylphenidate may increase with repeat dosing with Daytrana; on average, steady-state is likely to have been achieved by approximately 14 days of dosing.

In the single-and multiple dose study described above, exposure to *l*-methylphenidate was 46% of the exposure to *d*-methylphenidate in children and 40% in adolescents. *l*-methylphenidate is less pharmacologically active than *d*-methylphenidate.

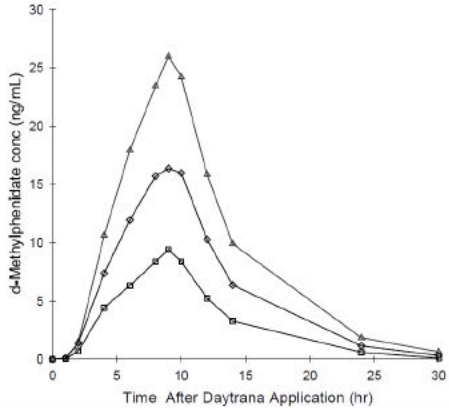
In a phase 2 PK/PD study in children aged 6-12 years, 2/3 of patients had 2-hour *d*-MPH concentrations < 5 ng/mL on chronic dosing, and at 3 hours 40% of patients had *d*-MPH concentrations < 5 ng/mL.

When Daytrana is applied to inflamed skin both the rate and extent of absorption are increased as compared with intact skin. When applied to inflamed skin, lag time is no greater than 1 hour, Tmax is 4 hours, and both Cmax and AUC are approximately 3-fold higher.

When heat is applied to Daytrana after patch application, both the rate and the extent of absorption are significantly increased. Median Tlag occurs 1 hour earlier, Tmax occurs 0.5 hours earlier, and median Cmax and AUC are 2-fold and 2.5-fold higher, respectively.

Application sites other than the hip can have different absorption characteristics and have not been adequately studied in safety or efficacy studies.

Dose Proportionality
Following a single 9-hour application of Daytrana patch doses of 10 mg / 9 hours to 30 mg / 9 hours patches to 34 children with ADHD, Cmax and AUC0-t of *d*-methylphenidate were proportional to the patch dose. Mean plasma concentration-time plots are shown in the following Figure. Cmax of *l*-methylphenidate was also proportional to the patch dose. AUC0-t of *l*-methylphenidate was only slightly greater than proportional to patch dose.

	Mean Concentration-time Profiles for *d*-Methylphenidate in all Patients (N=34) Following Administration of Single Applications (9-Hour Wear Time) of *d,l*-Methylphenidate Using Daytrana 10 mg (□), 20 mg (◊) and 30 mg (△) per 9-Hour Patches 
Distribution	Upon removal of Daytrana, methylphenidate plasma concentrations in children with ADHD decline in a biexponential manner. This may be due to continued distribution of MPH from the skin after patch removal.
Tmax	In patients with ADHD, peak plasma levels of methylphenidate are reached at about 10 hours after single application and 8 hours after repeat patch applications (12.5 cm^2 to 37.5 cm^2) when worn up to 9 hours.
Metabolism	Methylphenidate is metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity. Transdermal administration of methylphenidate exhibits much less first pass effect than oral administration. Consequently, a much lower dose of Daytrana on a mg/kg basis compared to oral dosages may still produce higher exposures of *d*-MPH with transdermal administration compared to oral administration. In addition, very little, if any, *l*-methylphenidate is systemically available after oral administration due to first pass metabolism, whereas after transdermal administration of racemic methylphenidate exposure to *l*-methylphenidate is nearly as high as to *d*-methylphenidate. The Cmax and AUC of d-methylphenidate were approximately 50% lower in adolescents, compared to children, following either a 1-day or 7-day administration of Daytrana (10mg/9 hr). Multiple-dose administration of Daytrana did not result in significant accumulation of methylphenidate; following 7 days of Daytrana administration (10 mg/ 9 hr) in children and adolescents, the accumulation index of methylphenidate was 1.1, based on the mean steady state area under the plasma concentration-time curve (AUCss) relative to that anticipated on the basis of single dose pharmacokinetics (AUC0-∞).
Half-life	The mean elimination t1/2 from plasma of *d*-methylphenidate after removal of Daytrana in children aged 6 to 12 years and adolescents aged 13-17 years was approximately 4 to 5 hours. The t1/2 of *l*-methylphenidate was shorter than for *d*-methylphenidate and ranged from 1.4 to 2.9 hours, on average.

Dosage and Administration	It is recommended that Daytrana be applied to the hip area 2 hours before an effect is needed and should be removed 9 hours after application. Dosage should be titrated to effect. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient.
Maximum Daily Dose	30 mg
Drug Specific Issues (if any)	**Black Box Warning** **WARNING: DRUG DEPENDENCE** **Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.**

3.3 OGD Recommendations for Drug Product[6]

Number of studies recommended:	2

1.	**Type of study:**	BE with PK Endpoints Study
	Design:	Single-dose, fasting, two-treatment, two-period crossover, *in vivo*
	Strength:	30 mg/9 hr
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	The transdermal patch should be applied to the hip, as recommended in the approved reference listed drug (RLD) and worn for 9 hours.

2.	**Type of study:**	Skin Irritation, Sensitization and Adhesion Study
	Design:	Randomized, evaluator-blinded, in vivo within-subject repeat test
	Strength:	10 mg/9 hr
	Subjects:	Healthy males and nonpregnant females, general population.
	Additional Comments:	Refer to "Additional comments regarding the skin irritation, irritation, sensitization and adhesion study" in the Bioequivalence Recommendations for Specific Drug Products for Methylphenidate Transdermal Film

Analytes to measure (in plasma/serum/blood):	Methylphenidate in plasma, using an achiral assay for *d*- and *l*-methylphenidate (PK study only)
Bioequivalence based on (90% CI):	Methylphenidate (PK study only)

[6] The following BE recommendations are based on the currently-posted BE Guidance on Methylphenidate Transdermal Film (recommended July 2010). However, please see Section 4.4.1 (ORS Consult), which indicates a possible future update in the BE Guidance recommendation including partial AUC analysis.

<table>
<tr><td>Waiver request of in-vivo testing*:</td><td>10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr based on (i) acceptable bioequivalence studies on the 30 mg/9 hr strength, (ii) proportional similarity of the 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr formulations to the 30 mg/9 hr strength, and (iii) acceptable in vitro dissolution testing of all strengths.</td></tr>
<tr><td>Source of most recent recommendations:</td><td>Bioequivalence Recommendations for Specific Drug Products for Methylphenidate Transdermal Film (Recommended Jul 2010) posted at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf</td></tr>
<tr><td>Control correspondence related to the posted BE guidance</td><td>Control Correspondence #06-1662: Review of Five Controlled Correspondences #06-1662, 07-1474, 08-0184, 08-0686, 09-0566 (Methylphenidate TDS NDA21514 Memo to Support Posting Draft Guidance.doc) located at \\cdsnas\OGDS6\CONTROLS\2006-docs\06-1662.pdf
(regarding overlay issue, please refer to the comments under Study Information in Section 4.1.1.1)

Control Correspondence #07-1474 located at \\cdsnas\OGDS6\CONTROLS\2007-docs\07-1474.pdf</td></tr>
<tr><td>Dissolution Method</td><td>The FDA-recommended dissolution method for this drug product posted in External Dissolution Database[7]
<table>
<tr><th>Drug Name</th><th>Dosage Form</th><th>USP Apparatus</th><th>Speed (RPMs)</th><th>Medium</th><th>Volume (mL)</th><th>Recommended Sampling Times (minutes)</th><th>Date Updated</th></tr>
<tr><td>Methylphenidate</td><td>Transdermal Patch</td><td>VI (Cylinder)</td><td>50</td><td>0.01 N HCl at 32°C</td><td>900</td><td>0.5, 1.5, 3, 4 hours and until at least 80% released</td><td>04/15/2008</td></tr>
</table></td></tr>
<tr><td>Summary of OGD or DB History</td><td>
<table>
<tr><td>Pending ANDAs (Not Yet Reviewed)</td><td>Yes</td></tr>
<tr><td>Approved ANDAs</td><td>No</td></tr>
<tr><td>Previously Reviewed ANDAs</td><td>Yes</td></tr>
<tr><td>Protocols</td><td>No</td></tr>
<tr><td>Controls</td><td>Yes</td></tr>
<tr><td>Citizen Petitions</td><td>Yes (see the following comments)
Docket# FDA-2013-P-1710</td></tr>
</table></td></tr>
</table>

The Noven Pharmaceuticals, Inc. submitted the Citizen Petition requesting the following issue (This petition was denied on 05/20/2014; docket # FDA-2013-P-1710**):**
Based on recent statements from FDA regarding the importance of testing the adhesion of a Methylphenidate TDS under "real world" conditions, Noven requests that FDA refuse to approve any ANDA that cites as its Reference Listed Drug ("RLD") Daytrana® TDS unless and until the sponsor of such ANDA demonstrates in a usability study conducted in adults, adolescents, and children under "real world" conditions that its proposed generic drug product is not inferior to Daytrana® TDS with respect to patch adhesion performance.

[7] External Dissolution Database (http://www.accessdata fda.gov/scripts/cder/dissolution/index.cfm); keyword search: diclofenac epolamine; accessed on 09/15/2015

3.4 Pre-Study Bioanalytical Method Validation

Bioanalytical Method Validation for Study MPTP-12012

Information Requested	Data
Bioanalytical method validation report location	Methylphenidate Bioanalytical Method Validation Report, Sections 5.3.1.4, See Methylphenidate Validation Addendum 3, Table 2
Analyte	Methylphenidate (MPHE)
Internal Standard (IS)	Methylphenidate $-d_9$ (MPHD)
Method Description	Liquid-liquid; LC/MS/MS - ESI
Limit of Quantitation (ng/mL)	0.5
Average Recovery of Drug (%)	90.45%[a]
Average Recovery of IS (%)	99.53% [a]
Standard Curve Concentrations (ng/mL)	0.5, 1.0, 1.5, 2.5, 5, 10, 15, 25, 35, 50
QC Concentrations (ng/mL)	1.5, 5, 15, 30
QC Intraday Precision Range (%)	0.35% to 7.87% [a]
QC Intraday Accuracy Range (%)	-4.40% to 10.93% [a]
QC Interday Precision Range (%)	1.95% to 4.83% [a]
QC Interday Accuracy Range (%)	-0.90% to 2.07% [a]
Bench-Top Stability (hrs)	25 hours @ Room Temperature [c]
Stock Stability (days)	MPHE Stock Solution 14 days @ 4°C[a] MPHE Working Solution 14 days @ 4°C[a] MPHD Stock Solution 14 days @ 4°C[a] MPHD Working Solution 14 days @ 4°C[a]
Room Temperature Solution Stability (hours)	MPHE Stock Solution – 6 hours [a] MPHE Working Solution – 19 hours [a] MPHD Stock Solution – 6 hours [a] MPHD Working Solution – 17 hours [a]
Processed Stability (hrs)	92.25 hours @ room temperature a
Freeze-Thaw Stability (cycles)	4 cycles [c]
Long-Term Storage Stability (days)	121 days @ -15°C and -70°C [d]
Dilution Integrity	Concentration diluted five-fold [a]
Selectivity	No interfering peaks noted in six blank plasma samples[a]
Whole Blood Stability	2.0 hours (120 minutes) [b]
Hemolysis Effect	No hemolysis effect observed [b]

Reviewer's Comments:

- LC/MS/MS method was used to estimate methylphenidate in human plasma containing K_2EDTA as anti-coagulant in the pre-study bioanalytical validation and the study sample analysis.

- The assay was linear over the range of 0.5 to 50 ng/mL, and all "r" values obtained for the nineteen calibration curves were ≥0.9996.

- The firm submitted adequate Long Term Storage Stability (LTSS) data of methylphenidate in K_2EDTA human plasma established for 121 days at -15°C and -70°C which covers the study sample storage period of 30 days for the PK BE study.

- The recovery (%) of methylphenidate HQC, MQC, LQC and IS from matrix samples are 95.31, 86.80, 89.25 and 99.56 (%CV<11.16) and acceptable.

- The sensitivity comparison among in-house ANDAs is listed in Section 4.1.1.4 in this review.

SOPs submitted	Yes
Does the duration of the each of the LTSS stability parameters support the sample preparation and assay dates?	Yes

The results of pre-study bioanalytical method validation are **adequate**.

3.5 *In Vivo* Study

Table 1. Summary of *in vivo* PK Bioequivalence Study

Summary of Bioavailability Study for Study MPTP-12012

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs), Mean (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC0-t (ng/mL•hr)	AUC∞ (ng/mL•hr)	$T_{1/2}$ (hr)	Kel (hr^{-1})	
					Methylphenidate						
MPTP-12012	Randomized, irritation evaluator blinded, 3-period, 2-treatment, crossover, bioequivalence study of Mylan's Methylphenidate Transdermal System, 30 mg/9 hrs and Noven's Daytrana®, 30 mg/9 hrs (reference) following a Single dose patch application in healthy volunteers under fasting condition	Single center, randomized single-dose, irritation evaluator blinded, 2-treatment, 3-way, crossover bioequivalence study	A=Methylphenidate Transdermal System, 30 mg/9 hrs 1 × 30 mg/9 hrs topical Lot:R6D0014 *B= Daytrana®, 30 mg/9 hrs 1 × 30 mg/9 hrs topical Lot 58415	48 Dosed 37 Completed 37 PK & Statistical Analysis (M:22, F:15) Healthy Subjects Mean Age: 27.4 yrs (Range: 19 to 45 yrs)	15.59 ± 5.15	9.50 (8.50 – 10.00)	129.48 ± 40.89	135.06 ± 41.16	4.49 ± 0.73	0.158 ± 0.025	Section 5.3.1.2
					17.70 ± 7.36*	9.50 (8.50 – 20.00)*	143.89 ± 57.99*	151.73 ± 56.33‡	4.52 ± 0.70‡	0.157 ± 0.023‡	

*Subjects received the reference formulation on two separate occasions. Thus, n = 74; ‡n=73

Reviewer's Note: Subject (b) (6) at period 3 displayed the first measurable methylphenidate plasma concentration at 10 hours and Tmax at 20 hours. There were not sufficient terminal phase concentrations observed to calculate the elimination rate constant. The median Tmax values (range) for methylphenidate for test and reference products were comparable.

Table 2. Reanalysis of Study Samples
Reanalysis of Study Samples for Study MPTP-12012

MPTP-12012 – Fasting Study Repeat Analysis Results for Methylphenidate Additional Information in Table 5 of the Bioanalytical Report for MPTP-12012								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual Number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A[1]	13	19	0.69%	1.01%	13	19	0.69%	1.01%
Reason B[2]	1	0	0.05%	0.00%	1	0	0.05%	0.00%
Reason C[3]	1	1	0.05%	0.05%	1	1	0.05%	0.05%
Total	0	0	0.80%	1.06%	0	0	0.80%	1.06%

[1]Abnormal Internal Standard (IS) Response
[2]Documented Sample Processing error – sample was not aliquotted.
[3]Documented Sample Processing error – cracked vial, sample lost

Reviewer's Note: The total numbers listed in the table above are typographical errors. The correct total number of repeated samples for test and reference are 15 and 20, respectively.

Table 3. SOPs Dealing with Bioanalytical Repeats of Study Samples for MPTP-12012

SOP No.	Effective Date of SOP	SOP Title
MGW-BIO-SOP-BIO-GEN-0020	04/30/2012	Re-assay or Re-injection of Clinical Samples

Is there any other particular concern related to repeat analysis that should be investigated further?	No

Comments from the Reviewer on Repeat Analysis:

- For the PK endpoint BE study #MPTP-12012, the reanalysis of study samples included a total of 1.86% (0.80% test; 1.06% reference) re-assay repeats for methylphenidate.

- Out of 35 repeats, 32 repeats were due to abnormal IS response (no original concentration is provided). There was no PK repeat in the PK BE study #MPTP-12012, and no additional PK calculation would be needed.

.

3.6 Waiver Request(s)

Strengths for which waivers are requested, if applicable	10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr
Waiver regulation cited?	Yes[8]
Proportional to strength tested *in vivo*?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	Yes
If not then why?	--

[8] DARRTS, ANDA206497, SDN1, Module 1.12.15 dated 12/13/2013

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-Dose PK Bioequivalence Study MPTP-12012 for 30 mg/9 hr

4.1.1.1 Study Design

Table 4. Study Information

Study Number	MPTP-12012
Study Title	Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers
Study Type	☒ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other (Specify)
Submission Location:	
Study Report	Section 5.3.1.2
Validation Report	Section 5.3.1.4
Bioanalytical Report	Section 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Kendle International Inc a subsidiary of INC Research LLC 763 Chestnut Ridge Road Morgantown WV 26505, USA Tel#: 304-599-1197 Fax#: 304-599-1254
Principal Clinical Investigator (Name, Email)	Dorian Williams, MD williams.dorianj@kendle.com
Dosing Dates	Period I: 30-April-2012 Period II: 03-May-2012 Period III: 06-May-2012
Analytical Site (Name, Address, Phone #, Fax #)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505 Tel#:304-598-5430 Fax#:304-285-6478
Analysis Dates	15-May-2012 – 30-May-2012
Principal Analytical Investigator (Name, Email)	Patrick T. Vallano, PhD Pat.vallano@mylan.com
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range <e.g. -20°C to -80°C>**	 Methylphenidate: 30 days at -70°C [Date of 1st sample collection 30-April-2012; Date of last sample analysis: 30-May-2012] -70°C (all analyzed samples stored at this temperature)
Long Term Storage Stability Coverage <e.g. no. of days @ temp °C>	Up to 121 days at -70°C and -15°C.

Reviewer's note:

Overlay: The pivotal PK endpoint BE study # MPTP-12012 used **Bioclusive™ Overlay**. The firm stated that "overlay applied over the system at the time of application in order to insure adhesion over the entire wear period." This overlay was applied consistently on all the test and reference products. , The current Daytrana® labeling states that "*patches **should not be applied or re-applied with dressings, tape, or other common adhesives***." Based on the following information, we consider that it is acceptable to use an overlay in this single dose PK endpoint BE study.

In the review of Control Correspondence #06-1662 from (b) (4) the firm asked the following question:
5) The prescribing information for Daytrana® does not include taping/occlusion of the patch during application. Can the PK study be performed by taping the patch for the time of application to time of removal? If taping is used, the study will not be used for adhesion assessment.

OGD Response:
Yes, consistent reinforcement of all patches with tape from the time of application to the time of removal is acceptable for the BE with PK Endpoints Study. The OGD recommends formally evaluating and comparing the adhesion performance of only the first applied, intact, to-be-marketed test product and reference listed drug (RLD) at 9 hours after application in the skin irritation, sensitization and adhesion study. After the first application, the adhesion performance of subsequent same site applications could be affected by skin stripping or residual adhesive. No patch reinforcement is allowed when the study is being used to establish adequate adhesion performance to support product approval; thus, no patch reinforcement should be permitted for the first applied test product and RLD patches for their first 9 hours of application. Adhesion should also be evaluated prior to patch removal throughout the entire study period to ensure adequate skin contact for maximal induction of irritation and sensitization.

PK results using overlay
Overlay was not used in the PK endpoint BE studies for other in-house ANDAs and for one of the pilot study submitted in the current application. In the current application, adhesion performance of the patch was evaluated in a separate study (MPTP 12130).

ANDA	PK Study	Overlay
(b) (4)		
(b) (4)		
206497 (Current)	Pilot (MPTP-11030)	No
	Pilot (MPTP-11125)	**Yes**
	Pivotal (MPTP-12012)	**Yes**

We noted that on the two pilot studies (#MPTP-11030 **without overlay**, #MPTP-11125 **with overlay**) in this application, **adhesive scores improved slightly with overlays**, especially for the RLD product.

Additionally, the RLD, Daytrana®, displayed higher AUCs and Cmax in Study #MPTP-11030 (first pilot) without an overlay than those in Study #MPTP-11125 (pilot) and Study #12012 (pivotal) with an overlay (see the table below).

Daytrana® PK Parameters

	Overlay		Daytrana® 30 mg/9 hr
MPTP-11030 (pilot: N=24) Lot#50893	**No**	AUC0-t (ng*hr/ml)	155.78
		AUC∞ (ng*hr/ml)	165.96
		Cmax (ng/mL)	16.54
MPTP-11125 (pilot: N=34) Lot#50893	**Yes**	AUC0-t (ng*hr/ml)	138.20
		AUC∞ (ng*hr/ml)	149.31
		Cmax (ng/mL)	14.80
MPTP-12012 (pivotal: N=37) Different Sampling Time Lot#58415	**Yes**	AUC0-t (ng*hr/ml)	130.57
		AUC∞ (ng*hr/ml)	138.79
		Cmax (ng/mL)	15.77

For the test product, the patch size (with same formulation and thickness of adhesive) was reduced based on the results of pilot studies to match AUCs and Cmax with those from the reference product. To roughly compare the AUCs and Cmax of the test product among these 3 studies, AUCs and Cmax were normalized by the patch sizes (see the table below). The Test/Size ratio in Study MPTP-11030 without an overlay is similar to Study MPTP-11125 using an overlay. Therefore, **there is no apparent impact of overlay on bioavailability of Mylan's product, as well as Daytrana**.

Mylan's Test Product PK Parameters

	Overlay	Size of Patch (cm^2)		Test	Test/Size
MPTP-11030 Treatment B (pilot: N=24)	**No**	**34**	AUC0-t (ng*hr/ml)	177.50	5.2
			AUC∞ (ng*hr/ml)	186.88	5.5
			Cmax (ng/mL)	17.63	0.5
MPTP-11125 (pilot: N=34)	**Yes**	**31.2**	AUC0-t (ng*hr/ml)	157.30	5.0
			AUC∞ (ng*hr/ml)	166.46	5.3
			Cmax (ng/mL)	17.27	0.6
MPTP-12012 (pivotal: N=37) Different Sampling Time	**Y s**	**28.8**	AUC0-t (ng*hr/ml)	122.52	4.3
			AUC∞ (ng*hr/ml)	128.37	4.5
			Cmax (ng/mL)	14.68	0.5

Overall, the PK results using overlay in the PK endpoint BE study of Methylphenidate Transdermal System in this application is **acceptable**. This issue was also discussed in an OB meeting and "acceptable" outcome was agreed upon by OB management and the expert in TDS products from ORS[9].

[9] The OB management meeting was held on 04/13/2016 and attendees were Conner, Dale P; Raney, Sameersingh; Li, Bing; Stier, Ethan; Jiang, Xiaojian; Chandaroy, Parthapratim; Pan, Yuzhuo; Fang, Lanyan (Lucy); Chen, Alicia; Fan, Ying; Tse, Sunny; Makary, Moheb and Harigaya, Yoriko.

Adhesion
Adhesion of the patch was assessed at the end of the dosing period at 9 hours in this PK endpoint BE study. If there was observed lift of the patch (not the overlay) ≥15%; the subject was discontinued from the study as follows:

For assessment of adhesion, a 12-point scale was utilized, where a score of '100' indicated 100% adhered to the skin, while a score of '0' indicated the transdermal system was completely detached from the skin. Adhesion scores of ≥85% were required in order for subjects to be included in the pharmacokinetic and statistical analysis (see Section 4.1.1.2 for the results).

Adhesion Evaluation Scoring System

Score	Adhesion
100	100%
95	>90% to <100%
85	>80% to 90%
75	>70% to 80%
65	>60% to 70%
55	>50% to 60%
45	>40% to 50%
35	>30% to 40%
25	>20% to 30%
15	>10% to 20%
5	>0% to 10%
0	Fall-off

In the irritation, Sensitization and Adhesion Study #MPTP-12130, an overlay was not used for 9 applications over 21 days and demonstrated that the **adhesive** performance of Mylan's Methylphenidate Transdermal System is **non-inferior** to the RLD, Daytrana®[10].

Irritation
Per the DCR review[10], the assessment of acute dermal irritation in Study #MPTP-12012 is **not recommended to review** because the study duration is only for 9 hours.

Briefly, for the assessment of **acute dermal irritation**, one 8-point scale for Dermal Response and one 6-point scale for Other Effects were utilized. In the Dermal Response scale, a score of '0' indicated either no irritation or no effect observed, while a score of '7' indicated a strong reaction spreading beyond the application site. In the Other Effects scale, a score of 'A' indicated a slightly glazed appearance, while a score of 'H' indicated small petechial erosions and/or scabs.

[10] GDRP, ANDA206497, ORIG-1-RESCIND, Clinical Primary Review, A206497N000DCR.docx, dated 3/28/2016

Dermal Response

Scale	Irritation
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test (i.e., application) site

Other Effects*

Scale	Appearance
A (0)	Slighty glazed appearance
B (1)	Marked glazed appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudates covering all or part of the patch site
H (3)	Small petechial erosions and/or scabs

*The numbers in parentheses represent the numerical equivalence of the letter score. These numerical equivalences will be utilized for statistical purposes.

Table 5. Product Information

Product	Test	Reference
Study No.	**MPTP-12012**	
Treatment ID	Treatment A	Treatment B
Product Name	Methylphenidate Transdermal System	Daytrana®
Manufacturer	Mylan Technologies Inc	Noven Pharmaceuticals Inc
Batch/Lot No.	R6D00014	58415
Manufacture Date	3/2012	N/A
Expiration Date	N/A	2/2013
Strength	30 mg/9 hr (3.3 mg/hr)	30 mg/9 hr (3.3 mg/hr)
Dosage Form	Patch	Patch
Bio-batch Size	(b) (4)	
Production Batch Size		
Potency	98.8%	97.0%
Content Uniformity (mean, %CV)	98.8% ± 1.4%	N/A
Dose Administered	30 mg/9 hr (3.3 mg/hr)	30 mg/9 hr (3.3 mg/hr)
Route of Administration	Topical	Topical

Reviewer's note:

- The content uniformity acceptance value (RSD%) was 3.5 (1.4%)[11].

[11] DARRTS, ANDA206497, SDN1, Module 3.2.P.5.4, Mylan COA Lot R6D00014 dated 12/13/2013

Table 6. Study Design, Single-Dose PK Endpoint Bioequivalence Study

Number of Subjects	Forty-eight subjects were enrolled and dosed in the study, while 37 subjects completed the clinical portion of the study and all 37 subjects were analyzed and used in the PK analysis.
No. of Sequences	2
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	3 days
Randomization Scheme (Sequence of T and R)	Yes (sequence of ABB, BAB and BBA, apply on the right or left hip; A=T and B=R)
Blood Sampling Times	Pre-dose (0.0 hour) and at 1, 3, 5, 7, 8, 8.5, 9 (prior to patch removal), 9.5, 10, 11, 12, 14, 16, 20, 24 and 30* hours. *Collected ambulatory (regarding sampling time points, see Section 4.6.2.4)
Blood Sample Processing & Storage (include storage temperature)	Blood samples were collected via catheter or by direct venipuncture. Blood collection tubes were inverted 5-10 times immediately after collection. The collected blood samples were cooled in an ice bath or sample cooling rack (e.g., Kryorack®) and centrifuged under refrigeration as soon as possible at 4±2°C at 3000 rpm for 10 minutes. Plasma was extracted, divided equally into two 1 mL aliquots and stored in suitably labeled tubes containing 10 mcL of a 250 mg/mL citric acid at -70°C ± 15°C until shipping to the analytical site.

Reviewer's Note: The currently approved Daytrana® labeling states that the T1/2 of *l*-methylphenidate and *d*-methylphenidate ranged from 4 to 5 hours and 1.4 to 2.9 hours, respectively, in ADHD patients 6 to 17 years old. The T1/2 of methylphenidate in adult is not provided in the labeling. The mean T1/2 of methylphenidate observed in this study was 4.5 hours for both test and reference, and there was no measurable concentration in pre-dose samples in period 2 and period 3. Therefore, 3 day washout period is acceptable.

Comments on Study Design:

- The subjects were on overnight fasting for at least 10.00 hours pre-patch application to 4.00 hours post-patch application in each period. All subjects were housed in the clinic from the evening prior to dosing until at least 24 hours post dosing (i.e. patch application) in each period. The 30 hour post-application samples were collected on ambulatory basis. The in-house period and fasting period are acceptable.

- The (b) (4) Overlay was used in this pivotal PK endpoint BE study (see comments following Study Information Table in Section 4.1.1.1).

- The PK endpoint BE study design is **adequate**.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

FASTING BIOEQUIVALENCE STUDY MYLAN STUDY NUMBER: MPTP-12012			
		TREATMENT GROUPS	
		Test Product N =37	Reference Product N = 37
Age (years)	Mean ± SD Range	27.4 ±6.7 19 - 45	27.4 ±6.7 19 - 45
Age Groups	<18 18-40 41-64 65-75 >75	0 (0.0%) 34 (91.9%) 3 (8.1%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 34 (91.9%) 3 (8.1%) 0 (0.0%) 0 (0.0%)
Sex	Female Male	15 (40.5%) 22 (59.5%)	15 (40.5%) 22 (59.5%)
Race	Asian Black Caucasian Hispanic Other	1 (2.7%) 7 (18.9%) 28 (75.7%) 3 (8.1%) 1 (2.7%)	1 (2.7%) 7 (18.9%) 28 (75.7%) 3 (8.1%) 1 (2.7%)
BMI	Mean ± SD Range	24.8 ± 3.3 19 – 30	24.8 ± 3.3 19 – 30
Other Factors		N/A	N/A

Table 8. Dropout Information, PK Bioequivalence Study

Study No. MPTP-12012				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Subject was discontinued post Period III patch application due to poor patch adhesion (≤ 85%). Treatment B	III	No	N/A
	Subject was discontinued post Period III patch application due to poor patch adhesion (≤ 85%). Treatment B	III	No	N/A
	Subject was discontinued from the study post Period II patch application due to an adverse event. Treatment B	II	No	N/A
	Subject was discontinued from the study prior to Period III patch application due to an adverse event. Treatment B	II	No	N/A
	Subject was discontinued post Period III patch application due to poor patch adhesion (≤ 85%). Treatment B	III	No	N/A
	Subject was discontinued post Period II patch application due to poor patch adhesion (≤ 85%). Treatment B	II	No	N/A
	Subject was discontinued post Period III patch application due to poor patch adhesion (≤ 85%). Treatment B	III	No	N/A
	Subject was discontinued Post Period I patch application due to poor patch adhesion (≤ 85%). Treatment B	I	No	N/A
	Subject was discontinued Post Period I patch application due to poor patch adhesion (≤ 85%). Treatment B	I	No	N/A
	Subject was dismissed from the study at Period III check-in due to protocol non-compliance (positive urine drug screen). Treatment A	II	No	N/A
	Subject was discontinued post Period II patch application due to poor patch adhesion (≤ 85%). Treatment B	II	No	N/A

Note: All dropouts were not analyzed in the bioanalytical study. Regarding the adhesion study, please see comments under Section 4.1.1.1.

Table 9. Study Adverse Events, PK Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups		
	Fasting Bioequivalence Study Mylan Study Number: MPTP-12012		
	Non-Local	Test	Reference
	N[2]=48 n[3] (%)	N[2]=43 n[3] (%)	N[2]=48 n[3] (%)
Gastrointestinal Disorders			
Abdominal Discomfort	0 (0.0%)	1 (2.3%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	0 (0.0%)	1 (2.1%)
Nausea	0 (0.0%)	0 (0.0%)	2 (4.2%)
General Disorders and Administration Site Conditions			
Application site irritation	0 (0.0%)	37 (86.0%)	44 (91.7%)
Application site reaction	0 (0.0%)	2 (4.7%)	8 (16.7%)
Application site pain (right hip)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Application site pruritus (left hip)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Peripheral oedema (left ankle)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Adhesive cover site irritation	20 (41.7%)	0 (0.0%)	0 (0.0%)
Cover site reaction	10 (20.8%)	0 (0.0%)	0 (0.0%)
Anaemia	1 (2.0%)	0 (0.0%)	0 (0.0%)
Investigations			
Heart rate increased	0 (0.0%)	0 (0.0%)	1 (2.1%)
Metabolism and Nutrition Disorders			
Decreased appetite	0 (0.0%)	1 (2.3%)	0 (0.0%)
Nervous System Disorders			
Dizziness	0 (0.0%)	0 (0.0%)	1 (2.1%)
Headache	0 (0.0%)	0 (0.0%)	1 (2.1%)
Psychiatric Disorders			
Anxiety	0 (0.0%)	0 (0.0%)	1 (2.1%)
Total Subjects Reporting at Least One Adverse Event	22 (45.8%)	38 (88.4%)	45 (93.8%)

(1) MedDRA Version 15.0
(2) N = Number of subjects dosed for each treatment
(3) n =Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100% (n/N%)

Reviewer's note: Non-local: Not transdermal patch application site

Was the adverse event (AE) profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Forty-seven subjects experienced a total of 186 AE over the course of the study. All AEs were mild in severity. Application site irritation was the most frequent AE experienced by subjects following administration of Treatment A and Treatment B and each was reported by 37/43 (86.0%) and 44/48 (91.7%) subjects, respectively.

Acute skin irritation was evaluated at 30 to 35 minutes after removal according to the criteria listed under Section 4.1.1.1, although the irritation in this study is not recommended for review per the DCR review[10].

Acute Dermal Irritation Results:

Mean (± s.d.) Acute Dermal Irritation of the Patch	
Treatment A Methylphenidate Trandsdermal System (Mylan)*	**Treatment B Daytrana® (Shire)****
1.68 ± 0.75	1.69 ± 0.89
*n = 37; ** n = 74	

Mean acute irritation scores are similar between Mylan's Methylphenidate transdermal system 30 mg/9 hours and Shire's Daytrana® (methylphenidate transdermal system), 30 mg/9 hrs.

Overall, the AE profile observed during the PK BE study is comparable for the test and reference product.

Are there any serious AEs or death? If so, are they reported to the OGD Safety Committee?
There were no serious adverse events in the study.

Are there any other safety concerns based on the AE profile?
No

Table 10. Protocol Deviations, PK Bioequivalence Study

Study No. MPTP-12012		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Blood Collection Time Deviations	(b) (6)	
Missed Blood Collection		
Repeat Pulse not obtained ((b) (6) Pd I Predose)		
Repeat Pulse obtained late ((b) (6) Pd II 9.0 hrs.)		
Vitals obtained prior to last PK sample (b) (6) Exit)		
Repeat Temperature not obtained ((b) (6) Exit)		
Volunteer consumed <75% of lunch ((b) (6) Period I 4.0 hrs.)		
Volunteer were given lunch less than 4 hrs. after application ((b) (6) Period III)		
Irritation evaluation obtained <30 minutes after removal ((b) (6) Pd II 0.5hr)		
Volunteer did not return for exit procedures ((b) (6))		

*Superscript represents the numbers of occurrences experienced by the subject.

Comments on Dropouts/Protocol Deviations/Adverse Events:

- Per the dataset provided, the actual time of sample collection was used in the PK analyses of plasma concentration data. Therefore, no impact of protocol deviation is foreseen on the outcome of the study.

- Mean patch adhesion was ≥ 85% for both treatments for 9 hours. However, eight subjects (Subjects (b) (6)) were dropped from the study due to patch (Daytrana® 30 mg/9 hrs) adhesion of less than 85%.

Mean Adhesion Results for Transdermal Patch:

Hour	Arithmetic Mean (%CV) A = Mylan	Arithmetic Mean (%CV) B = Daytrana®
9	94.65 (4.67%)	89.62 (12.40%)

The **patch adhesion** scores for those 8 dropouts were (b) (6) and (b) (4) although **overlay adhesion** scores were greater than or equal to 85%.

4.1.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control Fasting Study

Bioequivalence Study MPTP-12012 METHYLPHENIDATE										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.5000	1.000	1.500	2.500	5.000	10.00	15.00	25.00	35.00	50.00
Inter day Precision (%CV)	0.46	0.79	0.88	0.63	0.69	0.91	0.61	0.56	0.61	0.51
Inter day Accuracy (%Actual)	100.10	99.14	101.07	100.20	99.16	100.50	100.40	99.72	99.97	99.76
Linearity	0.9994 - 1.0000									
Linearity Range (ng/mL)	0.5000 - 50.00									
Sensitivity/LOQ (ng/mL)	0.5000									

Bioequivalence Study MPTP-12012 METHYLPHENIDATE				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	1.500	5.000	15.00	30.00
Inter day Precision (%CV)	1.72	2.25	1.68	6.22
Inter day Accuracy (%Actual)	103.13	102.42	103.67	101.67

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes (See comments under Section 3.4)
Are there any concerns related to sample analysis (including reanalysis, run rejection, etc.)?	No

Were 20% of chromatograms included?	Yes [8/37 (21.6%); subjects (b) (6) (b) (6). Subjects (b) (6) were dropped out from the study.

Table 12. SOPs Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
MGWBIO-SOP-BIO-GEN-0018	April 30, 2012	Evaluation and Acceptance Criteria for Analytical Runs

Comments on Study Assays:

- The standard curve (i.e., 0.5 to 50 ng/mL) for methylphenidate covers all the plasma concentrations of methylphenidate observed in the PK BE study. The maximum drug concentration in the PK BE study was 37.83 ng/mL (reference product at period 1).
- One run was rejected and repeated in the entirety due to instrument malfunction[12].
- The results of the study assay are adequate.

4.1.1.4 Pharmacokinetic Results

Table 13. Arithmetic Mean Pharmacokinetic Parameters-Reviewer Calculated

		Test		Reference 1		Reference 2		Ratio T/R1	Ratio T/R2	Ratio R1/R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUCT	ng hr/mL	129.482	31.58	144.501	41.75	143.282	39.35	0.90	0.90	1.01
AUCI	ng hr/mL	135.058	30.47	150.872	39.66	152.604	34.94	0.90	0.89	0.99
CMAX	ng/mL	15.586	33.03	17.559	39.44	17.846	44.10	0.89	0.87	0.98
TMAX	hr	9.500	.	9.500	.	9.500	.	1.00	1.00	1.00
KE	hr^{-1}	0.158	15.60	0.152	14.00	0.162	15.31	1.04	0.98	0.94
THALF	hr	4.491	16.25	4.647	14.62	4.386	16.05	0.97	1.02	1.06

Table28. Geometric Means and 90% Confidence Intervals - Firm Calculated

Summary of Statistical Analysis – PK Endpoint BE Study

METHYLPHENIDATE TRANSDERMAL SYSTEM, 30 MG/9 HOURS
Number of Subjects Completed = 37
Dose (30 mg/9 hours)
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fasting Bioequivalence Study (MPTP-12012)
Methylphenidate

Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC0-t (ng×mL/hr)	122.52	37	130.79	74	0.94	87.21% - 100.62%
AUC∞ (ng×mL/hr)	128.37	37	138.90	73	0.92	86.57% - 98.66%
C_{max} (ng/mL)	14.68	37	15.81	74	0.93	85.09% - 101.26%

*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$
**Used Natural Log Transformed Parameter

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCT	0.93	86.98%	100.44%	0.0424	0.2058	-0.01145	ABE	Pass
LAUCI	0.92	85.89%	97.98%	0.0369	0.1921	-0.00410	ABE	Pass
LCMAX	0.93	84.51%	101.28%	0.0563	0.2373	-0.01317	ABE	Pass

[12] DARRTS, ANDA206497, SDN1, Module 5.3.1.4, Analytical Run Summary Study dated 12/13/2013

Table 29. Geometric Means and 90% Confidence Intervals – Reviewer Calculated

Summary of Statistical Analysis - Reference-Scaled Data – PK Endpoint BE Study

Methylphenidate Transdermal System, Dose: 1 × 30 mg/9 hr (9 hours) Bioequivalence Study, Study No. MPTP-12012, N=37 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Parameter (units)	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**S2wr**	**Swr**	**Criteria Bound**	**Method Used**	**Outcome**
	Analyte: methylphenidate							
AUC0-t (ng*hr/ml)	0.93	87.02	100.85	0.042	0.205	-0.011453	Unscaled	PASS*
AUC∞ (ng*hr/ml)	0.92	86.47	98.67	0.036	0.192	-0.004097	Unscaled	PASS*
Cmax (ng/mL)	0.93	84.52	102.01	0.056	0.237	-0.013167	Unscaled	PASS*

*Scaled data is not applicable. Please see the unscaled data below.

Summary of Statistical Analysis - Unscaled Data – PK Endpoint BE Study

Methylphenidate Transdermal System, Dose: 1 × 30 mg/9 hr (9 hours) Bioequivalence Study, Study No. MPTP-12012, N=37 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Analyte: methylphenidate					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/ml)	122.32	130.57	0.94	87.02	100.85
AUC∞ (ng*hr/ml)	128.20	138.79	0.92	86.47	98.67
Cmax (ng/mL)	14.64	15.77	0.93	84.52	102.01

Table 30. Additional Study Information

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CONTINU	
Reason(s) for Selecting Above SAS Program Macro	The elimination phase was well captured.	
sWR, AUC0-t	0.2115	
sWR, AUC∞	0.1921	
sWR, Cmax	0.2554	
	Test	**Reference**
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n***	**Mean**	**Minimum**	**Maximum**
Test	37	0.95	0.86	0.98
Reference	73*	0.95	0.81	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

***Reviewer's Note:** Subject (b) (6) at period 3 (reference) displayed the first measurable methylphenidate plasma concentration at 10 hours and Tmax at 20 hours. There were insufficient terminal phase concentrations observed to calculate the elimination rate constant for this subject.

Overall Comment:

- The firm conducted a single-dose, 3-way, partially-replicated crossover PK endpoint BE study. Based on the applicant's study results, the within-subject standard deviation (SD) (Swr) for AUC_{0-t}, AUC_{∞}, and C_{max} were less than 0.294 for methylphenidate. Therefore, the unscaled average bioequivalence (ABE) approach was used to calculate BE statistics.

- As per the study protocol, the firm's analysis included samples from all subjects who completed all the periods of the clinical phase. The reviewer agrees with the firm's decision of excluding subjects (b) (6) who did not complete all the study periods for PK and statistical analyses. Eight of them were dropped out from the study due to poor patch adhesion (adhesion scores less than 85%).

- Per the ORS consult (see Section 4.4.2), the BE guidance for Methylphenidate Transdermal Film may possibly be updated to include partial AUC2h-9h (AUC_{2-9}) to evaluate PK profile similarity to ensure therapeutic equivalence[13].

  Since there is no sampling time point at 2 hours post-application (i.e., actual sampling time points: 0, 1, 3, 5, 7, 8, 8.5, 9, 9.5, 10, 11, 12, 14, 16, 20, 24 and 30 hours) in the pivotal PK BE study for the current application, methylphenidate plasma concentrations at 2 hours were estimated by linear interpolation using the

[13] The ORS, OB, OCP and OPQ meeting was held on 2/29/2016. The attendees were Conner, Dale P; Sharp, Trueman; Zhao, Liang; Jiang, Wenlei; Fang, Lanyan (Lucy); Stier, Ethan; Jiang, Xiaojian; Chandaroy, Parthapratim; Li, Bing; Munshi, Utpal; Braddy, Yang, Xiaoyan; Zheng, Nan; April; Furlong, Lesley-Anne; Shetty, Daiva;; Shivva, Vittal; Raney, Sameersingh; Zhu, Hao, Huang, Yih Chain; Rege, Bhagwant; Fine, Andrew; Kim, Carol Y; Uppoor, Ramana S; Ritter, Mark; Harigaya, Yoriko. Another OB meeting was held on 4/5/2016. The attendees were Zhao, Liang; Yoo, Jae Wook *; Yang, Xiaoyan *; Zheng, Nan; Conner, Dale P; Sharp, Trueman; Stier, Ethan; Jiang, Xiaojian; Shetty, Daiva; Lionberger, Robert; Jiang, Wenlei; Shivva, Vittal *; Raney, Sameersingh; Zhu, Hao; Rege, Bhagwant; Mehta, Mehul U; Uppoor, Ramana S; Ritter, Mark; Fang, Lanyan (Lucy); Tworzyanski, Jeffrey; Huang, Yih Chain; Pan, Yuzhuo and Harigaya, Yoriko.

two nearest data points (1 and 3 hours). Additionally, AUC_{3-9} and AUC_{1-9} were calculated without using interpolation. As the Swr of AUC_{3-9}, AUC_{2-9} and AUC_{1-9} for methylphenidate were >0.294 in the PK BE study, BE of AUC_{3-9}, AUC_{2-9} and AUC_{1-9} for methylphenidate were based on the reference-scaled average BE approach. Also, since at least 4 non-zero measurements of concentrations are recommended for each partial AUCs, AUC_{3-9}, AUC_{2-9} and AUC_{1-9} were calculated excluding 3 subjects (i.e., Subjects (b) (6)) who did not display at least 4 non-zero measurements of concentrations.

Subjects with at least 4 non-zero measurements of concentrations (n=34)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC1-9	0.99	87.22	112.82	0.1092477	0.3305264	-0.055817	Scaled/PE	PASS
AUC2-9*	1.01	89.49	116.53	0.1156215	0.3400316	-0.060607	Scaled/PE	PASS
AUC3-9	1.01	89.80	117.26	0.1173671	0.3425888	-0.061111	Scaled/PE	PASS

		Test		Reference 1		Reference 2		RatioT1R1	RatioT1R2	RatioR1R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUC1-9	ng hr/mL	48.244	50.94	53.167	69.44	49.370	52.24	0.91	0.98	1.08
AUC2-9*	ng hr/mL	49.300	48.59	54.888	63.85	50.264	49.32	0.90	0.98	1.09
AUC3-9	ng hr/mL	49.812	49.16	55.379	65.02	50.582	49.54	0.90	0.98	1.09

* Methylphenidate plasma concentrations at 2 hours were estimated by linear interpolation.

As shown in the tables above, the 95% upper confidence bound of the AUC_{2-9} using linear interpolation was less than 0. Also, the point estimate for the AUC_{2-9} was within 0.8 and 1.25. AUC_{3-9} and AUC_{1-9} calculated without using interpolation displayed similar results as well. Therefore, the result suggests that AUC_{2-9} of the test and reference products were comparable.

Previously, partial AUC calculation using interpolation was considered as an acceptable method for Zolpidem Tartrate Extended-Release Tablets, ANDA090153[14]. For ANDA090153, the reviewer interpolated the plasma concentrations at1.5 hours using the two nearest data points (1.33 hours and 1.67 hours). However, the partial $AUC_{0-1.5}$ using interpolation as well as $AUC_{0-1.33}$ and $AUC_{0-1.66}$ without using interpolation did not meet the BE criteria. Therefore, the firm was requested to repeat the PK study for ANDA090153.

Overall, for the current application, the results of partial AUC_{2-9} using linear interpolation is acceptable.

- Per the ORS consult (see Section 4.4.1), a qualitative visual inspection of PK profile is recommended to ensure comparable T_{lag}. The reviewer compared test and reference within-subject T_{lag} differences in the PK BE study. The median T_{lag} (range) for the test and reference products were 1 hour (1 to 5 hours) and 3 hours (0 to 9.5 hours), respectively (see tables below).

[14] DARRTS, ANDA090153, REV-BIOEQ-01(General Review) dated 8/3/2009

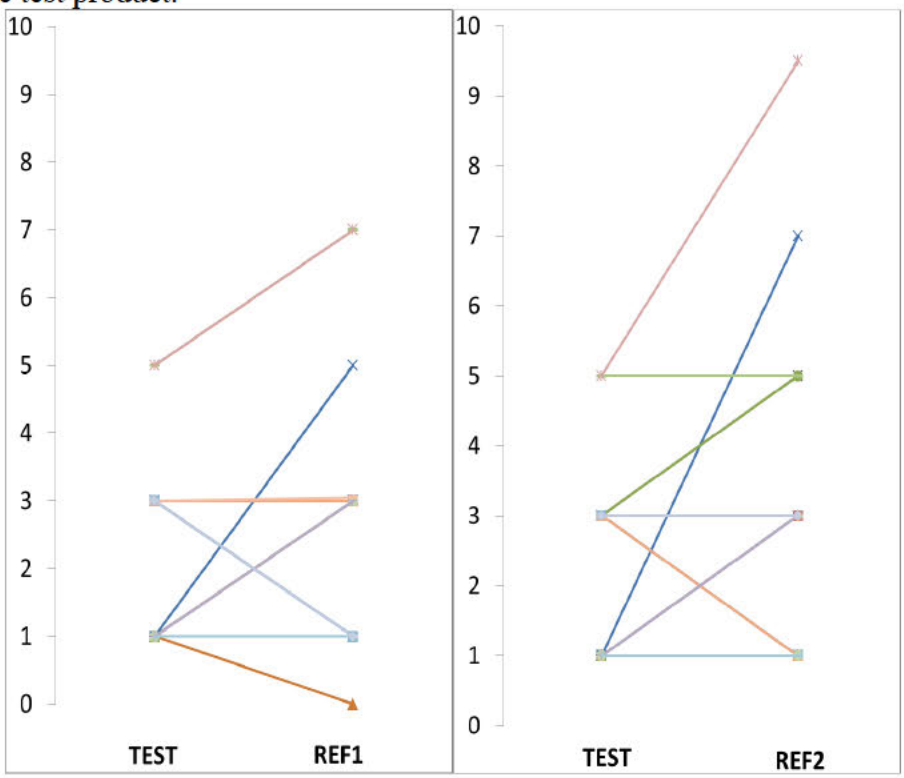
T_{lag} in the PK BE Study # MPTP-12012

TREAT	Mean	CV%	Min	Median	Max
TEST	2.03	59.84	1.00	1.00	5.00
REF	2.45	70.94	0.00	3.00	9.50

PK BE Study T_{lag} Data

SUB	TEST	REF1	REF2	Ratio T/R1	Ratio T/R2
(b) (6)	1	1	1	1.00	1.00
	1	3	3	0.33	0.33
	1	3	1	0.33	1.00
	3	3	5	1.00	0.60
	3	1	1	3.00	3.00
	1	1	1	1.00	1.00
	1	3	3	0.33	0.33
	1	1	1	1.00	1.00
	1	1	1	1.00	1.00
	1	1	1	1.00	1.00
	1	1	1	1.00	1.00
	1	0	1	NA	1.00
	1	5	7	0.20	0.14
	3	3	3	1.00	1.00
	3	3	5	1.00	0.60
	1	3	3	0.33	0.33
	3	3	3	1.00	1.00
	1	1	1	1.00	1.00
	3	1	3	3.00	1.00
	3	3	3	1.00	1.00
	1	1	1	1.00	1.00
	3	3	3	1.00	1.00
	3	3	1	1.00	3.00
	1	3	3	0.33	0.33
	1	3	3	0.33	0.33
	1	3	1	0.33	1.00
	5	7	5	0.71	1.00
	3	3	1	1.00	3.00
	3	1	1	3.00	3.00
	3	3	1	1.00	3.00
	3	1	3	3.00	1.00
	5	7	9.5	0.71	0.53
	1	3	1	0.33	1.00
	1	3	3	0.33	0.33
	1	1	1	1.00	1.00
	3	3.05	3	0.98	1.00
	3	1	3	3.00	1.00

As shown in the stick plots below comparing test and reference within-subject T_{lag} differences, the reference product tends to display higher T_{lag} compared to that of the test product.



The median T_{lag} (range) for other in-house ANDAs for this product are listed in the tables below.

(b) (4)

It is noted that other in-house ANDAs for this product displayed higher T_{lag} compared to the current test product (ANDA206497). (b) (4) The RLD product displayed similar T_{lag} profiles to the test product in each study.

The assay sensitivity of bioanalytical study may contribute to the T_{lag} differences in these ANDAs and NDA. Per the BE guidance for Methylphenidate Transdermal Film, the recommended analyte to be measured is methylphenidate in plasma, using an achiral assay for *d*- and *l*-methylphenidate.

The assay sensitivity [lower limit of quantification (LLOQ)] of bioanalytical study for each ANDA is listed in the following table. (b) (4) displayed higher median T_{lag} than that of ANDA204697 even though the LLOQ is higher for ANDA204697. Thus, among these three applications, no clear impact of the assay sensitivity of bioanalytical studies on the T_{lag} was observed.

LLOQ Table for in-house ANDAs

ANDA	Methylphenidate	d-Methylphenidate	l-Methylphenidate	RLD Tlag Median (range) Hr
206497	0.5 ng/mL	NA	NA	3 (0 to 9.5)
(b) (4)				

Overall, the T_{lag} profile of the current test product is acceptable.

- The (b) (4) Overlay was used in this PK endpoint BE study (see comments following Study Information Table in Section 4.1.1.1).

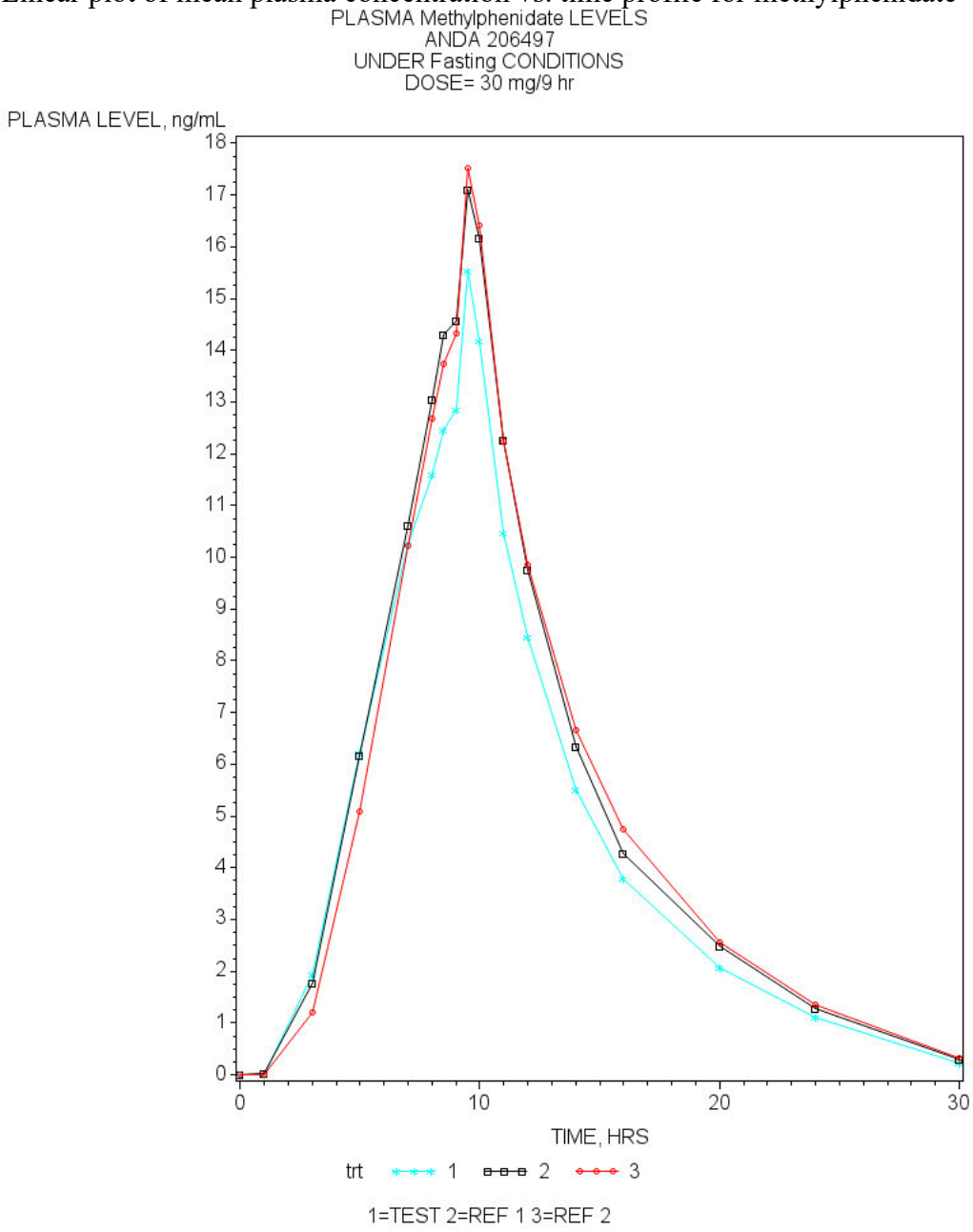
- The PK BE study # MPTP-12012 is **adequate**.

Table 13. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study
Mean plasma methylphenidate concentrations (ng/mL)

	Test (n=37)		Reference 1 (n=37)		Reference 2 (n=37)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
0.00	0.00	.	0.00	.	0.00	.	.	.	.
1.00	0.00	.	0.03	608.28	0.00	.	0.00	.	.
3.00	1.94	139.28	1.78	209.58	1.20	135.18	1.09	1.61	1.48
5.00	6.22	70.25	6.18	94.18	5.10	74.94	1.01	1.22	1.21
7.00	10.24	40.00	10.62	58.48	10.22	53.63	0.96	1.00	1.04
8.00	11.59	34.17	13.05	51.77	12.69	49.17	0.89	0.91	1.03
8.50	12.45	32.33	14.29	49.59	13.74	47.14	0.87	0.91	1.04
9.00	12.85	33.13	14.56	46.29	14.32	44.99	0.88	0.90	1.02
9.50	15.54	33.31	17.09	38.50	17.52	44.33	0.91	0.89	0.98
10.00	14.18	30.44	16.18	36.69	16.42	44.04	0.88	0.86	0.99
11.00	10.48	29.39	12.26	35.85	12.25	42.81	0.85	0.86	1.00
12.00	8.46	30.42	9.77	33.43	9.85	37.37	0.87	0.86	0.99
14.00	5.50	28.89	6.35	34.36	6.65	32.96	0.87	0.83	0.96
16.00	3.78	31.97	4.28	34.29	4.74	30.61	0.88	0.80	0.90
20.00	2.07	42.59	2.47	44.54	2.56	36.37	0.84	0.81	0.96
24.00	1.11	44.73	1.28	48.09	1.36	39.59	0.86	0.81	0.94
30.00	0.22	175.22	0.29	155.59	0.32	134.70	0.74	0.67	0.91

Figure 1. Mean Plasma Concentrations, Single-Dose PK BE Study (n=37)

Linear plot of mean plasma concentration vs. time profile for methylphenidate



4.2 Formulation Data

Ingredient	Amount (mg)				Amount (%)/Patch			
	10 mg/9 hrs (1.1 mg/hr) 9.6 cm²	15 mg/9 hrs (1.6 mg/hr) 14.4 cm²	20 mg/9 hrs (2.2 mg/hr) 19.2 cm²	30 mg/9 hrs (3.3 mg/hr) 28.8 cm²	10 mg/9 hrs (1.1 mg/hr) 9.6 cm²	15 mg/9 hrs (1.6 mg/hr) 14.4 cm²	20 mg/9 hrs (2.2 mg/hr) 19.2 cm²	30 mg/9 hrs (3.3 mg/hr) 28.8 cm²
Active Ingredient								
Methylphenidate								
Inactive Ingredients – Adhesive Matrix								
Hydrophobic Colloidal Silica, NF								
Mineral Oil, NF								
Polyisobutylene Adhesive								
Total Matrix Weight								
Inactive Ingredients – Backing Film, Release Liner and Printing Ink								
Ethylene-Vinyl Acetate Polyester Film								
Fluoropolymer-Coated Release Liner								
White Ink								
Total Drug Product Weight (excluding Release Liner)								

Inactive Ingredients and IIG Limits in the Test Product Formulation

Component	30 mg/ 9 hours (28.8 cm²)	% w/w	Amount based on MDD[15]	IIG limits (mg) per unit
Hydrophobic Colloidal Silica NF				
Mineral Oil NF				
Polyisobutylene Adhesive				

*See comments below.

[15] The maximum daily dose of this product is 30 mg per 9-hour transdermal patch/day.

Reviewer's Comments:
The test product contains methylphenidate in the solid matrix reservoir[16], while the reference product contains the methylphenidate in the adhesive as a single layer. The amount of methylphenidate/patch in the test product is lower than that in the reference product. The size of the patchs for the test product are smaller than that for the reference product (see table below).

	10 mg/ 9 hr		**15 mg/ 9 hr**		**20 mg/ 9 hr**		**30 mg/ 9 hr**	
	API mg	cm^2	API mg	cm^2	API mg	cm^2	API mg	cm^2
Test	(b) (4)	9.6	(b) (4)	14.4	(b) (4)	19.2	(b) (4)	28.8
Reference		12.5		18.75		25		37.5

Residual assay results indicated the average theoretical dose delivered was (b) (4) mg for Mylan's Methylphenidate transdermal system, 30 mg/9 hrs and was (b) (4) mg for Noven's

[16] The reservoir also contains adhesive like the RLD. However, there is a separate adhesive layer in the test product, unlike the RLD.

Daytrana® Patch 30 mg/9 hrs following a single 9 hour application. The firm states that 30 mg is nominal dose delivered over 11 to 12 hours[17].

Justification of acceptance of hydrophobic colloidal silica in test formulation:

The maximum daily application of hydrophobic colloidal sillica is (b) (4) Mylan has conducted the following safety assessment of hydrophobic colloidal silica[18].

Silica (silicon dioxide) is normally present in all body tissues and occurs naturally in a variety of foods, particularly grains such as oats, barley or rice. The systemic absorption of hydrophobic colloidal silica is minimal following oral administration of silica[19],[20].

Little information is available regarding the dermal absorption of silicas. However, due to the lack of lipid solubility, absorption and subsequent systemic bioavailability is anticipated to be very low. Recently, studies have been conducted to analyze whether nanoparticles of silica are absorbed through the skin. One such study examined the skin penetration and cellular uptake of silica particles with sizes ranging (b) (4) *in human skin explants with partially disrupted stratum corneum which decreases the barrier to absorption (Rancan 2012). Even in this optimal scenario for dermal silica absorption, only the* (b) (4) *particles were found to be associated with epidermal cells, providing strong evidence that typical systemic absorption of dermally applied silica preparations is minimal.*

In mice, the NOAEL for 21 months of daily oral exposure to silicon dioxide was the highest dose employed (b) (4)

The firm has conducted a clinical study #MPTP-12130 to evaluate the cumulative irritation and sensitization potential of a single formulation of Mylan's Methylphenidate Transdermal Systems l0 mg/9 hours (which included the (b) (4) (b) (4) compared to Noven's Daytrana 10mg (releasing 10 mg/9hours) in healthy male and female volunteer (n=100).

On Day 1, each subject received a single transdermal application of 10 mg/9 hours (1 x 10 mg/9 hours patch) of the test product, methylphenidate transdermal system, and a single transdermal dose of 10 mg/9 hours (1 x 10 mg/9 hours patch) of the reference product, Daytrana® patch, to either the left or right side of the hip based upon a randomization schedule. Patches were placed for a 2 to 3-day wear cycle per application over a total of 9 applications (21 days), followed by a 14-day rest phase and a subsequent 48 hour Challenge Phase, which was followed by a 3-day observation and irritation evaluation. Patches were applied on Days: 1, 3, 5, 8, 10, 12, 15, 17, 19 with the last patches removed on Day 22 for the Induction Phase and were applied once for a 48 hour wear period during the Challenge and Re-Challenge Phases (if applicable). Only those

[17] DARRTS, NDA021514, SDN1, CMC, Product, dated 6/27/2002

[18] DARRTS_ADNA206497_SDN1_Module 3 2 P 1 a safety assessment_dated 12/13/2013

(b) (4)

subjects who demonstrated possible sensitization were re-challenged 4 to 8 weeks after completion of the Challenge Phase. An irritation evaluation occurred 30 to 45 minutes after each patch application removal during the Induction Phase and at 0.5. 24. 48, and 72 hours after patch removal during the Challenge and Re-Challenge Phases.

The skin irritation evaluation scoring system, frequency of irritation scores, and the frequency of sensitization results are provided in the tables below.

SKIN IRRITATION EVALUATION SCORING SYSTEM

Dermal Response

Scale	Irritation	Scale	Irritation
0	No evidence of irritation	4	Definite edema
1	Minimal erythema, barely perceptible	5	Erythema, edema, and papules
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	6	Vesicular eruption
3	Erythema and papules	7	Strong reaction spreading beyond test (i.e., application) site

Other Effects

A (0)	Slighty glazed appearance
B (1)	Marked glazed appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudates covering all or part of the patch site
H (3)	Small petechial erosions and/or scabs

Frequency of Irritation Scores* Observed In Ninety-two Healthy Adult Subjects Following Repeat Application of Methylphenidate Transdermal System 10 mg/9 hours and Daytrana® 10 mg Every 48-72 Hours for 9 Applications Over 21 Days

Time after Initial Patch Application^	Treatment A Methylphenidate Transdermal System 10 mg/9 hours (Mylan)									Treatment B Daytrana® 10 mg (Noven)								
Score	0	1	2	3	4	5	6	7	Total	0	1	2	3	4	5	6	7	Total
Day 3	23	63	6	0	0	0	0	0	92	12	73	7	0	0	0	0	0	92
Day 5	5	85	2	0	0	0	0	0	92	2	78	12	0	0	0	0	0	92
Day 8	1	86	5	0	0	0	0	0	92	3	72	17	0	0	0	0	0	92
Day 10	0	81	6	0	4	0	0	1	92	1	55	30	0	5	0	0	1	92
Day 12	0	59	15	0	15	0	0	3	92	0	35	33	1	20	0	0	3	92
Day 15	0	42	22	0	25	0	0	3	92	0	23	33	0	29	0	2	5	92
Day 17	0	23	37	0	28	0	1	3	92	1	9	31	1	34	6	5	5	92
Day 19	0	19	35	0	31	3	1	3	92	1	4	26	0	38	12	6	5	92
Day 22	0	21	30	0	32	5	1	3	92	0	8	20	0	41	12	6	5	92
Total	29	479	158	0	135	8	3	16	828	20	357	209	2	167	30	19	24	828

*Scores represent the sum of the Dermal Response and Other Effects Scores. ^Irritation scores were recorded every 48-72 hrs.

Frequency Of Sensitization Following Nine Applications Of Mylan's Methylphenidate Transdermal System And Noven's Daytrana For 48-72 Hours Over A Period Of 21 Days To Healthy Adult Male And Female Volunteers For 48-72 Hours For 9 Applications Over 21 Days

Treatment	Sensitization		
	Yes	No	Total
Methylphenidate Transdermal System 10 mg/9 hours (Mylan)	10	66	76
Daytrana® 10 mg (Noven)	11	65	76
Total	21	131	152

Per the study results above, both the cumulative irritation scores and frequency of sensitization were similar for the test and the reference patch.

Considering that hydrophobic colloidal silica in the formulation of Mylan's Methylphenidate Transdermal System is not listed in the CDER's Inactive Ingredient Guidance (IIG) for FDA-Approved Drug Products, the reviewer sent a clinical consult to

DCR and inquired if the presence of such amount of hydrophobic colloidal silica should be of a safety concern. Per the DCR/OND consult, the current proposed levels of not more than (b) (4) in a 28.8 cm^2 patch (b) (4) of (b) (4) in Mylan's Methylphenidate Transdermal System is considered **acceptable**. Please refer to Section 4.4.2 for details.

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	No
If no, are they all above/within IIG (per day) limits?	See consult comments above
If no, are additional data or Pharm/Tox consult necessary?	N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	Yes
Are all strengths of the RLD product dose-proportional?	Yes
Are all strengths of the test formulation acceptable	Yes
Additional Attachment for Formulation Calculations	N/A

4.3 Dissolution Data

Dissolution Review Path	The dissolution study was reviewed separately [GDRP, ANDA206497, Biopharmaceutics Quality Review, A206497N000DB_D12132013.doc]. Please refer to the review for further details.

In May 2013, the firm conducted drug release tests using the FDA-recommended method with three sampling time ranges (i.e., 0-0.5 hr, 0.5-2 hr, 2-6 hr). In October 2013, the firm re-conducted the drug release tests for all strengths using the FDA-recommended method with six sampling time points as follows:

Table 24. Dissolution Data

Comparative Dissolution Profile of Methylphenidate Transdermal System 10 mg/9 hr (1.1 mg/hr)

Dissolution Conditions		**Apparatus:**	Apparatus VI - Cylinder									
		Speed of Rotation:	50 rpm									
		Medium:	0.01N Hydrochloric Acid									
		Volume:	900 mL									
		Temperature:	32°C ± 0.5°C									
Firm's Proposed Specifications			(b) (4)									
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)			Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478									
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						0.5 hr	**1.5 hr**	**2 hr**	**3 hr**	**4 hr**	**6 hr**	
N/A	10/31/13	Methylphenidate Transdermal System Lot R6D0023 April 2012	1.1 mg/hr	12	Mean µg/hr/cm^2	32	56	63	74	80	85	3.2.P.5.4
					RSD%	1.6	1.8	1.4	1.5	1.6	1.7	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 64166 January 2014	1.1 mg/hr	12	Mean µg/hr/cm^2	31	55	63	75	82	91	
					RSD%	1.3	1.0	0.9	1.0	1.1	1.4	
					Range µg/hr/cm^2	(b) (4)						

Note: The unit of µg/hr/cm^2 listed in the table above is an error[21]. The correct unit is % label claim. The actual amount of methylphenidate per patch is considered as 100% (e.g., For Daytrana 30 mg/ 9 hr, 82.5 mg of methylphenidate is considered as 100%)

[21] DARRTS, ANDA206497,SDN1, Module 3.2.P.5.4, dated 12/13/2013

15 mg/9 hr (1.6 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/29/13 – 10/30/13	Methylphenidate Transdermal System Lot R6D0035 November 2012	1.6 mg/hr	12	Mean µg/hr/cm²	35	61	69	80	86	91	3.2.P.5.4
					RSD%	1.1	0.7	0.9	0.7	0.8	0.9	
					Range µg/hr/cm²	(b) (4)						
N/A	10/28/13	Daytrana® Lot 65474 February 2014	1.6 mg/hr	12	Mean µg/hr/cm²	30	54	62	73	80	89	
					RSD%	1.6	1.2	1.0	1.7	1.1	1.5	
					Range µg/hr/cm²	(b) (4)						

Note: The unit of µg/hr/cm² listed in the table above is an error. The correct unit is % label claim.

20 mg/9 hr (2.2 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	(b) (4)	
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/30/13	Methylphenidate Transdermal System Lot R6D0036 November 2012	2.2 mg/hr	12	Mean µg/hr/cm^2	37	64	72	83	90	96	3.2.P.5.4
					RSD%	1.1	0.8	0.5	0.6	1.0	0.9	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/29/13	Daytrana® Lot 64925 January 2014	2.2 mg/hr	12	Mean µg/hr/cm^2	30	52	60	71	78	87	
					RSD%	1.7	1.0	0.6	1.0	0.7	0.7	
					Range µg/hr/cm^2	(b) (4)						

Note: The unit of µg/hr/cm^2 listed in the table above is an error. The correct unit is % label claim.

30 mg/9 hr (3.3 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)		Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/31/13	Methylphenidate Transdermal System Lot R6D0014 March 2012	3.3 mg/hr	12	Mean µg/hr/cm^2	34	59	67	78	84	90	3.2.P.5.4
					RSD%	0.8	0.9	0.8	0.8	0.7	0.7	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 66085 March 2014	3.3 mg/hr	12	Mean µg/hr/cm^2	31	54	62	74	82	89	
					RSD%	1.7	0.8	0.9	0.8	0.8	0.6	
					Range µg/hr/cm^2	(b) (4)						

Note: The unit of µg/hr/cm^2 listed in the table above is an error. The correct unit is % label claim.

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Reviewer's Comments:
As mentioned in Section 4.2, the test product contains methylphenidate in the solid matix reservoir, while the reference product contains the methylphenidate in the adhesive. The amount of methylphenidate / patch in the test product is lower than that in the reference product, and the size of the patchs for the test product are smaller than that for the reference product (see the table below).

	10 mg/ 9 hr	**15 mg/ 9 hr**	**20 mg/ 9 hr**	**30 mg/ 9 hr**

	API amount (mg)	Patch Size (cm^2)	API amount (mg)	Patch Size (cm^2)	API amount (mg)	Patch Size (cm^2)	API amount (mg)	Patch Size (cm^2)
Test	(b) (4)	9.6	(b) (4)	14.4	(b) (4)	19.2	31.10	28.8
Reference	27.5	12.5	41.25	18.75	55.0	25	82.5	37.5

Using the FDA-recommended drug release test method, the f2 values for 30 mg/9 hr test vs 10 mg/9 hr, 15 mg/9 hr or 20 mg/9 hr test were all greater than 50. The f2 values for the reference vs. the test for all strengths were greater than 50, except for 20 mg/9 hr strength (48.14). For 20 mg/ 9 hr strength, the test drug release rate is slightly faster than that of the reference. The results suggest that the dissolution profiles of the test 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr strengths are similar to that of the test bio-strength 30 mg/9 hr, and the data from 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr strengths of the test product using the FDA-recommended method are **adequate** to support bio-waiver of the 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr strengths of the test product.

The firm also conducted drug release studies in multi-media. The f2 values for reference vs. reference, test vs. test, and test vs. reference are all greater than 50.

4.4 Consult Reviews

4.4.1 ORS Consult

The DB requested the ORS to evaluate the necessity of partial AUCs and other PK parameters such as T_{lag} for Methylphenidate Transdermal Films.

The ORS provided the following recommendations to the DB[22].

RESPONSE TO OB QUESTIONS

1. Whether partial AUCs or other parameters (T_{max}, T_{lag}) should be included in current guidance

Even though the transdermal patch is not a multiphasic drug release delivery system, considering that MPH demonstrated strong PK/PD link (i.e., the shape of PK profile has impact on the PD response) and the patch is labeled to have 9-h wear time after patch application, this reviewer **recommends that partial AUC during 2 to 9h (AUC_{2-9}) be included in BE evaluation**. Additionally, this partial AUC is not over sensitive to formulation differences and has reasonable within-subject variability that is not associated with significantly large sample size. Additionally, the firms can choose to evaluated BE using RSABE approach.

2. Whether there is any issue, such as T_{lag}, etc. in ANDA 206497

Daytrana® label has a specific wording on the lag time and need to be applied 2 h before the effect is needed. **A qualitative visual inspection of PK profile is recommended to ensure comparable T_{lag}.** Adequate PK samples are needed before 2 h to ensure that minimal MPH are released before 2 h and similar to Daytrana®, but **statistical evaluations are not recommended** considering the great variability associated with low MPH concentration values before 2 h and the AUC_{2-9} assessment.

In the pivotal study in ANDA 206497, the average PK profiles of the test and reference products are superimposable. By visual inspection, there appears to be no significant differences in T_{lag}, T_{max}, C_{max}, and the initial rate of increase in plasma level, between the test and reference products.

Reviewer's Comments
Per the ORS recommendation, the product specific BE guidance will be revised to include partial AUC_{2-9}. The reviewer calculated partial AUC_{2-9} using linear interpolation for the current application, as there is no plasm samples obtained at 2 hours in the pivotal PK BE study (see Section 4.1.1.4).

[22] GDRP, ANDA-206497-ORIG-1-RESCIND, Bioequivalence Primary Review, Methylphenidate_Patch_206497.doc dated 03/15/2016

4.4.2 DCR Consult

The DB requested the DCR to evaluate whether the amount of **hydrophobic colloidal silica** used in the formulation of Mylan's Methylphenidate Transdermal System (ANDA 206497, current application) should be of a safety concern.

The DCR consulted the Office of New Drugs (OND) and this consult was reviewed by the Division of Psychiatry Products (DPP).

The DPP provided the following recommendations to the DCR[23].

Based on an informal ONDQA chemistry consult, this Reviewer understands that hydrophobic colloidal silica is a derivative of hydrophilic silicon dioxide (silica). Furthermore the modifications to the surface of hydrophilic silicon dioxide, by adding more hydrophobic groups to convert the product to hydrophobic colloidal silica, does not alter its toxicological profile. The Sponsor of this ANDA, Mylan Technologies, submitted a limited data summary on (b) (4) (b) (4) leading to the conclusion that toxicities derived from systemic exposure are not overly concerning. However, no long-term local toxicity data with the excipient were provided by the Sponsor. Based on its chemical properties (b) (4) is considered to be minimally absorbed through the skin.

The Inactive Ingredient Guide (IIG) database lists up to 49 mg of silicon dioxide in a previously approved patch. These levels reflect an exposure of (b) (4) Accordingly, local toxicity findings that may arise from (b) (4) in a patch size of 28.8 cm^2 (i.e. (b) (4) present in Mylan's methylphenidate transdermal system should be covered by the previous approval of (b) (4) of silicon dioxide. Moreover, a clinical study comparing irritation and sensitization potential for Mylan's methylphenidate and Noven's Daytrana® patch (the reference product) showed no significant differences. Therefore, the current proposed levels of not more than (b) (4) in a 28.8 cm^2 patch (b) (4) of (b) (4) in Mylan's Methylphenidate Transdermal System is considered acceptable from a Pharmacology/Toxicology perspective.

Reviewer's Comments
The DCR concurred with DPP's recommendations. Per the DCR/DPP consult, the current proposed formulation for Mylan's Methylphenidate Transdermal System is considered acceptable (see Section 4.2).

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[23] GDRP, ANDA-206497-ORIG-1-RESCIND, Pharm/Tox Primary Review, OND DPP PharmTox Consult review ANDA 206497 Hydrophobic Colloidal Silica.pdf dated 02/24/2016

4.5 SAS Output

4.5.1 PK Study

Study #MPTP-12012 (30 mg / 9 hr Fasting)

PK Study Data	PK Study Codes	PK Study Output
ANDA 206497 PK Study.xls	HV-RefScale3Period-Crossover3-ParamNotConv.sas Three way crossover methylphenidate.sas	206497_Fasting_table_Methylphenidate.doc 206497-ANALYSIS.doc

4.6 Additional Pilot PK Bioequivalence Studies

The firm also submitted results of two pilot PK endpoint BE studies: #MPTP-11030 comparing the test product, lot#R6C0003 and R6C0004 to the reference product, Daytrana® (methylphenidate Transdermal Film), lot #50893, and #MPTP-11125 comparing the test product, lot#R6C00016 to the reference product, Daytrana® (methylphenidate Transdermal Film), lot #50893. The pilot PK endpoint BE studies were designed as single-dose, two-way crossover study in healthy male and female subjects.

The test formulation of the lots (#R6C0004 and #R6C00016) used in the two pilot PK BE studies are the same as that (#R6D00014) used in the pivotal PK BE study. The additional test formulation of the lot (#R6C0003) used in the pilot PK BE study (MPTP-11030) contains higher amount of adhesive than that (#R6D00014) used in the pivotal PK BE study. The test patch sizes in the pilot PK BE studies are larger than that used in the pivotal PK BE study.

Per FDA's Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs (May 2011), the firm submitted 16 bioequivalence summary tables for the pilot PK BE studies, which is provided in Section 4.6.1 and 4.6.2.

4.6.1 Failed PK Bioequivalence Study MPTP-11030

4.6.1.1 Study Design

Table 37. Study Information

Study Number	MPTP-11030
Study Title	Single-Dose Pilot Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers
Study Type	☒ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other (Specify)
Submission Location:	
Study Report	Section 5.3.1.2
Validation Report	Section 5.3.1.4
Bioanalytical Report	Section 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Celerion, Inc. 2420 West Baseline Road Tempe, AZ 85283, USA Tel: 602-437-0097 ext 67162 Fax: 602-437-3386
Principal Clinical Investigator (Name, Email)	Mark J. Allison, MD, CPI mark.allison@celerion.com
Dosing Dates	Period 1: 28-March-2011 Period 2: 3-April-2011 Period 3: 9-April-2011
Analytical Site (Name, Address, Phone #, Fax #)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505 Tel#:304-598-5430 Fax#:304-285-6478
Analysis Dates	20-April-2011 – 28-April-2011
Principal Analytical Investigator (Name, Email)	Patrick T. Vallano, PhD Pat.vallano@mylan.com
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range <e.g. -20°C to -80°C>**	Methylphenidate: 30 days at -70°C [Date of 1st sample collection 28-March-2011; Date of last sample analysis: 28-April-2011] -70°C (all analyzed samples stored at this temperature)
Long Term Storage Stability Coverage <e.g. no. of days @ temp °C>	Up to 121 days at -70°C and -15°C.

Table 38. Product Information

Product	Test	Test	Reference
Study No.	MPTP-11007 & MPTP-11030		
Treatment ID	Treatment A	Treatment B	Treatment C
Product Name	Methylphenidate Transdermal System	Methylphenidate Transdermal System	Daytrana®
Manufacturer	Mylan Technologies Inc	Mylan Technologies Inc	Noven Pharmaceuticals Inc
Batch/Lot No.	R6C0003	R6C0004	50893
Manufacture Date	2/2011	2/2011	N/A
Expiration Date	N/A	N/A	12/2012
Strength	30 mg/9 hr (3.3 mg/hr)	30 mg/9 hr (3.3 mg/hr)	30 mg/9 hr (3.3 mg/hr)
Dosage Form	Patch	Patch	Patch
Bio-batch Size	(b) (4)		
Production Batch Size			
Potency	99.4%	101.1%	99.8%
Content Uniformity (mean, %CV)	99.4% ± 2.0%	101.1% ± 1.3%	N/A
Dose Administered	30 mg/9 hr (3.3 mg/hr)	30 mg/9 hr (3.3 mg/hr)	30 mg/9 hr (3.3 mg/hr)
Route of Administration	Topical	Topical	Topical

4.6.1.2 Clinical Results

Table 39. Demographics Profile of Subjects Completing the Bioequivalence Study

PILOT BIOEQUIVALENCE-ADHESION-ACUTE IRRITATION STUDY MYLAN STUDY NUMBER: MPTP-11030				
		TREATMENT GROUPS		
		Test Product (A) N = 24	Test Product (B) N = 24	Reference Product (C) N = 24
Age (years)	Mean ± SD Range	35.5 ± 7.40 20 - 45	35.5 ± 7.40 20 - 45	35.5 ± 7.40 20 - 45
Age Groups	<18 18-40 41-64 65-75 >75	0 (0.0%) 14 (58.3%) 10 (41.7%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 14 (58.3%) 10 (41.7%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 14 (58.3%) 10 41.7%) 0 (0.0%) 0 (0.0%)
Sex	Female Male	12 (50.0%) 12 (50.0%)	12 (50.0%) 12 (50.0%)	12 (50.0%) 12 (50.0%)
Race	Asian Black Caucasian Hispanic Other	0 (0.0%) 0 (0.0%) 24 (100.0%) 20 (83.3%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 24 (100.0%) 20 (83.3%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 24 (100.0%) 20 (83.3%) 0 (0.0%)
BMI	Mean ± SD Range	26.0 ± 2.3 22 - 29	26.0 ± 2.3 22 - 29	26.0 ± 2.3 22 - 29
Other Factors		N/A	N/A	N/A

Comments on Demographic Profile:

- The age range of subjects enrolled in the pivotal PK BE study (i.e., age between 19-45 years) was similar to that in the pilot PK BE study (i.e., age between 20-45 years). The

body mass index in the pivotal PK BE study (i.e., between 19 – 30 kg/m^2) was similar to that in the pilot PK BE study (i.e., between 22 – 29 kg/m^2).

- The clinical site for the pivotal PK BE study (MPTP-12012) is located at Kendle International Inc in Morgantown WV, whereas the clinical site for the pilot PK BE study (MPTP-11030) is located at Celerion, Inc.in Tempe AZ.

Table 40. Dropout Information, Pilot Fasting Bioequivalence Study

Study No. MPTP-11030				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
N/A	N/A	N/A	N/A	N/A

Table 41. Study Adverse Events, Pilot Fasting Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups		
	Pilot Bioequivalence-Adhesion-Acute Irritation Study Mylan Study Number: MPTP-11030		
	Test (A)	Test (B)	Reference (C)
	N[2]=24 n[3] (%)	N[2]=24 n[3] (%)	N[2]=24 n[3] (%)
Cardiac disorders			
Palpitations	1 (4.2%)	1 (4.2%)	1 (4.2%)
Eye disorders			
Vision blurred	0 (0.0%)	0 (0.0%)	1 (4.2%)
Gastrointestinal disorders			
Abdominal distension	0 (0.0%)	1 (4.2%)	0 (0.0%)
Abdominal pain	1 (4.2%)	0 (0.0%)	0 (0.0%)
Dry mouth	0 (0.0%)	1 (4.2%)	0 (0.0%)
Nausea	0 (0.0%)	2 (8.3%)	1 (4.2%)
General disorders and administration site conditions			
Application site cold feeling	0 (0.0%)	1 (4.2%)	0 (0.0%)
Application site discolouration	1 (4.2%)	0 (0.0%)	1 (4.2%)
Application site erythema	23 (95.8%)	24 (100%)	24 (100%)
Application site oedema	0 (0.0%)	0 (0.0%)	1 (4.2%)
Application site pain	6 (25.0%)	2 (8.3%)	4 (17.7%)
Application site papules	0 (0.0%)	1 (4.2%)	1 (4.2%)
Application site pruritus	4 (17.7%)	2 (8.3%)	1 (4.2%)
Application site warmth	0 (0.0%)	1 (4.2%)	0 (0.0%)
Chest discomfort	2 (8.3%)	2 (8.3%)	1 (4.2%)
Chest pain	0 (0.0%)	0 (0.0%)	1 (4.2%)
Feeling hot	0 (0.0%)	1 (4.2%)	1 (4.2%)
Thirst	0 (0.0%)	1 (4.2%)	0 (0.0%)
Infections and infestations			
Upper respiratory tract infection	1 (4.2%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders			
Decreased appetite	0 (0.0%)	1 (4.2%)	1 (4.2%)
Musculoskeletal and connective tissue Disorders			
Myalgia	0 (0.0%)	0 (0.0%)	1 (4.2%)
Nervous system disorders			
Disturbance in attention	0 (0.0%)	0 (0.0%)	1 (4.2%)
Dizziness	2 (8.3%)	0 (0.0%)	1 (4.2%)
Dizziness postural	0 (0.0%)	0 (0.0%)	1 (4.2%)
Headache	2 (8.3%)	4 (17.7%)	3 (12.5%)
Paraesthesia	0 (0.0%)	1 (4.2%)	0 (0.0%)
Sensory disturbance	1 (4.2%)	0 (0.0%)	0 (0.0%)
Somnolence	0 (0.0%)	3 (12.5%)	3 (12.5%)
Tremor	0 (0.0%)	1 (4.2%)	0 (0.0%)
Psychiatric disorders			
Anxiety	0 (0.0%)	1 (4.2%)	0 (0.0%)
Insomnia	0 (0.0%)	1 (4.2%)	1 (4.2%)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	1 (4.2%)	1 (4.2%)	0 (0.0%)
Epistaxis	0 (0.0%)	1 (4.2%)	0 (0.0%)
Nasal congestion	1 (4.2%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders			
Hyperhidrosis	0 (0.0%)	1 (4.2%)	0 (0.0%)
Total Subjects Reporting at Least One Adverse Event	24 (100%)	24 (100%)	24 (100%)

(1) MedDRA Version 15.0
(2) N = Number of subjects dosed for each treatment
(3) n =Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100% (n/N%)

Table 42. Protocol Deviations, Pilot Fasting Bioequivalence Study

Study No. MPTP-11030			
Type	**Subject #s (Test A)**	**Subject #s (Test B)**	**Subject #s (Reference C)**
Section 7.4 of the protocol states "The labels on each subject's dispensed drug(s) will not provide any information about the subject other than the randomization number (i.e. subject number)". Celerion standard Clinquick bar-coded label includes subject's screening identification number (SID), subject's initials, in addition to the client identification number or randomization number. Sponsor is aware of our processes and deems them adequate per email correspondence dated 22-Mar-2011.	(b) (6)		
According to the SOP the PI or designee must pre-approve planned deviations prior to the execution of that deviation. On 22 March 2011 the client approved a planned deviation to the drug labeling process outlined in the protocol however the PI was not notified.			
According to the protocol blood samples were to be obtained within 2 minutes of the scheduled time. Some samples for the following subjects were drawn outside of this window (sample timepoints for each subject are presented in Appendix 16.2.2.1).			

Comments on Dropouts/Adverse Events/Protocol Deviations:

- Twenty four subjects were enrolled in the study. Five subjects (1 test, 4 references) were dropped out from the study in Treatment A due to poor patch adhesion. Two subjects (1 test, 1 reference) were dropped out from the study in Treatment B due to poor patch adhesion.

4.6.1.3 Bioanalytical Results

Table 43. Pre-study Bioanalytical Method Validation (same as that provided for the pivotal PK end-point study)

Information Requested	Data
Bioanalytical method validation report location	Methylphenidate Bioanalytical Method Validation Report, Sections 5.3.1.4, See Methylphenidate Validation Addendum 3, Table 2
Analyte	Methylphenidate (MPHE)
Internal Standard (IS)	Methylphenidate $-d_9$ (MPHD)
Method Description	Liquid-liquid; LC/MS/MS - ESI
Limit of Quantitation (ng/mL)	0.5
Average Recovery of Drug (%)	90.45%[a]
Average Recovery of IS (%)	99.53% [a]
Standard Curve Concentrations (ng/mL)	0.5, 1.0, 1.5, 2.5, 5, 10, 15, 25, 35, 50
QC Concentrations (ng/mL)	1.5, 5, 15, 30
QC Intraday Precision Range (%)	0.35% to 7.87% [a]
QC Intraday Accuracy Range (%)	-4.40% to 10.93% [a]
QC Interday Precision Range (%)	1.95% to 4.83% [a]
QC Interday Accuracy Range (%)	-0.90% to 2.07% [a]
Bench-Top Stability (hrs)	25 hours @ Room Temperature [c]
Stock Stability (days)	MPHE Stock Solution 14 days @ 4°C[a] MPHE Working Solution 14 days @ 4°C[a] MPHD Stock Solution 14 days @ 4°C[a] MPHD Working Solution 14 days @ 4°C[a]
Room Temperature Solution Stability (hours)	MPHE Stock Solution – 6 hours [a] MPHE Working Solution – 19 hours [a] MPHD Stock Solution – 6 hours [a] MPHD Working Solution – 17 hours [a]
Processed Stability (hrs)	92.25 hours @ room temperature a
Freeze-Thaw Stability (cycles)	4 cycles [c]
Long-Term Storage Stability (days)	121 days @ -15°C and -70°C [d]
Dilution Integrity	Concentration diluted five-fold [a]
Selectivity	No interfering peaks noted in six blank plasma samples[a]
Whole Blood Stability	2.0 hours (120 minutes) [b]
Hemolysis Effect	No hemolysis effect observed [b]

Table 44. Assay Validation – Within the Failed Fasting Bioequivalence Study

Bioequivalence Study MPTP-11030 METHYLPHENIDATE										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.5000	1.000	1.500	2.500	5.000	10.00	15.00	25.00	35.00	50.00
Inter day Precision (%CV)	0.60	0.95	0.97	1.00	0.61	0.61	0.65	0.95	0.71	0.51
Inter day Accuracy (%Actual)	100.46	99.65	100.07	98.56	99.44	100.70	99.93	100.44	100.57	100.24
Linearity	0.9997 - 1.0000									
Linearity Range (ng/mL)	0.5000 - 50.00									
Sensitivity/LOQ (ng/mL)	0.5000									

Bioequivalence Study MPTP-11030 METHYLPHENIDATE				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	1.500	5.000	15.00	30.00
Inter day Precision (%CV)	2.21	2.34	2.31	2.52
Inter day Accuracy (%Actual)	102.60	101.14	100.67	99.87

Table 45. Reanalysis of Study Samples

MPTP-11030* – Fasting Study Repeat Analysis Results for Methylphenidate Additional Information in Section 1.6 of the Bioanalytical Report for MPTP-11030								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual Number		**% of total assays**		**Actual Number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Total	0	0	0.00	0.00	0	0	0.00	0.00

*There were no miscellaneous repeats for this study.

SOPs Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
MGW-BIO-SOP-BIO-GEN-0020	02/21/2011	Re-assay or Re-injection of Clinical Samples

4.6.1.4 Pharmacokinetic Results

Table 47. Arithmetic Mean Pharmacokinetic Parameters – Firm Calculated

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs), Mean (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC0-t (ng/mL•hr)	AUC∞ (ng/mL•hr)	$T_{1/2}$ (hr)	Kel (hr^{-1})	
					Methylphenidate						
MPTP-11030	Randomized, irritation evaluator blinded, 3-treatment 3-period, crossover, bioequivalence study of two formulations of Mylan's Methylphenidate Transdermal System, 30 mg/9 hrs and Noven's Daytrana®, 30 mg/9 hrs (reference) following a Single dose patch application in healthy volunteers	Single center, randomized single-dose, irritation evaluator blinded, 3-way, crossover bioequivalence study	A=Methylphenidate Transdermal System, 30 mg/9 hrs 1 × 30 mg/9 hrs topical Lot:R6C0003 B= Methylphenidate Transdermal System, 30 mg/9 hrs; 1 × 30 mg/9 hrs topical Lot: R6C0004 C= Daytrana®, 30 mg/9 hrs 1 × 30 mg/9 hrs topical Lot 50893	24 Dosed 24 Completed (M:12, F:12) Healthy Subjects Mean Age: 35.5 yrs (Range: 20 to 45 yrs) 19 PK Analysis* (Trt A) 22 PK Analysis (Trt B)‡	21.95 ± 8.67	8.00 (4.00 – 10.00)	211.99 ± 81.23	220.79 ± 81.63	4.12 ± 0.62	0.171 ± 0.021	Section 5.3.1.2
					19.17 ± 6.49	9.00 (8.00 – 10.00)	188.33 ± 64.28	196.37 ± 64.00	4.27 ± 0.69	0.166 ± 0.022	
					17.76 ± 6.80	9.00 (8.00 – 10.00)	164.68 ± 59.15	174.11 ± 59.06	4.58 ± 0.62	0.154 ± 0.020	

*1 subject discontinued due to poor patch adhesion of Treatment C and 4 subjects discontinued due to poor patch adhesion for Treatment A
‡1 subject discontinued due to poor patch adhesion of Treatment C and 1 subject discontinued due to poor patch adhesion for Treatment B

Table 48. Geometric Means and 90% Confidence Intervals - Firm Calculated

METHYLPHENIDATE TRANSDERMAL SYSTEM, 30 MG/9 HOURS Number of Subjects Completed = 24 Dose (30 mg/9 hours) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (MPTP-11030) Treatment A† - Methylphenidate						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC0-t (ng×mL/hr)	190.94	19	155.78	19	1.23	112.23% - 133.87%
AUC∞ (ng×mL/hr)	200.93	19	165.96	19	1.21	111.45% - 131.52%
C_{max} (ng/mL)	19.70	19	16.54	19	1.19	109.21% - 129.98%
Fasting Bioequivalence Study (MPTP-11030) Treatment B - Methylphenidate						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC0-t (ng×mL/hr)	177.50	22	155.78	22	1.14	104.87% - 123.80%
AUC∞ (ng×mL/hr)	186.88	22	165.96	22	1.13	104.16% - 121.73%
C_{max} (ng/mL)	17.63	22	16.54	22	1.07	98.23% - 115.71%

*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$
**Used Natural Log Transformed Parameter
†1 subject discontinued due to poor patch adhesion of Treatment C (RLD) and 4 subjects discontinued due to poor patch adhesion for Treatment A
‡1 subject discontinued due to poor patch adhesion of Treatment C (RLD) and 1 subject discontinued due to poor patch adhesion for Treatment B

Comments on Pharmacokinetic and Statistical Analysis:

For Treatment A with thinner adhesive than the final formulation, the results of the pilot PK endpoint BE study showed that 90% confidence intervals for T/R ratios for AUC0-t, AUC∞ and Cmax for methylphenidate failed to meet the acceptable limits of 80% -125%.

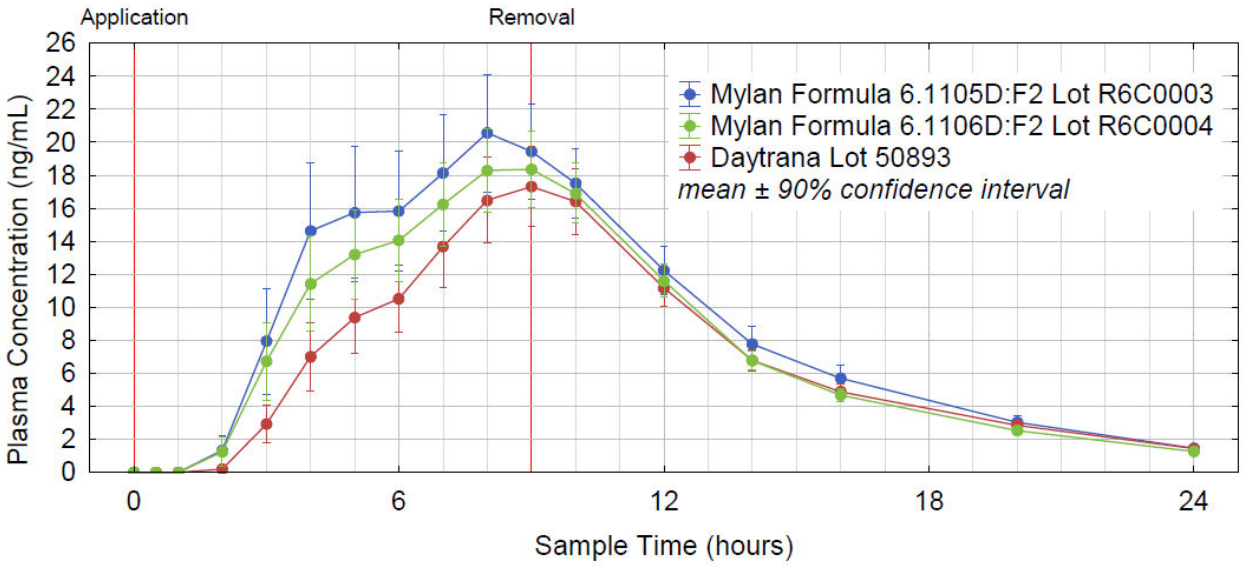
For Treatment B with the same amount of adhesive as the final formulation, the results of the pilot PK endpoint BE study showed that 90% confidence intervals for T/R ratios for AUC0-t, AUC∞ and Cmax for methylphenidate meet the acceptable limits of 80% -125%.

4.6.1.5 Formulation Data

Component	Formulation 6.1105D:F2 Lot R6C0003		Formulation 6.1106D:F2 Lot R6C0004	
	30 mg/ 9 hrs (34 cm^2)	% w/w in component layer	30 mg/ 9 hrs (34 cm^2)	% w/w in component layer
Solid Matrix Drug Reservoir				(b) (4)
Methylphenidate				
Hydrophobic Colloidal Silica NF (b) (4)				
(b) (4) Mineral Oil NF (b) (4)				
Polyisobutylene Adhesive (b) (4)				
Skin Contact Adhesive				
Hydrophobic Colloidal Silica NF (b) (4)				
(b) (4) Mineral Oil NF (b) (4)				
Polyisobutylene Adhesive (b) (4)				
Total Matrix Weight				
Other Components				
Backing Film	Ethylene-Vinyl Acetate (b) (4) Polyester Film (b) (4)			
Release Liner	(b) (4) Fluoropolymer Coated Polyester Release Liner (b) (4)			
Imprinting Ink	White Ink (b) (4)			

The test formulation of the lot (#R6C0004) used in the pilot PK BE study is the same as that (#R6D00014) used in the pivotal PK BE study. The test formulation of the lot (#R6C0003) in the pilot PK BE study contains lower amount of skin contact adhesive than that (#R6D00014) used in the pivotal PK BE study.

The test patch sizes of lot#R6C0004 and lot#R6D0003 in the pilot PK BE study are larger than that used in the pivotal PK BE study.


Application
Removal
Plasma Concentration (ng/mL)
Sample Time (hours)
Mylan Formula 6.1105D:F2 Lot R6C0003
Mylan Formula 6.1106D:F2 Lot R6C0004
Daytrana Lot 50893
mean ± 90% confidence interval

4.6.2 Failed PK Bioequivalence Study MPTP-11125

4.6.2.1 Study Design

Table 37. Study Information

Study Number	MPTP-11125
Study Title	Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers
Study Type	☒ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other (Specify)
Submission Location:	
Study Report	Section 5.3.1.2
Validation Report	Section 5.3.1.4
Bioanalytical Report	Section 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Celerion, Inc. 2420 West Baseline Road Tempe, AZ 85283, USA Tel: 602-437-0097 Ext 67162 Fax: 602-437-3386
Principal Clinical Investigator (Name, Email)	Dennis Swearingen, MD, CPI dennis.swearingen@celerion.com
Dosing Dates	Period I: 12-December-2011 Period II: 15-December-2011
Analytical Site (Name, Address, Phone #, Fax #)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505 Tel#:304-598-5430 Fax#:304-285-6478
Analysis Dates	13-January-2012 – 23-January-2012
Principal Analytical Investigator (Name, Email)	Patrick T. Vallano, PhD Pat.vallano@mylan.com
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range <e.g. -20°C to -80°C>**	Methylphenidate: 43 days at -70°C; 19 days at -15°C [Date of 1st sample collection 12-December-2011; Date of last sample analysis: 23-January-2012] -70°C (all analyzed samples stored at this temperature)
Long Term Storage Stability Coverage <e.g. no. of days @ temp °C>	Up to 121 days at -70°C and -15°C.

Table 38. Product Information

Product	Test	Reference
Study Number	**MPTP-11125**	
Treatment ID	Treatment A	Treatment B
Product Name	Methylphenidate Transdermal System	Daytrana®
Manufacturer	Mylan Technologies Inc	Noven Pharmaceuticals Inc
Batch/Lot No.	R6C00016	50893
Manufacture Date	11/2011	N/A
Expiration Date	N/A	12/2012
Strength	30 mg/9 hr (3.3 mg/hr)	30 mg/9 hr (3.3 mg/hr)
Dosage Form	Patch	Patch
Bio-batch Size	(b) (4)	
Production Batch Size		
Potency	98.4%	99.8%
Content Uniformity (mean, %CV)	98.4% ± 1.5%	N/A
Dose Administered	30 mg/9 hr (3.3 mg/hr)	30 mg/9 hr (3.3 mg/hr)
Route of Administration	Topical	Topical

4.6.2.2 Clinical Results

Table 39. Demographics Profile of Subjects Completing the Bioequivalence Study

BIOEQUIVALENCE STUDY MYLAN STUDY NUMBER: MPTP-11125			
		TREATMENT GROUPS	
		Test Product N= 34	Reference Product N= 34
Age (years)	Mean ± SD Range	33.8 ± 7.03 18 - 45	33.8 ± 7.03 18 - 45
Age Groups	<18 18-40 41-64 65-75 >75	0 (0.0%) 28 (82.4%) 6 (17.6%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 28 (82.4%) 6 (17.6%) 0 (0.0%) 0 (0.0%)
Sex	Female Male	17 (50.0%) 17 (50.0%)	17 (50.0%) 17 (50.0%)
Race	Asian Black Caucasian Hispanic Other	0 (0.0%) 3 (8.8%) 31 (91.2%) 26 (76.5%) 0 (0.0%)	0 (0.0%) 3 (8.8%) 31 (91.2%) 26 (76.5%) 0 (0.0%)
BMI	Mean ± SD Range	25.5 ± 2.4 21 – 30	25.5 ± 2.4 21– 30
Other Factors		N/A	N/A

Comments on Demographic Profile:

- The age range of subjects enrolled in the pivotal PK BE study (i.e., age 19-45 years) is similar to that in the pilot PK BE study (i.e., age 18-45). The body mass index in the pivotal PK BE study (i.e., between 19 – 30 kg/m^2) was similar to that in the pilot PK BE study (i.e., between 21 – 30 kg/m^2).

- The clinical site for the pivotal PK BE study (MPTP-12012) is located at Kendle International Inc in Morgantown WV, whereas the clinical site for the pilot PK BE study (MPTP-11125) is located at Celerion, Inc. in Tempe AZ.

Table 40. Dropout Information, Pilot Fasting Bioequivalence Study

Study No. MPTP-11125				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Subject discontinued from study on Day 1 of Period 1 dosing due to damage to patch Treatment B	1	No	N/A
	Subject discontinued from study on Day 1 of Period 1 dosing due to damage to patch Treatment B	1	No	N/A

Table 41. Study Adverse Events, Failed Fasting Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups	
	Bioequivalence Study Mylan Study Number: MPTP-11125	
	Test	Reference
	N[2]=34 n[3] (%)	N[2]=36 n[3] (%)
Gastrointestinal disorders		
Diarrhoea	1 (2.9%)	0 (0.0%)
Nausea	2 (5.9%)	0 (0.0%)
Vomiting	2 (5.9%)	0 (0.0%)
General disorders and administration site conditions		
Application site erythema	33 (97.1%)	35 (97.1%)
Application site pain	0 (0.0%)	1 (2.8%)
Application site papules	0 (0.0%)	2 (5.6%)
Application site pruritus	0 (0.0%)	1 (2.8%)
Application site warmth	1 (2.9%)	0 (0.0%)
Vessel puncture site pain	0 (0.0%)	1 (2.8%)
Vessel puncture site paraesthesia	1 (2.9%)	0 (0.0%)
Nervous system disorders		
Dizziness	1 (2.9%)	1 (2.8%)
Headache	2 (5.9%)	2 (5.6%)
Presyncope	1 (2.9%)	0 (0.0%)
Somnolence	0 (0.0%)	1 (2.8%)
Psychiatric disorders		
Anxiety	1 (2.9%)	1 (2.8%)
Insomnia	0 (0.0%)	1 (2.8%)
Renal and urinary disorders		
Dysuria	1 (2.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	1 (2.9%)	0 (0.0%)
Skin and subcutaneous tissue disorders		
Dermatitis contact	2 (5.9%)	1 (2.8%)
Total Subjects Reporting at Least One Adverse Event	33 (97.1%)	35 (97.1%)

(1) MedDRA Version 14.1
(2) N = Number of subjects dosed for each treatment
(3) n =Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100% (n/N%)

Reviewer's Note: Emesis will not affect plasma concentrations following topical application. Those two subjects experiencing emesis were included in the PK analysis correctly.

Table 42. Protocol Deviations, Failed Fasting Bioequivalence Study

Study No. MPTP-11125		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
According to the protocol, plasma sample tubes will be numbered sequentially for each subject across all periods. For all subjects, all sample tubes were not numbered in this manner per sponsor approval.	(b) (6)	
According to the protocol, blood samples following transdermal system application collected within 2 minutes of schedule will not be considered protocol deviations. Some samples for the following subjects were drawn outside of this window (sample time points for each subject are presented in Appendix 16.2.2.1).		
According to the protocol, if less than 75% of a meal (e.g. lunch, snack) is consumed, it will be considered a protocol deviation. The following subjects consumed <75% of their meal in Period 1: Subjects (b) (6) at -14 hr and Subject (b) (6) at -10.08 hr.		
According to the protocol, The time interval between sample collection and the start of centrifugation should not exceed 30 minutes. The following deviations occurred at Period 2, 9 hr: the time intervals for Subject (b) (6) and Subject (b) (6) and 31 minutes, respectively.		

Comments on Dropouts/Adverse Events/Protocol Deviations:

- Two subjects were dropped out from the study, and 18 subjects completed the study periods.

4.6.2.3 Bioanalytical Results

Table 43. Pre-study Bioanalytical Method Validation (same as that provided for the pivotal PK end-point study)

Information Requested	Data
Bioanalytical method validation report location	Methylphenidate Bioanalytical Method Validation Report, Sections 5.3.1.4, See Methylphenidate Validation Addendum 3, Table 2
Analyte	Methylphenidate (MPHE)
Internal Standard (IS)	Methylphenidate $-d_9$ (MPHD)
Method Description	Liquid-liquid; LC/MS/MS - ESI
Limit of Quantitation (ng/mL)	0.5
Average Recovery of Drug (%)	90.45%[a]
Average Recovery of IS (%)	99.53% [a]
Standard Curve Concentrations (ng/mL)	0.5, 1.0, 1.5, 2.5, 5, 10, 15, 25, 35, 50
QC Concentrations (ng/mL)	1.5, 5, 15, 30
QC Intraday Precision Range (%)	0.35% to 7.87% [a]
QC Intraday Accuracy Range (%)	-4.40% to 10.93% [a]
QC Interday Precision Range (%)	1.95% to 4.83% [a]
QC Interday Accuracy Range (%)	-0.90% to 2.07% [a]
Bench-Top Stability (hrs)	25 hours @ Room Temperature [c]
Stock Stability (days)	MPHE Stock Solution 14 days @ 4°C[a] MPHE Working Solution 14 days @ 4°C[a] MPHD Stock Solution 14 days @ 4°C[a] MPHD Working Solution 14 days @ 4°C[a]
Room Temperature Solution Stability (hours)	MPHE Stock Solution – 6 hours [a] MPHE Working Solution – 19 hours [a] MPHD Stock Solution – 6 hours [a] MPHD Working Solution – 17 hours [a]
Processed Stability (hrs)	92.25 hours @ room temperature a
Freeze-Thaw Stability (cycles)	4 cycles [c]
Long-Term Storage Stability (days)	121 days @ -15°C and -70°C [d]
Dilution Integrity	Concentration diluted five-fold [a]
Selectivity	No interfering peaks noted in six blank plasma samples[a]
Whole Blood Stability	2.0 hours (120 minutes) [b]
Hemolysis Effect	No hemolysis effect observed [b]

Table 44. Assay Validation – Within the Failed Fasting Bioequivalence Study

Bioequivalence Study MPTP-11125 METHYLPHENIDATE										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.5000	1.000	1.500	2.500	5.000	10.00	15.00	25.00	35.00	50.00
Inter day Precision (%CV)	0.53	1.17	0.90	0.70	0.84	0.73	0.54	0.49	0.47	0.69
Inter day Accuracy (%Actual)	100.98	99.11	99.67	98.04	98.68	101.10	101.07	100.04	101.14	100.22
Linearity	0.9996 - 0.9998									
Linearity Range (ng/mL)	0.5000 - 50.00									
Sensitivity/LOQ (ng/mL)	0.5000									

Bioequivalence Study MPTP-11125 METHYLPHENIDATE				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	1.500	5.000	15.00	30.00
Inter day Precision (%CV)	1.23	2.04	1.16	1.12
Inter day Accuracy (%Actual)	98.13	95.60	97.33	96.30

Table 45. Reanalysis of Study Samples

MPTP-11125 – Fasting Study Repeat Analysis Results for Methylphenidate Additional Information in Table 5 of the Bioanalytical Report for MPTP-11125								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual Number		**% of total assays**		**Actual Number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Reason A[1]	0	2	0.00%	0.17%	0	2	0.00%	0.17%
Reason B[2]	1	0	0.09%	0.00%	1	0	0.09%	0.00%
Total	0	0	0.00%	0.17%	0	0	0.00%	0.17%

[1] Documented Sample Processing error – broken glass sample vial.
[2] Documented Sample Processing error – empty well in final sample plate

SOPs Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
MGW-BIO-SOP-BIO-GEN-0020	02/21/2011	Re-assay or Re-injection of Clinical Samples

4.6.2.4 Pharmacokinetic Results

Table 47. Arithmetic Mean Pharmacokinetic Parameters – Firm Calculated

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs), Mean (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC0-t (ng/mL·hr)	AUC∞ (ng/mL·hr)	$T_{1/2}$ (hr)	Kel (hr^{-1})	
					Methylphenidate						
MPTP-11125	Randomized, irritation evaluator blinded, 2-period, 2-treatment crossover, bioequivalence study of Mylan's Methylphenidate Transdermal System, 30 mg/9 hrs and Noven's Daytrana®, 30 mg/9 hrs (reference) following a Single dose patch application in healthy volunteers under fasting condition	Single center, randomized single-dose, irritation evaluator blinded, 2-treatment, 2-way, crossover bioequivalence study	A=Methylphenidate Transdermal System, 30 mg/9 hrs 1 × 30 mg/9 hrs topical Lot:R6C0016 B= Daytrana®, 30 mg/9 hrs 1 × 30 mg/9 hrs topical Lot 50893	36 Dosed 34 Completed 34 PK & Statistical Analysis (M:17, F:17) Healthy Subjects Mean Age: 33.8 yrs (Range: 18 to 45 yrs)	18.03 ± 5.10	10.00 (5.00 – 10.00)	163.55 ± 44.29	172.34 ± 44.12	4.89 ± 0.82	0.145 ± 0.022	Section 5.3.1.2
					17.00 ± 8.22	10.00 (5.00 – 12.00)	154.66 ± 68.57	164.53 ± 68.44	4.97 ± 0.88	0.144 ± 0.023	

Table 48. Geometric Means and 90% Confidence Intervals - Firm Calculated

METHYLPHENIDATE TRANSDERMAL SYSTEM, 30 MG/9 HOURS Number of Subjects Completed = 34 Dose (30 mg/9 hours) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (MPTP-11125) Methylphenidate						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC0-t (ng×mL/hr)	157.30	34	138.20	34	1.14	102.69% - 126.15%
AUC∞ (ng×mL/hr)	166.46	34	149.31	34	1.11	101.60% - 122.34%
C_{max} (ng/mL)	17.27	34	14.80	34	1.17	103.61% - 131.32%

*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$

**Used Natural Log Transformed Parameter

Comments on Pharmacokinetic and Statistical Analysis:

The results of the pilot PK endpoint study showed that 90% confidence intervals for T/R ratios for AUC0-t and Cmax for methylphenidate failed to meet the acceptable limits 80% -125%.

Even though the size of the test transdermal system was reduced from 34 cm² to 31.2 cm² (using same formulation and thickness of adhesive), the LSMeans ratios calculated for AUC0-t, AUC∞ and Cmax were equal or greater than those measured in the 1st pilot PK endpoint BE study MPTP-11030, and the upper confidence intervals for Cmax and AUC0-t were outside of the acceptance criteria for pharmacokinetic bioequivalence.

When AUCs and Cmax are normalized by the size of the patches, the AUCs and Cmax in the 1st pilot study MPTP-11030 are similar to those in the 2nd pilot study MPTP-11125 (see the table below and comments under Study Information in Section 4.1.1.1).

Mylan's Product PK Profiles

	Overlay	Size of Patch (cm2)		Test	Test/Size
MPTP-11030 Treatment B (pilot: N=24)	**No**	**34**	AUC0-t (ng*hr/ml)	177.50	5.2
			AUC∞ (ng*hr/ml)	186.88	5.5
			Cmax (ng/mL)	17.63	0.5
MPTP-11125 (pilot: N=34)	**Yes**	**31.2**	AUC0-t (ng*hr/ml)	157.30	5.0
			AUC∞ (ng*hr/ml)	166.46	5.3
			Cmax (ng/mL)	17.27	0.6
MPTP-12012 (pivotal: N=37) Different Sampling Time	**Yes**	**28.8**	AUC0-t (ng*hr/ml)	122.52	4.3
			AUC∞ (ng*hr/ml)	128.37	4.5
			Cmax (ng/mL)	14.68	0.5

The RLD lot used in the two pilot studies #MPTP-11030 and MPTP-11125 was lot #50893, which is different from the lot used in the pivotal PK BE study (lot #58415). For the RLD product, AUCs were lower in the pivotal PK BE study compared to those in the two pivotal studies using the same bioanalytical study method, although Cmax in the pilot and pivotal studies were similar (see comments below Study Information Table, Section 4.1.1.1). This could be due to inter-study variability and/or possible lot-to-lot variability.

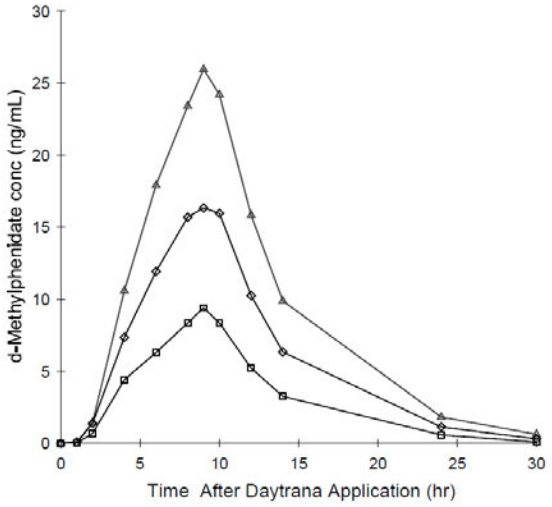
Study No.	Sampling Time Points
MPTP-12012 (pivotal)	Pre-dose (0.0 hour) and at 1, 3, 5, 7, 8, 8.5, 9 (prior to patch removal), 9.5, 10, 11, 12, 14, 16, 20, 24 and 30 hours
MPTP-11030 MPTP-11125 (pilot)	Pre-dose (0.0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 (prior to patch removal), 10, 12, 14, 16, 20 and 24 hours

The firm increased sampling time points around Cmax (Tmax) in the pivotal BE study. However, the sampling time points around T_{lag} for the pivotal BE study are sparser than those in the pilot BE studies. Median T_{lag} for test and reference products are 1 and 3, respectively, in the pivotal BE study (see the table below). However, it should be noted that 2 hour sample was not obtained in the pivotal BE study, unlike the two pilot BE studies.

Pilot Study 11030	**Tmax**	**Tlag**
Test	9 [8,10]	2 [1, 5]
Ref	9 [8, 10]	2 [1, 5]
Pivotal Study 12012	**Tmax**	**Tlag**
Test	9.5 [8.5, 10]	1 [1, 5]
Ref	9.5 [8.5, 20]	3 [0, 9.5]

In NDA021514, the PK sampling time points were less robust compared to the current application (see the figure below). This study is a single 9-hour application of Daytrana patch doses of 10 mg / 9 hours to 30 mg / 9 hours patches in 34 children with ADHD.

Mean Concentration-time Profiles for *d*-Methylphenidate in all Patients (N=34) Following Administration of Single Applications (9-Hour Wear Time) of *d,l*-Methylphenidate Using Daytrana 10 mg (□), 20 mg (◊) and 30 mg (△) per 9-Hour Patches



For the test product, variability in AUCs and Cmax is lower in the 2nd pilot study MPTP-11125 compared to the 1st pilot study MPTP-11030, which could be partially due to the greater number of subjects enrolled in the 2nd pilot study MPTP-11125 (n=34) than that in the 1st pilot study MPTP-11030 (n=24). On the other hand, for the reference product, variability increased in the 2nd pilot study MPTP-11125 compared to the 1st pilot study MPTP-11030 regardless of enrolling more subjects in the 2nd pilot study, presumably due to higher within lot variability of the reference product.

Overall, the sampling time difference would not impact the PK profile comparison between the test and reference.

Regarding the (b) (4) Overlay used in this pilot study, please refer to the comments under Study Information in Section 4.1.1.1.

4.6.2.5 Formulation Data

Component	Formulation 6.1110D:F1 Lot R6C0016	
	30 mg/ 9 hrs (31.2 cm²)	% w/w in component layer
Solid Matrix Drug Reservoir		(b) (4)
Methylphenidate		
Hydrophobic Colloidal Silica NF (b) (4)		
(b) (4) Mineral Oil NF (b) (4)		
Polyisobutylene Adhesive (b) (4)		
Skin Contact Adhesive		
Hydrophobic Colloidal Silica NF (b) (4)		
(b) (4) Mineral Oil NF (b) (4)		
Polyisobutylene Adhesive (b) (4)		
Total Matrix Weight		
Other Components		
Backing Film	Ethylene-Vinyl Acetate (b) (4) Polyester Film	
Release Liner	(b) (4) Fluoropolymer Coated Polyester Release Liner (b) (4)	
Imprinting Ink	White Ink (b) (4)	

The test formulation of the lot (#R6C00016) used in the pilot PK BE study is the same as that (#R6D00014) used in the pivotal PK BE study (using same formulation and thickness of adhesive). The test patch size of lot#R6C00016 in the pilot PK BE study is larger than that used in the pivotal PK BE study (see Section 4.6.2.4).

As a result of study MPTP-11125, the system area for Mylan's Methylphenidate Transdermal System 30 mg/9 hrs (3.3 mg/hr) was further adjusted. The pharmacokinetic results from studies MPTP-11030 and MPTP-11125 were aggregated and a new area of 28.8 cm² was calculated to match the size-adjusted pharmacokinetic parameters of Mylan's Methylphenidate Transdermal System 30 mg/9 hrs (3.3 mg/hr) to the RLD.

4.7 OSIS Inspection Status for ANDA 206497

A. Clinical Site

Clinical Site Name:	Kendle International Inc a subsidiary of INC Research LLC
Clinical Site Address:	763 Chestnut Ridge Road Morgantown WV 26505
Clinical Study Dates:	Study: MPTP-12012 4/30/2012-5/06/2012

Application (ANDA/NDA)	Inspected BE Study Type (In Vivo, In Vitro)	Inspection Type (Routine or For Cause)	EIR Report Date	Inspection Outcome (NAI, VAI, OAI)	Study dates of inspected clinical studies		Current ANDA clinical study dates[24]		Were the Current ANDA clinical studies conducted within 3.5 years of the inspected clinical studies? (Yes/No)	Conclusion (Relevant, Irrelevant)
					Start Date (MM/DD/YY)	End Date (MM/DD/YY)	Start Date (MM/DD/YY)	End Date (MM/DD/YY)		
(b) (4)										
NDA 21799	In Vivo	Routine	3/8/2012	NAI	Period I: 3/20/09 Period II: 3/27/09 Period III: 4/3/09	Period I: 4/5/09 Period II: 4/12/09 Period III: 4/19/09	4/29/2012	5/7/2012	Yes	Relevant
(b) (4)										

NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated; CAN: Inspection cancelled.

[24] The dates of pivotal BE study #MPTP-12012 are considered here

B. Analytical Site

Analytical Site Name:	Mylan Pharmaceuticals Inc.
Analytical Site Address:	Bioanalytical Department 3711 Collins Ferry Rd., Morgantown, WV 26505
Analytical Study Dates:	Study: MPTP-12012 5/15/2012-5/30/2012

Application (ANDA/NDA)	**Inspected BE Study Type (In Vivo, In Vitro)**	**Inspection Type (Routine or For Cause)**	**EIR Report Date**	**Inspection Outcome (NAI, VAI, OAI)**	**Study dates of inspected analytical studies**		**Current ANDA analytical study dates[24]**		**Were the Current ANDA analytical studies conducted within 3.5 years of the inspected analytical studies? (Yes/No)**	**Conclusion (Relevant, Irrelevant)**
					Start Date (MM/DD/YY)	**End Date (MM/DD/YY)**	**Start Date (MM/DD/YY)**	**End Date (MM/DD/YY)**		
ANDA 204595	In Vivo	Routine	1/15/2014	NAI	2/24/2012	3/12/2012	5/15/2012	5/30/2012	Yes	Relevant
ANDA 203371	In Vivo	Routine	7/11/2013	NAI	6/17/2011	7/6/2011	5/15/2012	5/30/2012	Yes	Relevant
										(b) (4)

NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated.

Reviewer's Comments

Clinical Site: Status of all relevant clinical site inspections is NAI. Therefore, OSIS status of clinical site of ANDA 206497 is adequate.

Analytical Site: Status of all relevant analytical site inspections is NAI. Therefore, OSIS status of analytical site of ANDA 206497 is adequate.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	206497
APPLICANT:	Mylan Technologies, Inc.
DRUG PRODUCT:	Methylphenidate Transdermal System, 10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr

The Division of Bioequivalence (DB) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director,
Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	206497
Drug Product Name	Methylphenidate Transdermal System
Strengths	10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr
Applicant Name	Mylan Technologies, Inc.
Address	110 Lake Street, St. Albans, VT 05478
Applicant's Point of Contact	Joseph J. Sobecki, Vice President, Regulatory Affairs 781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504-4310
Telephone Number	(304) 599-2595 x 6429
Fax Number	(304) 285-6407
Email Address	Joseph.Sobecki@mylan.com
Original Submission Date	December 13, 2013
Submission Date of Amendment Under Review	N/A
Reviewer	Yoriko Harigaya, Pharm.D.

Dissolution Method	**ADEQUATE**		
OVERALL REVIEW RESULT	**INADEQUATE**		
COMMUNICATION	☐ **ECD** ☐ **IR** ☒ **NOT APPLICABLE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Drug Release**	10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr	**INADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of the drug release testing data only.

Mylan Technologies, Inc. submitted drug release testing data for its Methylphenidate Transdermal System 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr in the original ANDA submission dated December 13, 2013. The reference product is Noven Pharms

Inc.'s Daytrana® (methylphenidate) Extend Release Transdermal Film 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr, under NDA 021514 approved on April 6, 2006[1].

Based on the FDA database, two ANDAs have been submitted for this product (i.e., ANDA206597 and (b) (4) Mylan Technologies, Inc.'s submission, ANDA206497, has been identified as the first generic as per the filing review[2,3].

There is no USP method for this drug product, but there is an FDA-recommended method [900 mL of 0.01 N HCl, USP Apparatus VI (Cylinder) at 50 rpm]. The firm's drug release testing data for all the strengths using the FDA-recommended method is acceptable.

However, the firm's proposed specifications of (b) (4) (b) (4) (b) (4) are not acceptable. Based on the submitted dissolution testing data, the DB recommends the following specifications for the test product: (b) (4) in 0.5 hr; (b) (4) (b) (4) in 1.5 hr; (b) (4) in 4 hr.

The firm should indicate if it accepts the following FDA-recommended dissolution method and specifications.

Medium	0.01 N HCl
Volume	900 mL
Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications	(b) (4) n 0.5 hr in 1.5 hr in 4 hr

The drug release testing is **incomplete**.

II. DISSOLUTION REVIEW

II.1 Submission Content Checklist

Information	YES	NO	N/A

[1] Orange Book
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021514&TABLE1=OB_Rx
accessed on 9/22/2015

[2] DARRTS, ANDA206497, REV-BIOEQ-07(Filing Review) dated on 1/19/2014.

[3] The original application submitted on December 13, 2013 was refused to receive. The division of filing review (DFR) has concluded that the original refuse-to-receive action was erroneously issued because DCR's characterization of the issues with Mylan's ANDA as major deficiencies was based on an evaluation of the sufficiency of the information in the ANDA for *review* purposes, not the sufficiency of such information for *filing* purposes. Thus, the receipt date for this ANDA is restored to the original December 13, 2013, date.

Is there a posted dissolution method on the FDA website?	☒	☐	☐
Did the firm use the above method?	☒	☐	☐
Is there a USP dissolution method?	☐	☒	☐
Did the firm use the USP dissolution method?	☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing?	☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)?	☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method?	☐	☒	☐
Did the firm submit dissolution method validation?	☒	☐	☐

II.2 Dissolution Method As Posted on the FDA Website (if any)

External dissolution database[4]:

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Methylphenidate	Transdermal Patch	VI (Cylinder)	50	0.01 N HCl at 32°C	900	0.5, 1.5, 3, 4 hours and until at least 80% released	04/15/2008

Internal dissolution database[5]:

None

II.3 USP Method (if any)[6]

None

[4] External dissolution database keyword search "methylphenidate" accessed on 9/22/2015 http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm
[5] OGD Internal dissolution reference http://fdswv04385/bio/DissGrid.ASP accessed on 9/22/2015
[6] USP-NF keyword search "methylphenidate" http://www.uspnf.com/uspnf/login accessed on 9/22/2015

II.4 Summary of In Vitro Drug Release Data

In May 2013, the firm conducted drug release tests using the FDA-recommended method with three sampling time ranges (i.e., 0-0.5 hr, 0.5-2 hr, 2-6 hr). In October 2013, the firm re-conducted the drug release tests for all strengths using the FDA-recommended method with six sampling time points as follows:

10 mg/9 hr (1.1 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)		Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/31/13	Methylphenidate Transdermal System Lot R6D0023 April 2012	1.1 mg/hr	12	Mean µg/hr/cm^2	32	56	63	74	80	85	3.2.P.5.4
					RSD%	1.6	1.8	1.4	1.5	1.6	1.7	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 64166 January 2014	1.1 mg/hr	12	Mean µg/hr/cm^2	31	55	63	75	82	91	
					RSD%	1.3	1.0	0.9	1.0	1.1	1.4	
					Range µg/hr/cm^2	(b) (4)						

15 mg/9 hr (1.6 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/29/13 – 10/30/13	Methylphenidate Transdermal System Lot R6D0035 November 2012	1.6 mg/hr	12	Mean µg/hr/cm^2	35	61	69	80	86	91	3.2.P.5.4
					RSD%	1.1	0.7	0.9	0.7	0.8	0.9	
					Range µg/hr/cm^2	[redacted] (b) (4)						
N/A	10/28/13	Daytrana® Lot 65474 February 2014	1.6 mg/hr	12	Mean µg/hr/cm^2	30	54	62	73	80	89	
					RSD%	1.6	1.2	1.0	1.7	1.1	1.5	
					Range µg/hr/cm^2	[redacted] (b) (4)						

20 mg/9 hr (2.2 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	(b) (4)	
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/30/13	Methylphenidate Transdermal System Lot R6D0036 November 2012	2.2 mg/hr	12	Mean µg/hr/cm^2	37	64	72	83	90	96	3.2.P.5.4
					RSD%	1.1	0.8	0.5	0.6	1.0	0.9	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/29/13	Daytrana® Lot 64925 January 2014	2.2 mg/hr	12	Mean µg/hr/cm^2	30	52	60	71	78	87	
					RSD%	1.7	1.0	0.6	1.0	0.7	0.7	
					Range µg/hr/cm^2	(b) (4)						

30 mg/9 hr (3.3 mg/hr)

Dissolution Conditions	**Apparatus:**	Apparatus VI - Cylinder
	Speed of Rotation:	50 rpm
	Medium:	0.01N Hydrochloric Acid
	Volume:	900 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)		Mylan Technologies, Inc. 110 Lake Street, St. Albans, Vermont 05478

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0.5 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	Study Report Location
N/A	10/31/13	Methylphenidate Transdermal System Lot R6D0014 March 2012	3.3 mg/hr	12	Mean µg/hr/cm^2	34	59	67	78	84	90	3.2.P.5.4
					RSD%	0.8	0.9	0.8	0.8	0.7	0.7	
					Range µg/hr/cm^2	(b) (4)						
N/A	10/28/13	Daytrana® Lot 66085 March 2014	3.3 mg/hr	12	Mean µg/hr/cm^2	31	54	62	74	82	89	
					RSD%	1.7	0.8	0.9	0.8	0.8	0.6	
					Range µg/hr/cm^2	(b) (4)						

Reviewer's Note: The test lot of the bio-strength (3.3 mg/hr: 30 mg/9 hr) used in the drug release testing is the same as that used in the PK bioequivalence study. The expiration date of the reference lot (#58415) used in the PK bioequivalence study was 2/2013. Thus, the new reference lot (#66085) was used for the drug release testing conducted in 10/2013.

Lot Numbers Used in the Drug Release Testing

Strength	Test (Manufacture Date)	Reference (Expiration Date)
10 mg/9 hr	R6D0023 (April 2012)	64166 (January 2014)
15 mg/9 hr	R6D0035 (November 2012)	65474 (February 2014)
20 mg/9 hr	R6D0036 (November 2012)	64925 (January 2014)
30 mg/9 hr	R6D0014 (March 2012)	66085 (March 2014)

III. Reviewer's Comments for Drug Release Testing

1. There is no USP method for Methylphenidate Transdermal System 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr, but there is an FDA-recommended method as follows:

Medium	0.01 N HCl
Volume	900 mL
USP Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C

   The *in vitro* drug release testing using the FDA-recommended method conducted by Mylan Technologies, Inc., on its test product, Methylphenidate Transdermal System, 10 mg/9 hr (Lot # R6D0023), 15 mg/9 hr (Lot # R6D0035), 20 mg/9 hr (Lot # R6D0036) and 30 mg/9 hr (Lot # R6D0014), comparing it to Noven Pharms Inc.'s Daytrana® (methylphenidate) ER Transdermal Film, 10 mg/9 hr (Lot # 64166), 15 mg/9 hr (Lot # 65474), 20 mg/9 hr (Lot # 64925) and 30 mg/9 hr (Lot # 66085) is acceptable.

2. The firm's proposed specifications are based on the rate of drug release as follows:
   (b) (4)

   However, the FDA recommends the specification to be based on percent of labeled content and expressed in ranges in line with the USP General Chapter <724> (Transdermal Delivery Systems) Drug Release - General Drug Release Standards for Apparatus 6 and its Acceptance Table.

3. Per the submitted drug release testing data using the FDA-recommended method, the DB recommends the following specifications:
   (b) (4) in 0.5 hr
   in 1.5 hr
   in 4 hr

   The firm's drug release testing for 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr met the DB proposed specifications at the L1 level.

4. The firm has submitted the all raw data and the method validation report (#STM-0819) for the FDA recommended method for measurement of methylphenidate in the drug release test.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 206497

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr

The Division of Bioequivalence (DB) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

The dissolution testing on your test product, Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr using the FDA-recommended dissolution method is incomplete. Your proposed specifications of (b) (4) are not acceptable. Based on the data submitted, the DB recommends following method and specifications:

Medium	0.01 N HCl
Volume	900 mL
Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications*	(b) (4) in 0.5 hr in 1.5 hr in 4 hr

*percent of labeled content

With your response, please indicate if you accept the above FDA recommended method and specifications.

For your future applications, please provide specifications in percent of labeled content expressed in ranges per the USP General Chapter <724> Transdermal Delivery Systems – General Drug Release Standards, and its Acceptance Table.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director,
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

STATISTICAL REVIEWS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM TO REVIEW COMPLETED IN JAN 2016

ANDA/Serial Number:	206497 Amendment-15
Drug Name:	Methylphenidate Transdermal System 10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
Reference Listed Drug:	Daytrana Transdermal System, 3.3 mg/hr
Applicant:	Mylan Pharmaceuticals Inc
Date(s):	Submitted on 7/27/2017
Biometrics Division:	DBVIII
Statistical Reviewer:	Wanjie Sun, Ph.D.
Concurring Reviewers:	Yu-te Wu, Ph.D.
Medical Division:	Division of Clinical Review in OGD/OPS/CDER
Clinical Team:	Sunny Tse, Ph.D. Ying Fan, Ph.D.
Keywords:	Sensitization

1 EXECUTIVE SUMMARY

In the Agency's Complete Response Letter dated July 27, 2016, it stated, "The sensitization data in Study MPTP 12130 is not adequate to ensure that the sensitization potential of the proposed generic methylphenidate transdermal system (TEST) is no worse than that of the refence listed drug product (RLD) as follows.

We do not agree with your number of subjects sensitized or potentially sensitized to each product. When we applied the four criteria described in the FDA product-specific bioequivalence guidance to your data, of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the RLD, respectively, with 100% more test sites than reference sites showing potential sensitization.

We note that you interpreted the term generally higher in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we reevaluated your data using your interpretation. Using your interpretation of generally higher, 33 test versus 27 RLD skin sites show potential sensitization. The proportions are 50% for test versus 40.9% for RLD, with 22% more test sites than RLD sites showing sensitization…"

Mylan responded on July 17, 2017, "Mylan strongly believe that study MPTP12130, provided in the original filing, demonstrates non-inferiority of the Mylan product regarding potential sensitization compared with the RLD…. The rationale for why Mylan believes that its methylphenidate transdermal system is no more sensitizing than the RLD relates to OGD's interpretation of "criteria c", provided by OGD on Sep 9, 2016, in response to Mylan's post-Complete Response teleconference meeting request (Sequence No. 0012) …. Since it is understood that sensitization can develop in much less time than 21 days, for example 7-10 days…..we evaluated the data by interpreting 'criteria c' on the basis comparing maximum irritation scores form Challenge and Re-Challenge Phases to the maximum irritation score observed during Induction, up to Day 7 (first 3 time points of Induction)…Based on this analysis, it may be inferred that the Mylan product is non-inferior to the RLD with respect to conclusions of sensitization across these subjects regardless of the difference in maximum scores considered…."

The purpose of this review is to provide a list of individual sensitization data for potentially sensitized subjects as per the request of DCR and to conduct sensitivity analyses for sensitization of MPTP12130 in response to Mylan's response.

Conclusions and Recommendations

Sensitization

MPTP 12130:

It is up to the clinical reviewers to determine whether Mylan's proposal of using the first 7 days of Induction Phase for comparison of sensitization with the Challenge (and Re-Challenge) phase is acceptable. Regarding 'criteria c', for this particular study, we agree that it put the TEST product in a disadvantageous position for sensitization evaluation due to its improved irritation performance during the Induction Phase.

Sensitivity analysis is conducted by excluding 'Criteria c' from the definition of Potential Sensitization such that we can evaluate the impact of 'Criteria c' on the conclusion of the sensitivity analysis for this study. After excluding 'Criteria c' from the definition of Potential Sensitization, TEST has 53% of potential sensitization, which is less (in point estimate) than that of RLD (56.1%).

2 STATISTICAL EVALUATION OF SENSITIZATION STUDY MPTP-12130

2.1 FDA's Complete Response (CR) Letter

In the Agency's Complete Response Letter dated July 27, 2016, it stated, "The sensitization data in Study MPTP 12130 is not adequate to ensure that the sensitization potential of the proposed generic methylphenidate transdermal system (TEST) is no worse than that of the refence listed drug product (RLD) as follows.

We do not agree with your number of subjects sensitized or potentially sensitized to each product. When we applied the four criteria described in the FDA product-specific bioequivalence guidance to your data, of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the RLD, respectively, with 100% more test sites than reference sites showing potential sensitization.

We note that you interpreted the term generally higher in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we reevaluated your data using your interpretation. Using your interpretation of generally higher, 33 test versus 27 RLD skin sites show potential sensitization. The proportions are 50% for test versus 40.9% for RLD, with 22% more test sites than RLD sites showing sensitization…"

2.2 Mylan's Response to CR

Mylan responded on July 17, 2017, "Mylan strongly believe that study MPTP12130, provided in the original filing, demonstrates non-inferiority of the Mylan product regarding potential sensitization compared with the RLD…. The rationale for why Mylan believes that its methylphenidate transdermal system is no more sensitizing than the RLD relates to OGD's interpretation of "criteria c", provided by OGD on Sep 9, 2016, in response to Mylan's post-Complete Response teleconference meeting request (Sequence No. 0012) …. Since it is understood that sensitization can develop in much less time than 21 days, for example 7-10 days…..we evaluated the data by interpreting 'criteria c' on the basis comparing maximum irritation scores form Challenge and Re-Challenge Phases to the maximum irritation score observed during Induction, up to Day 7 (first 3 time points of Induction)…Based on this analysis, it may be inferred that the Mylan product is non-inferior to the RLD with respect to conclusions of sensitization across these subjects regardless of the difference in maximum scores considered…."

2.3 FDA's Review

2.3.1 Individual Sensitization Data

As per the request of DCR, we provided a list of potentially sensitized subjects with their individual irritation scores during the Induction Phase, Challenge Phase, and Re-Challenge Phase. The list is attached in the Appendix.

2.3.2 Sensitivity Analysis for Sensitization

It is up to the clinical reviewers to determine whether Mylan's proposal is reasonable. For this particular study, the 'criteria c' is possibly biased against the TEST product to pass sensitization due to its improved irritation performance compared to the RLD product during the Induction Phase.

2.3.2.1 FDA's definition of Potential Sensitization

A subject should be considered potentially sensitized if all the following criteria are met:

a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the challenge phase TDS.
b. The subject has a combined "dermal response" and "other effects" numeric score of at least 2 at their last evaluation during the challenge phase.
c. The combined "dermal response" and "other effects" numeric scores obtained during the challenge phase evaluations are generally higher than the combined "dermal response" and "other effects" numeric scores obtained during the induction phase.
d. The above three criteria were met during both the challenge phase and the re-challenge phase, if the subject completed a re-challenge phase.

2.3.2.2 Irritation of MPTP-12130

Mylans' TEST product passed the NI test for irritation. The TEST mean irritation is 1.99, which is improved over the RLD product: RLD mean irritation = 2.45. The 95% upper confidence bound of $\mu_T - 1.25\mu_R = -0.96 < 0$. Therefore, NI is established for irritation.

Table 1. A206497 Study MPTP-12130 Irritation NI Test

Test Mean Irritation Score (std. error)	**RLD Mean Irritation Score (std. error)**	**95% UB of $\mu_T - 1.25\mu_R$**	**Pass or Fail NI**
1.99 (0.12)	2.45 (0.12)	-0.96 (<0)	Pass NI

2.3.2.3 Sensitization of MPTP-12130

However, the improvement of irritation of TEST over RLD put the TEST product in a disadvantageous position when evaluating sensitization according to 'Criteria c'. Since TEST has lower irritation scores on average than RLD in the Induction Phase, the baseline level is not balanced between the two treatment groups. It is easier for TEST to have higher irritation scores in the Challenge Phase than in the Induction Phase compared to RLD, therefore, making it easier for TEST to be potentially sensitized.

Sensitivity analysis is conducted by excluding 'Criteria c' from the definition of Potential Sensitization such that we can evaluate the impact of 'Criteria c' on the conclusion of the sensitivity analysis for this

particular study. In Table 2, the left side is sensitivity analysis with all of the criteria a, b, c and d. For 'Criteria c', 'generally higher' is interpreted as comparing the maximum score between the Induction and the Challenge (Re-Challenge) Phase. As previously discussed, TEST (27.3%) has 2 folds of potential sensitization rate compared to RLD (13.6%). After excluding 'Criteria c' from the definition of Potential Sensitization, TEST has 53% of potential sensitization, which is less (in point estimate) than that of RLD (56.1%).

Table 2. Frequency of Final Potential Sensitization Combining Challenge and Re-Challenge Phases
A206497 Study MPTP-12130
With and Without Criteria C

FDA's Potential Sensitization With Criteria C (Compare Maximum Score)				**FDA's Potential Sensitization W/O Criteria C**			
Overall	**Potential Sensitization**			**Overall**	**Potential Sensitization**		
Treatment	**No**	**Yes**	**Total**	**Treatment**	**No**	**Yes**	**Total**
TEST	48 (72.7%)	18 (27.3%)	66 (100%)	**TEST**	31 (47.0%)	35 (53.0%)	66 (100%)
RLD	57 (86.4%)	9 (13.6%)	66 (100%)	**RLD**	29 (43.9%)	37 (56.1%)	66 (100%)
Total	105	27	132	**Total**	60	72	132

Appendix

List 1. Discrepant Potential Sensitization between Mylan and FDA
If Comparing Maximum Score between Induction and Challenge/Re-challenge Phase

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
1	(b) (6)	A	Induction	2	0	.	0	0	.	.				
2		A	Induction	3	1	.	1	1	.	.				
3		A	Induction	4	1	.	1	1	.	.				
4		A	Induction	5	1	.	1	1	.	.				
5		A	Induction	6	1	.	1	1	.	.				
6		A	Induction	7	1	.	1	1	.	.				
7		A	Induction	8	2	.	2	2	.	.				
8		A	Induction	9	4	.	4	4	.	.				
9		A	Induction	10	2	1	4	4	.	.				
10		A	Challenge	12	.	.	.	4	2	2	Yes	No	No	
11		A	Challenge	13	.	.	.	4	2	2	Yes	No	No	
12		A	Challenge	14	.	.	.	4	2	2	Yes	No	No	
13		A	Challenge	15	.	.	.	4	2	2	Yes	No	No	
14		B	Induction	2	1	.	1	1	.	.				
15		B	Induction	3	1	.	1	1	.	.				
16		B	Induction	4	1	.	1	1	.	.				
17		B	Induction	5	1	.	1	1	.	.				
18		B	Induction	6	2	.	2	2	.	.				
19		B	Induction	7	1	.	1	2	.	.				
20		B	Induction	8	2	.	2	2	.	.				
21		B	Induction	9	6	.	6	6	.	.				
22		B	Induction	10	4	1	6	6	.	.				
23		B	Challenge	12	.	.	.	6	2	2	Yes	No	No	
24		B	Challenge	13	.	.	.	6	2	2	Yes	No	No	

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
25	(b) (6)	B	Challenge	14	.	.	.	6	2	2	Yes	No	No	
26		B	Challenge	15	.	.	.	6	2	2	Yes	No	No	
27		A	Induction	2	2	.	2	2	.	.				
28		A	Induction	3	1	.	1	2	.	.				
29		A	Induction	4	1	.	1	2	.	.				
30		A	Induction	5	1	.	1	2	.	.				
31		A	Induction	6	1	.	1	2	.	.				
32		A	Induction	7	1	.	1	2	.	.				
33		A	Induction	8	1	.	1	2	.	.				
34		A	Induction	9	2	.	2	2	.	.				
35		A	Induction	10	2	.	2	2	.	.				
36		A	Challenge	12	.	.	.	2	4	4	No	Yes	Yes	Yes
37		A	Challenge	13	.	.	.	2	2	4	No	Yes	Yes	Yes
38		A	Challenge	14	.	.	.	2	2	4	No	Yes	Yes	Yes
39		A	Challenge	15	.	.	.	2	2	4	No	Yes	Yes	Yes
40		A	Re-Challenge	17	.	.	.	2	4	4	No	Yes	Yes	Yes
41		A	Re-Challenge	18	.	.	.	2	4	4	No	Yes	Yes	Yes
42		A	Re-Challenge	19	.	.	.	2	2	4	No	Yes	Yes	Yes
43		A	Re-Challenge	20	.	.	.	2	2	4	No	Yes	Yes	Yes
44		A	Induction	2	1	.	1	1	.	.				
45		A	Induction	3	1	.	1	1	.	.				
46		A	Induction	4	1	.	1	1	.	.				
47		A	Induction	5	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
48	(b) (6)	A	Induction	6	1	.	1	1	.	.				
49		A	Induction	7	1	.	1	1	.	.				
50		A	Induction	8	2	.	2	2	.	.				
51		A	Induction	9	2	.	2	2	.	.				
52		A	Induction	10	2	.	2	2	.	.				
53		A	Challenge	12	.	.	.	2	4	4	No	Yes	Yes	Yes
54		A	Challenge	13	.	.	.	2	4	4	No	Yes	Yes	Yes
55		A	Challenge	14	.	.	.	2	2	4	No	Yes	Yes	Yes
56		A	Challenge	15	.	.	.	2	2	4	No	Yes	Yes	Yes
57		A	Re-Challenge	17	.	.	.	2	4	4	No	Yes	Yes	Yes
58		A	Re-Challenge	18	.	.	.	2	4	4	No	Yes	Yes	Yes
59		A	Re-Challenge	19	.	.	.	2	4	4	No	Yes	Yes	Yes
60		A	Re-Challenge	20	.	.	.	2	2	4	No	Yes	Yes	Yes
61		A	Induction	2	1	.	1	1	.	.				
62		A	Induction	3	1	.	1	1	.	.				
63		A	Induction	4	1	.	1	1	.	.				
64		A	Induction	5	1	.	1	1	.	.				
65		A	Induction	6	1	.	1	1	.	.				
66		A	Induction	7	2	.	2	2	.	.				
67		A	Induction	8	2	.	2	2	.	.				
68		A	Induction	9	2	.	2	2	.	.				
69		A	Induction	10	2	.	2	2	.	.				
70		A	Challenge	12	.	.	.	2	4	4	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
71	(b) (6)	A	Challenge	13	.	.	.	2	2	4	No	Yes	Yes	Yes
72		A	Challenge	14	.	.	.	2	2	4	No	Yes	Yes	Yes
73		A	Challenge	15	.	.	.	2	2	4	No	Yes	Yes	Yes
74		A	Re-Challenge	17	.	.	.	2	4	4	No	Yes	Yes	Yes
75		A	Re-Challenge	18	.	.	.	2	4	4	No	Yes	Yes	Yes
76		A	Re-Challenge	19	.	.	.	2	4	4	No	Yes	Yes	Yes
77		A	Re-Challenge	20	.	.	.	2	2	4	No	Yes	Yes	Yes
78		A	Induction	2	1	.	1	1	.	.				
79		A	Induction	3	1	.	1	1	.	.				
80		A	Induction	4	1	.	1	1	.	.				
81		A	Induction	5	1	.	1	1	.	.				
82		A	Induction	6	1	.	1	1	.	.				
83		A	Induction	7	2	.	2	2	.	.				
84		A	Induction	8	2	.	2	2	.	.				
85		A	Induction	9	2	.	2	2	.	.				
86		A	Induction	10	2	.	2	2	.	.				
87		A	Challenge	12	.	.	.	2	2	2	Yes	No	No	
88		A	Challenge	13	.	.	.	2	2	2	Yes	No	No	
89		A	Challenge	14	.	.	.	2	2	2	Yes	No	No	
90		A	Challenge	15	.	.	.	2	2	2	Yes	No	No	
91		B	Induction	2	0	.	0	0	.	.				
92		B	Induction	3	1	.	1	1	.	.				
93		B	Induction	4	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
94	(b) (6)	B	Induction	5	1	.	1	1	.	.				
95		B	Induction	6	2	.	2	2	.	.				
96		B	Induction	7	2	.	2	2	.	.				
97		B	Induction	8	4	.	4	4	.	.				
98		B	Induction	9	4	1	4	4	.	.				
99		B	Induction	10	4	2	4	4	.	.				
100		B	Challenge	12	.	.	.	4	2	2	Yes	No	No	
101		B	Challenge	13	.	.	.	4	2	2	Yes	No	No	
102		B	Challenge	14	.	.	.	4	2	2	Yes	No	No	
103		B	Challenge	15	.	.	.	4	2	2	Yes	No	No	
104		A	Induction	2	0	.	0	0	.	.				
105		A	Induction	3	1	.	1	1	.	.				
106		A	Induction	4	1	.	1	1	.	.				
107		A	Induction	5	1	.	1	1	.	.				
108		A	Induction	6	1	.	1	1	.	.				
109		A	Induction	7	2	.	2	2	.	.				
110		A	Induction	8	2	.	2	2	.	.				
111		A	Induction	9	2	.	2	2	.	.				
112		A	Induction	10	2	.	2	2	.	.				
113		A	Challenge	12	.	.	.	2	4	4	No	Yes	Yes	Yes
114		A	Challenge	13	.	.	.	2	4	4	No	Yes	Yes	Yes
115		A	Challenge	14	.	.	.	2	2	4	No	Yes	Yes	Yes
116		A	Challenge	15	.	.	.	2	2	4	No	Yes	Yes	Yes
117		A	Re-Challenge	17	.	.	.	2	4	4	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
118	(b) (6)	A	Re-Challenge	18	.	.	.	2	4	4	No	Yes	Yes	Yes
119		A	Re-Challenge	19	.	.	.	2	2	4	No	Yes	Yes	Yes
120		A	Re-Challenge	20	.	.	.	2	2	4	No	Yes	Yes	Yes
121		B	Induction	2	1	.	1	1	.	.				
122		B	Induction	3	1	.	1	1	.	.				
123		B	Induction	4	1	.	1	1	.	.				
124		B	Induction	5	2	.	2	2	.	.				
125		B	Induction	6	2	.	2	2	.	.				
126		B	Induction	7	2	.	2	2	.	.				
127		B	Induction	8	6	.	6	6	.	.				
128		B	Induction	9	4	2	6	6	.	.				
129		B	Induction	10	4	7	7	7	.	.				
130		B	Challenge	12	.	.	.	7	4	4	Yes	No	No	No
131		B	Challenge	13	.	.	.	7	4	4	Yes	No	No	No
132		B	Challenge	14	.	.	.	7	2	4	Yes	No	No	No
133		B	Challenge	15	.	.	.	7	2	4	Yes	No	No	No
134		B	Re-Challenge	17	.	.	.	7	7	7	Yes	No	No	No
135		B	Re-Challenge	18	.	.	.	7	7	7	Yes	No	No	No
136		B	Re-Challenge	19	.	.	.	7	4	7	Yes	No	No	No
137		B	Re-Challenge	20	.	.	.	7	2	7	Yes	No	No	No
138		A	Induction	2	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
139	(b) (6)	A	Induction	3	1	.	1	1	.	.				
140		A	Induction	4	1	.	1	1	.	.				
141		A	Induction	5	1	.	1	1	.	.				
142		A	Induction	6	1	.	1	1	.	.				
143		A	Induction	7	4	.	4	4	.	.				
144		A	Induction	8	4	1	4	4	.	.				
145		A	Induction	9	4	4	4	4	.	.				
146		A	Induction	10	4	4	4	4	.	.				
147		A	Challenge	12	.	.	.	4	4	4	Yes	No	No	Yes
148		A	Challenge	13	.	.	.	4	4	4	Yes	No	No	Yes
149		A	Challenge	14	.	.	.	4	4	4	Yes	No	No	Yes
150		A	Challenge	15	.	.	.	4	2	4	Yes	No	No	Yes
151		A	Re-Challenge	17	.	.	.	4	7	7	Yes	No	No	Yes
152		A	Re-Challenge	18	.	.	.	4	4	7	Yes	No	No	Yes
153		A	Re-Challenge	19	.	.	.	4	7	7	Yes	No	No	Yes
154		A	Re-Challenge	20	.	.	.	4	5	7	Yes	No	No	Yes
155		B	Induction	2	1	.	1	1	.	.				
156		B	Induction	3	1	.	1	1	.	.				
157		B	Induction	4	2	.	2	2	.	.				
158		B	Induction	5	1	.	1	2	.	.				
159		B	Induction	6	2	.	2	2	.	.				
160		B	Induction	7	6	.	6	6	.	.				
161		B	Induction	8	4	1	6	6	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
162	(b) (6)	B	Induction	9	4	4	6	6	.	.				
163		B	Induction	10	4	4	6	6	.	.				
164		B	Challenge	12	.	.	.	6	4	4	Yes	No	No	Yes
165		B	Challenge	13	.	.	.	6	4	4	Yes	No	No	Yes
166		B	Challenge	14	.	.	.	6	4	4	Yes	No	No	Yes
167		B	Challenge	15	.	.	.	6	2	4	Yes	No	No	Yes
168		B	Re-Challenge	17	.	.	.	6	7	7	Yes	No	No	Yes
169		B	Re-Challenge	18	.	.	.	6	4	7	Yes	No	No	Yes
170		B	Re-Challenge	19	.	.	.	6	5	7	Yes	No	No	Yes
171		B	Re-Challenge	20	.	.	.	6	5	7	Yes	No	No	Yes
172		B	Induction	2	1	.	1	1	.	.				
173		B	Induction	3	1	.	1	1	.	.				
174		B	Induction	4	1	.	1	1	.	.				
175		B	Induction	5	1	.	1	1	.	.				
176		B	Induction	6	2	.	2	2	.	.				
177		B	Induction	7	2	.	2	2	.	.				
178		B	Induction	8	5	.	5	5	.	.				
179		B	Induction	9	4	2	5	5	.	.				
180		B	Induction	10	4	2	5	5	.	.				
181		B	Challenge	12	.	.	.	5	4	4	Yes	No	No	No
182		B	Challenge	13	.	.	.	5	4	4	Yes	No	No	No
183		B	Challenge	14	.	.	.	5	4	4	Yes	No	No	No
184		B	Challenge	15	.	.	.	5	2	4	Yes	No	No	No

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
185	(b) (6)	B	Re-Challenge	17	.	.	.	5	4	4	Yes	No	No	No
186		B	Re-Challenge	18	.	.	.	5	4	4	Yes	No	No	No
187		B	Re-Challenge	19	.	.	.	5	4	4	Yes	No	No	No
188		B	Re-Challenge	20	.	.	.	5	2	4	Yes	No	No	No
189		B	Induction	2	1	.	1	1	.	.				
190		B	Induction	3	1	.	1	1	.	.				
191		B	Induction	4	1	.	1	1	.	.				
192		B	Induction	5	2	.	2	2	.	.				
193		B	Induction	6	2	.	2	2	.	.				
194		B	Induction	7	2	.	2	2	.	.				
195		B	Induction	8	5	.	5	5	.	.				
196		B	Induction	9	4	2	5	5	.	.				
197		B	Induction	10	4	2	5	5	.	.				
198		B	Challenge	12	.	.	.	5	0	0	Yes	No	No	Yes
199		B	Challenge	13	.	.	.	5	4	4	Yes	No	No	Yes
200		B	Challenge	14	.	.	.	5	4	4	Yes	No	No	Yes
201		B	Challenge	15	.	.	.	5	2	4	Yes	No	No	Yes
202		B	Re-Challenge	17	.	.	.	5	7	7	Yes	No	No	Yes
203		B	Re-Challenge	18	.	.	.	5	5	7	Yes	No	No	Yes
204		B	Re-Challenge	19	.	.	.	5	4	7	Yes	No	No	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
205	(b) (6)	B	Re-Challenge	20	.	.	.	5	3	7	Yes	No	No	Yes
206		B	Induction	2	1	.	1	1	.	.				
207		B	Induction	3	1	.	1	1	.	.				
208		B	Induction	4	1	.	1	1	.	.				
209		B	Induction	5	1	.	1	1	.	.				
210		B	Induction	6	1	.	1	1	.	.				
211		B	Induction	7	2	.	2	2	.	.				
212		B	Induction	8	2	.	2	2	.	.				
213		B	Induction	9	2	.	2	2	.	.				
214		B	Induction	10	4	.	4	4	.	.				
215		B	Challenge	12	.	.	.	4	2	2	Yes	No	No	
216		B	Challenge	13	.	.	.	4	4	4	Yes	No	No	
217		B	Challenge	14	.	.	.	4	4	4	Yes	No	No	
218		B	Challenge	15	.	.	.	4	4	4	Yes	No	No	
219		B	Induction	2	1	.	1	1	.	.				
220		B	Induction	3	1	.	1	1	.	.				
221		B	Induction	4	1	.	1	1	.	.				
222		B	Induction	5	2	.	2	2	.	.				
223		B	Induction	6	2	.	2	2	.	.				
224		B	Induction	7	2	.	2	2	.	.				
225		B	Induction	8	5	.	5	5	.	.				
226		B	Induction	9	4	2	5	5	.	.				
227		B	Induction	10	4	2	5	5	.	.				
228		B	Challenge	12	.	.	.	5	2	2	Yes	No	No	No

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
229	(b) (6)	B	Challenge	13	.	.	.	5	4	4	Yes	No	No	No
230		B	Challenge	14	.	.	.	5	4	4	Yes	No	No	No
231		B	Challenge	15	.	.	.	5	4	4	Yes	No	No	No
232		B	Re-Challenge	17	.	.	.	5	4	4	Yes	No	No	No
233		B	Re-Challenge	18	.	.	.	5	4	4	Yes	No	No	No
234		B	Re-Challenge	19	.	.	.	5	4	4	Yes	No	No	No
235		B	Re-Challenge	20	.	.	.	5	2	4	Yes	No	No	No
236		B	Induction	2	1	.	1	1	.	.				
237		B	Induction	3	2	.	2	2	.	.				
238		B	Induction	4	1	.	1	2	.	.				
239		B	Induction	5	1	.	1	2	.	.				
240		B	Induction	6	2	.	2	2	.	.				
241		B	Induction	7	2	.	2	2	.	.				
242		B	Induction	8	5	.	5	5	.	.				
243		B	Induction	9	4	2	5	5	.	.				
244		B	Induction	10	2	4	5	5	.	.				
245		B	Challenge	12	.	.	.	5	4	4	Yes	No	No	
246		B	Challenge	13	.	.	.	5	4	4	Yes	No	No	
247		B	Challenge	14	.	.	.	5	4	4	Yes	No	No	
248		B	Challenge	15	.	.	.	5	4	4	Yes	No	No	
249		B	Induction	2	1	.	1	1	.	.				
250		B	Induction	3	2	.	2	2	.	.				
251		B	Induction	4	1	.	1	2	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
252	(b) (6)	B	Induction	5	2	.	2	2	.	.				
253		B	Induction	6	2	.	2	2	.	.				
254		B	Induction	7	1	.	1	2	.	.				
255		B	Induction	8	2	.	2	2	.	.				
256		B	Induction	9	2	.	2	2	.	.				
257		B	Induction	10	2	.	2	2	.	.				
258		B	Challenge	12	.	.	.	2	2	2	Yes	No	No	
259		B	Challenge	13	.	.	.	2	2	2	Yes	No	No	
260		B	Challenge	14	.	.	.	2	2	2	Yes	No	No	
261		B	Challenge	15	.	.	.	2	2	2	Yes	No	No	

List 2. Discrepant Potential Sensitization between Mylan and FDA
If Comparing Mean Score between Induction and Challenge/Re-challenge Phase

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
1	(b) (6)	B	Induction	2	1	.	1	.	.	.				
2		B	Induction	3	1	.	1	.	.	.				
3		B	Induction	4	1	.	1	.	.	.				
4		B	Induction	5	1	.	1	.	.	.				
5		B	Induction	6	2	.	2	.	.	.				
6		B	Induction	7	1	.	1	.	.	.				
7		B	Induction	8	2	.	2	.	.	.				
8		B	Induction	9	6	.	6	.	.	.				
9		B	Induction	10	4	1	6	2.33333	.	.				
10		B	Challenge	12	.	.	.	2.33333	2	2.00	Yes	No	No	
11		B	Challenge	13	.	.	.	2.33333	2	2.00	Yes	No	No	
12		B	Challenge	14	.	.	.	2.33333	2	2.00	Yes	No	No	
13		B	Challenge	15	.	.	.	2.33333	2	2.00	Yes	No	No	
14		A	Induction	2	1	.	1	.	.	.				
15		A	Induction	3	1	.	1	.	.	.				
16		A	Induction	4	1	.	1	.	.	.				
17		A	Induction	5	1	.	1	.	.	.				
18		A	Induction	6	1	.	1	.	.	.				
19		A	Induction	7	1	.	1	.	.	.				
20		A	Induction	8	1	.	1	.	.	.				
21		A	Induction	9	2	.	2	.	.	.				
22		A	Induction	10	4	.	4	1.44444	.	.				
23		A	Challenge	12	.	.	.	1.44444	4	2.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
	(b) (6)													
24		A	Challenge	13	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
25		A	Challenge	14	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
26		A	Challenge	15	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
27		A	Re-Challenge	17	.	.	.	1.44444	1	2.25	No	Yes	Yes	Yes
28		A	Re-Challenge	18	.	.	.	1.44444	4	2.25	No	Yes	Yes	Yes
29		A	Re-Challenge	19	.	.	.	1.44444	2	2.25	No	Yes	Yes	Yes
30		A	Re-Challenge	20	.	.	.	1.44444	2	2.25	No	Yes	Yes	Yes
31		B	Induction	2	1	.	1	.	.	.				
32		B	Induction	3	1	.	1	.	.	.				
33		B	Induction	4	1	.	1	.	.	.				
34		B	Induction	5	1	.	1	.	.	.				
35		B	Induction	6	2	.	2	.	.	.				
36		B	Induction	7	1	.	1	.	.	.				
37		B	Induction	8	2	.	2	.	.	.				
38		B	Induction	9	2	.	2	.	.	.				
39		B	Induction	10	4	.	4	1.66667	.	.				
40		B	Challenge	12	.	.	.	1.66667	4	2.50	No	Yes	Yes	Yes
41		B	Challenge	13	.	.	.	1.66667	2	2.50	No	Yes	Yes	Yes
42		B	Challenge	14	.	.	.	1.66667	2	2.50	No	Yes	Yes	Yes
43		B	Challenge	15	.	.	.	1.66667	2	2.50	No	Yes	Yes	Yes
44		B	Re-Challenge	17	.	.	.	1.66667	4	3.75	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
45	(b) (6)	B	Re-Challenge	18	.	.	.	1.66667	7	3.75	No	Yes	Yes	Yes
46		B	Re-Challenge	19	.	.	.	1.66667	2	3.75	No	Yes	Yes	Yes
47		B	Re-Challenge	20	.	.	.	1.66667	2	3.75	No	Yes	Yes	Yes
48		A	Induction	2	1	.	1	.	.	.				
49		A	Induction	3	0	.	0	.	.	.				
50		A	Induction	4	1	.	1	.	.	.				
51		A	Induction	5	1	.	1	.	.	.				
52		A	Induction	6	1	.	1	.	.	.				
53		A	Induction	7	1	.	1	.	.	.				
54		A	Induction	8	2	.	2	.	.	.				
55		A	Induction	9	2	.	2	.	.	.				
56		A	Induction	10	2	.	2	1.22222	.	.				
57		A	Challenge	12	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
58		A	Challenge	13	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
59		A	Challenge	14	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
60		A	Challenge	15	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
61		A	Re-Challenge	17	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
62		A	Re-Challenge	18	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
63		A	Re-Challenge	19	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
64		A	Re-Challenge	20	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
65	(b) (6)	B	Induction	2	1	.	1	.	.	.				
66		B	Induction	3	1	.	1	.	.	.				
67		B	Induction	4	1	.	1	.	.	.				
68		B	Induction	5	1	.	1	.	.	.				
69		B	Induction	6	1	.	1	.	.	.				
70		B	Induction	7	1	.	1	.	.	.				
71		B	Induction	8	2	.	2	.	.	.				
72		B	Induction	9	2	.	2	.	.	.				
73		B	Induction	10	2	.	2	1.33333	.	.				
74		B	Challenge	12	.	.	.	1.33333	1	1.75	No	Yes	Yes	Yes
75		B	Challenge	13	.	.	.	1.33333	2	1.75	No	Yes	Yes	Yes
76		B	Challenge	14	.	.	.	1.33333	2	1.75	No	Yes	Yes	Yes
77		B	Challenge	15	.	.	.	1.33333	2	1.75	No	Yes	Yes	Yes
78		B	Re-Challenge	17	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
79		B	Re-Challenge	18	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
80		B	Re-Challenge	19	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
81		B	Re-Challenge	20	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
82		A	Induction	2	1	.	1	.	.	.				
83		A	Induction	3	1	.	1	.	.	.				
84		A	Induction	4	1	.	1	.	.	.				
85		A	Induction	5	1	.	1	.	.	.				
86		A	Induction	6	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
	(b) (6)													
87		A	Induction	7	2	.	2	.	.	.				
88		A	Induction	8	2	.	2	.	.	.				
89		A	Induction	9	5	.	5	.	.	.				
90		A	Induction	10	4	4	5	2.11111	.	.				
91		A	Challenge	12	.	.	.	2.11111	4	3.00	No	Yes	Yes	Yes
92		A	Challenge	13	.	.	.	2.11111	4	3.00	No	Yes	Yes	Yes
93		A	Challenge	14	.	.	.	2.11111	2	3.00	No	Yes	Yes	Yes
94		A	Challenge	15	.	.	.	2.11111	2	3.00	No	Yes	Yes	Yes
95		A	Re-Challenge	17	.	.	.	2.11111	4	4.50	No	Yes	Yes	Yes
96		A	Re-Challenge	18	.	.	.	2.11111	4	4.50	No	Yes	Yes	Yes
97		A	Re-Challenge	19	.	.	.	2.11111	5	4.50	No	Yes	Yes	Yes
98		A	Re-Challenge	20	.	.	.	2.11111	5	4.50	No	Yes	Yes	Yes
99		B	Induction	2	1	.	1	.	.	.				
100		B	Induction	3	1	.	1	.	.	.				
101		B	Induction	4	1	.	1	.	.	.				
102		B	Induction	5	1	.	1	.	.	.				
103		B	Induction	6	1	.	1	.	.	.				
104		B	Induction	7	4	.	4	.	.	.				
105		B	Induction	8	4	1	4	.	.	.				
106		B	Induction	9	4	4	4	.	.	.				
107		B	Induction	10	4	5	7	2.66667	.	.				
108		B	Challenge	12	.	.	.	2.66667	4	4.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
109	(b) (6)	B	Challenge	13	.	.	.	2.66667	6	4.50	No	Yes	Yes	Yes
110		B	Challenge	14	.	.	.	2.66667	4	4.50	No	Yes	Yes	Yes
111		B	Challenge	15	.	.	.	2.66667	4	4.50	No	Yes	Yes	Yes
112		B	Re-Challenge	17	.	.	.	2.66667	4	4.00	No	Yes	Yes	Yes
113		B	Re-Challenge	18	.	.	.	2.66667	4	4.00	No	Yes	Yes	Yes
114		B	Re-Challenge	19	.	.	.	2.66667	2	4.00	No	Yes	Yes	Yes
115		B	Re-Challenge	20	.	.	.	2.66667	6	4.00	No	Yes	Yes	Yes
116		A	Induction	2	1	.	1	.	.	.				
117		A	Induction	3	1	.	1	.	.	.				
118		A	Induction	4	1	.	1	.	.	.				
119		A	Induction	5	1	.	1	.	.	.				
120		A	Induction	6	1	.	1	.	.	.				
121		A	Induction	7	1	.	1	.	.	.				
122		A	Induction	8	2	.	2	.	.	.				
123		A	Induction	9	4	.	4	.	.	.				
124		A	Induction	10	5	4	5	1.88889	.	.				
125		A	Challenge	12	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
126		A	Challenge	13	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
127		A	Challenge	14	.	.	.	1.88889	2	3.50	No	Yes	Yes	Yes
128		A	Challenge	15	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
129		A	Re-Challenge	17	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
130	(b) (6)	A	Re-Challenge	18	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
131		A	Re-Challenge	19	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
132		A	Re-Challenge	20	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
133		A	Induction	2	1	.	1	.	.	.				
134		A	Induction	3	1	.	1	.	.	.				
135		A	Induction	4	1	.	1	.	.	.				
136		A	Induction	5	1	.	1	.	.	.				
137		A	Induction	6	1	.	1	.	.	.				
138		A	Induction	7	4	.	4	.	.	.				
139		A	Induction	8	2	1	4	.	.	.				
140		A	Induction	9	4	4	4	.	.	.				
141		A	Induction	10	2	5	5	2.44444	.	.				
142		A	Challenge	12	.	.	.	2.44444	2	3.00	No	Yes	Yes	Yes
143		A	Challenge	13	.	.	.	2.44444	4	3.00	No	Yes	Yes	Yes
144		A	Challenge	14	.	.	.	2.44444	4	3.00	No	Yes	Yes	Yes
145		A	Challenge	15	.	.	.	2.44444	2	3.00	No	Yes	Yes	Yes
146		A	Re-Challenge	17	.	.	.	2.44444	4	4.50	No	Yes	Yes	Yes
147		A	Re-Challenge	18	.	.	.	2.44444	6	4.50	No	Yes	Yes	Yes
148		A	Re-Challenge	19	.	.	.	2.44444	4	4.50	No	Yes	Yes	Yes
149		A	Re-Challenge	20	.	.	.	2.44444	4	4.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
	(b) (6)													
150		A	Induction	2	2	.	2	.	.	.				
151		A	Induction	3	1	.	1	.	.	.				
152		A	Induction	4	1	.	1	.	.	.				
153		A	Induction	5	1	.	1	.	.	.				
154		A	Induction	6	1	.	1	.	.	.				
155		A	Induction	7	1	.	1	.	.	.				
156		A	Induction	8	1	.	1	.	.	.				
157		A	Induction	9	2	.	2	.	.	.				
158		A	Induction	10	2	.	2	1.33333	.	.				
159		A	Challenge	12	.	.	.	1.33333	4	2.50	No	Yes	Yes	Yes
160		A	Challenge	13	.	.	.	1.33333	2	2.50	No	Yes	Yes	Yes
161		A	Challenge	14	.	.	.	1.33333	2	2.50	No	Yes	Yes	Yes
162		A	Challenge	15	.	.	.	1.33333	2	2.50	No	Yes	Yes	Yes
163		A	Re-Challenge	17	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
164		A	Re-Challenge	18	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
165		A	Re-Challenge	19	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
166		A	Re-Challenge	20	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
167		B	Induction	2	1	.	1	.	.	.				
168		B	Induction	3	1	.	1	.	.	.				
169		B	Induction	4	1	.	1	.	.	.				
170		B	Induction	5	1	.	1	.	.	.				
171		B	Induction	6	2	.	2	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
172	(b) (6)	B	Induction	7	4	.	4	.	.	.				
173		B	Induction	8	4	2	4	.	.	.				
174		B	Induction	9	4	2	4	.	.	.				
175		B	Induction	10	4	5	5	2.55556	.	.				
176		B	Challenge	12	.	.	.	2.55556	4	4.50	No	Yes	Yes	Yes
177		B	Challenge	13	.	.	.	2.55556	4	4.50	No	Yes	Yes	Yes
178		B	Challenge	14	.	.	.	2.55556	6	4.50	No	Yes	Yes	Yes
179		B	Challenge	15	.	.	.	2.55556	4	4.50	No	Yes	Yes	Yes
180		B	Re-Challenge	17	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
181		B	Re-Challenge	18	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
182		B	Re-Challenge	19	.	.	.	2.55556	2	3.50	No	Yes	Yes	Yes
183		B	Re-Challenge	20	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
184		A	Induction	2	1	.	1	.	.	.				
185		A	Induction	3	1	.	1	.	.	.				
186		A	Induction	4	1	.	1	.	.	.				
187		A	Induction	5	1	.	1	.	.	.				
188		A	Induction	6	1	.	1	.	.	.				
189		A	Induction	7	1	.	1	.	.	.				
190		A	Induction	8	2	.	2	.	.	.				
191		A	Induction	9	2	.	2	.	.	.				
192		A	Induction	10	2	.	2	1.33333	.	.				
193		A	Challenge	12	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
194	(b) (6)	A	Challenge	13	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
195		A	Challenge	14	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
196		A	Challenge	15	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
197		A	Re-Challenge	17	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
198		A	Re-Challenge	18	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
199		A	Re-Challenge	19	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
200		A	Re-Challenge	20	.	.	.	1.33333	2	3.50	No	Yes	Yes	Yes
201		B	Induction	2	0	.	0	.	.	.				
202		B	Induction	3	1	.	1	.	.	.				
203		B	Induction	4	1	.	1	.	.	.				
204		B	Induction	5	1	.	1	.	.	.				
205		B	Induction	6	2	.	2	.	.	.				
206		B	Induction	7	2	.	2	.	.	.				
207		B	Induction	8	2	.	2	.	.	.				
208		B	Induction	9	4	.	4	.	.	.				
209		B	Induction	10	4	2	4	1.88889	.	.				
210		B	Challenge	12	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
211		B	Challenge	13	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
212		B	Challenge	14	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
213		B	Challenge	15	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
214		B	Re-Challenge	17	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
215	(b) (6)	B	Re-Challenge	18	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
216		B	Re-Challenge	19	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
217		B	Re-Challenge	20	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
218		A	Induction	2	1	.	1	.	.	.				
219		A	Induction	3	1	.	1	.	.	.				
220		A	Induction	4	1	.	1	.	.	.				
221		A	Induction	5	1	.	1	.	.	.				
222		A	Induction	6	1	.	1	.	.	.				
223		A	Induction	7	2	.	2	.	.	.				
224		A	Induction	8	2	.	2	.	.	.				
225		A	Induction	9	2	.	2	.	.	.				
226		A	Induction	10	2	.	2	1.44444	.	.				
227		A	Challenge	12	.	.	.	1.44444	4	2.50	No	Yes	Yes	Yes
228		A	Challenge	13	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
229		A	Challenge	14	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
230		A	Challenge	15	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
231		A	Re-Challenge	17	.	.	.	1.44444	4	3.50	No	Yes	Yes	Yes
232		A	Re-Challenge	18	.	.	.	1.44444	4	3.50	No	Yes	Yes	Yes
233		A	Re-Challenge	19	.	.	.	1.44444	4	3.50	No	Yes	Yes	Yes
234		A	Re-Challenge	20	.	.	.	1.44444	2	3.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
235	(b) (6)	B	Induction	2	2	.	2	.	.	.				
236		B	Induction	3	1	.	1	.	.	.				
237		B	Induction	4	1	.	1	.	.	.				
238		B	Induction	5	1	.	1	.	.	.				
239		B	Induction	6	2	.	2	.	.	.				
240		B	Induction	7	2	.	2	.	.	.				
241		B	Induction	8	4	.	4	.	.	.				
242		B	Induction	9	4	2	4	.	.	.				
243		B	Induction	10	4	4	4	2.33333	.	.				
244		B	Challenge	12	.	.	.	2.33333	4	2.50	No	Yes	Yes	Yes
245		B	Challenge	13	.	.	.	2.33333	2	2.50	No	Yes	Yes	Yes
246		B	Challenge	14	.	.	.	2.33333	2	2.50	No	Yes	Yes	Yes
247		B	Challenge	15	.	.	.	2.33333	2	2.50	No	Yes	Yes	Yes
248		B	Re-Challenge	17	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
249		B	Re-Challenge	18	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
250		B	Re-Challenge	19	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
251		B	Re-Challenge	20	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
252		A	Induction	2	0	.	0	.	.	.				
253		A	Induction	3	1	.	1	.	.	.				
254		A	Induction	4	1	.	1	.	.	.				
255		A	Induction	5	1	.	1	.	.	.				
256		A	Induction	6	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
257	(b) (6)	A	Induction	7	2	.	2	.	.	.				
258		A	Induction	8	2	.	2	.	.	.				
259		A	Induction	9	2	.	2	.	.	.				
260		A	Induction	10	2	.	2	1.33333	.	.				
261		A	Challenge	12	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
262		A	Challenge	13	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
263		A	Challenge	14	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
264		A	Challenge	15	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
265		A	Re-Challenge	17	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
266		A	Re-Challenge	18	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
267		A	Re-Challenge	19	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
268		A	Re-Challenge	20	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
269		B	Induction	2	0	.	0	.	.	.				
270		B	Induction	3	1	.	1	.	.	.				
271		B	Induction	4	1	.	1	.	.	.				
272		B	Induction	5	1	.	1	.	.	.				
273		B	Induction	6	2	.	2	.	.	.				
274		B	Induction	7	2	.	2	.	.	.				
275		B	Induction	8	4	.	4	.	.	.				
276		B	Induction	9	4	1	4	.	.	.				
277		B	Induction	10	4	2	4	2.11111	.	.				
278		B	Challenge	12	.	.	.	2.11111	2	2.00	Yes	No	No	

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
279	(b) (6)	B	Challenge	13	.	.	.	2.11111	2	2.00	Yes	No	No	
280		B	Challenge	14	.	.	.	2.11111	2	2.00	Yes	No	No	
281		B	Challenge	15	.	.	.	2.11111	2	2.00	Yes	No	No	
282		A	Induction	2	0	.	0	.	.	.				
283		A	Induction	3	1	.	1	.	.	.				
284		A	Induction	4	1	.	1	.	.	.				
285		A	Induction	5	1	.	1	.	.	.				
286		A	Induction	6	1	.	1	.	.	.				
287		A	Induction	7	1	.	1	.	.	.				
288		A	Induction	8	2	.	2	.	.	.				
289		A	Induction	9	2	.	2	.	.	.				
290		A	Induction	10	2	.	2	1.22222	.	.				
291		A	Challenge	12	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
292		A	Challenge	13	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
293		A	Challenge	14	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
294		A	Challenge	15	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
295		A	Re-Challenge	17	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
296		A	Re-Challenge	18	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
297		A	Re-Challenge	19	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
298		A	Re-Challenge	20	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
299		B	Induction	2	0	.	0	.	.	.				
300		B	Induction	3	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
301	(b) (6)	B	Induction	4	1	.	1	.	.	.				
302		B	Induction	5	1	.	1	.	.	.				
303		B	Induction	6	1	.	1	.	.	.				
304		B	Induction	7	1	.	1	.	.	.				
305		B	Induction	8	2	.	2	.	.	.				
306		B	Induction	9	2	.	2	.	.	.				
307		B	Induction	10	2	.	2	1.22222	.	.				
308		B	Challenge	12	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
309		B	Challenge	13	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
310		B	Challenge	14	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
311		B	Challenge	15	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
312		B	Re-Challenge	17	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
313		B	Re-Challenge	18	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
314		B	Re-Challenge	19	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
315		B	Re-Challenge	20	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
316		A	Induction	2	0	.	0	.	.	.				
317		A	Induction	3	0	.	0	.	.	.				
318		A	Induction	4	1	.	1	.	.	.				
319		A	Induction	5	1	.	1	.	.	.				
320		A	Induction	6	1	.	1	.	.	.				
321		A	Induction	7	1	.	1	.	.	.				
322		A	Induction	8	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
323	(b) (6)	A	Induction	9	2	.	2	.	.	.				
324		A	Induction	10	2	.	2	1.00000	.	.				
325		A	Challenge	12	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
326		A	Challenge	13	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
327		A	Challenge	14	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
328		A	Challenge	15	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
329		A	Re-Challenge	17	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
330		A	Re-Challenge	18	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
331		A	Re-Challenge	19	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
332		A	Re-Challenge	20	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
333		B	Induction	2	1	.	1	.	.	.				
334		B	Induction	3	1	.	1	.	.	.				
335		B	Induction	4	2	.	2	.	.	.				
336		B	Induction	5	1	.	1	.	.	.				
337		B	Induction	6	1	.	1	.	.	.				
338		B	Induction	7	2	.	2	.	.	.				
339		B	Induction	8	2	.	2	.	.	.				
340		B	Induction	9	2	.	2	.	.	.				
341		B	Induction	10	4	.	4	1.77778	.	.				
342		B	Challenge	12	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
343		B	Challenge	13	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
344		B	Challenge	14	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
345	(b) (6)	B	Challenge	15	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
346		B	Re-Challenge	17	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
347		B	Re-Challenge	18	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
348		B	Re-Challenge	19	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
349		B	Re-Challenge	20	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
350		B	Induction	2	1	.	1	.	.	.				
351		B	Induction	3	1	.	1	.	.	.				
352		B	Induction	4	1	.	1	.	.	.				
353		B	Induction	5	2	.	2	.	.	.				
354		B	Induction	6	2	.	2	.	.	.				
355		B	Induction	7	2	.	2	.	.	.				
356		B	Induction	8	2	.	2	.	.	.				
357		B	Induction	9	4	.	4	.	.	.				
358		B	Induction	10	4	2	4	2.11111	.	.				
359		B	Challenge	12	.	.	.	2.11111	4	2.50	No	Yes	Yes	Yes
360		B	Challenge	13	.	.	.	2.11111	2	2.50	No	Yes	Yes	Yes
361		B	Challenge	14	.	.	.	2.11111	2	2.50	No	Yes	Yes	Yes
362		B	Challenge	15	.	.	.	2.11111	2	2.50	No	Yes	Yes	Yes
363		B	Re-Challenge	17	.	.	.	2.11111	4	3.00	No	Yes	Yes	Yes
364		B	Re-Challenge	18	.	.	.	2.11111	4	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
365	(b) (6)	B	Re-Challenge	19	.	.	.	2.11111	2	3.00	No	Yes	Yes	Yes
366		B	Re-Challenge	20	.	.	.	2.11111	2	3.00	No	Yes	Yes	Yes
367		A	Induction	2	1	.	1	.	.	.				
368		A	Induction	3	1	.	1	.	.	.				
369		A	Induction	4	1	.	1	.	.	.				
370		A	Induction	5	1	.	1	.	.	.				
371		A	Induction	6	1	.	1	.	.	.				
372		A	Induction	7	1	.	1	.	.	.				
373		A	Induction	8	2	.	2	.	.	.				
374		A	Induction	9	2	.	2	.	.	.				
375		A	Induction	10	2	.	2	1.33333	.	.				
376		A	Challenge	12	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
377		A	Challenge	13	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
378		A	Challenge	14	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
379		A	Challenge	15	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
380		A	Re-Challenge	17	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
381		A	Re-Challenge	18	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
382		A	Re-Challenge	19	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
383		A	Re-Challenge	20	.	.	.	1.33333	2	3.50	No	Yes	Yes	Yes
384		B	Induction	2	1	.	1	.	.	.				
385		B	Induction	3	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
386	(b) (6)	B	Induction	4	1	.	1	.	.	.				
387		B	Induction	5	1	.	1	.	.	.				
388		B	Induction	6	1	.	1	.	.	.				
389		B	Induction	7	2	.	2	.	.	.				
390		B	Induction	8	2	.	2	.	.	.				
391		B	Induction	9	4	.	4	.	.	.				
392		B	Induction	10	4	4	4	1.88889	.	.				
393		B	Challenge	12	.	.	.	1.88889	4	2.50	No	Yes	Yes	Yes
394		B	Challenge	13	.	.	.	1.88889	2	2.50	No	Yes	Yes	Yes
395		B	Challenge	14	.	.	.	1.88889	2	2.50	No	Yes	Yes	Yes
396		B	Challenge	15	.	.	.	1.88889	2	2.50	No	Yes	Yes	Yes
397		B	Re-Challenge	17	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
398		B	Re-Challenge	18	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
399		B	Re-Challenge	19	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
400		B	Re-Challenge	20	.	.	.	1.88889	2	3.50	No	Yes	Yes	Yes
401		A	Induction	2	0	.	0	.	.	.				
402		A	Induction	3	1	.	1	.	.	.				
403		A	Induction	4	1	.	1	.	.	.				
404		A	Induction	5	1	.	1	.	.	.				
405		A	Induction	6	1	.	1	.	.	.				
406		A	Induction	7	2	.	2	.	.	.				
407		A	Induction	8	2	.	2	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
408	(b) (6)	A	Induction	9	2	.	2	.	.	.				
409		A	Induction	10	2	.	2	1.33333	.	.				
410		A	Challenge	12	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
411		A	Challenge	13	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
412		A	Challenge	14	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
413		A	Challenge	15	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
414		A	Re-Challenge	17	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
415		A	Re-Challenge	18	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
416		A	Re-Challenge	19	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
417		A	Re-Challenge	20	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
418		B	Induction	2	1	.	1	.	.	.				
419		B	Induction	3	1	.	1	.	.	.				
420		B	Induction	4	1	.	1	.	.	.				
421		B	Induction	5	2	.	2	.	.	.				
422		B	Induction	6	2	.	2	.	.	.				
423		B	Induction	7	2	.	2	.	.	.				
424		B	Induction	8	4	.	4	.	.	.				
425		B	Induction	9	4	2	4	.	.	.				
426		B	Induction	10	4	4	4	2.33333	.	.				
427		B	Challenge	12	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
428		B	Challenge	13	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
429		B	Challenge	14	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
430	(b) (6)	B	Challenge	15	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
431		B	Re-Challenge	17	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
432		B	Re-Challenge	18	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
433		B	Re-Challenge	19	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
434		B	Re-Challenge	20	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
435		B	Induction	2	1	.	1	.	.	.				
436		B	Induction	3	1	.	1	.	.	.				
437		B	Induction	4	1	.	1	.	.	.				
438		B	Induction	5	2	.	2	.	.	.				
439		B	Induction	6	2	.	2	.	.	.				
440		B	Induction	7	2	.	2	.	.	.				
441		B	Induction	8	6	.	6	.	.	.				
442		B	Induction	9	4	2	6	.	.	.				
443		B	Induction	10	4	7	7	3.11111	.	.				
444		B	Challenge	12	.	.	.	3.11111	4	3.00	Yes	No	No	Yes
445		B	Challenge	13	.	.	.	3.11111	4	3.00	Yes	No	No	Yes
446		B	Challenge	14	.	.	.	3.11111	2	3.00	Yes	No	No	Yes
447		B	Challenge	15	.	.	.	3.11111	2	3.00	Yes	No	No	Yes
448		B	Re-Challenge	17	.	.	.	3.11111	7	5.00	Yes	No	No	Yes
449		B	Re-Challenge	18	.	.	.	3.11111	7	5.00	Yes	No	No	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
450	(b) (6)	B	Re-Challenge	19	.	.	.	3.11111	4	5.00	Yes	No	No	Yes
451		B	Re-Challenge	20	.	.	.	3.11111	2	5.00	Yes	No	No	Yes
452		A	Induction	2	1	.	1	.	.	.				
453		A	Induction	3	1	.	1	.	.	.				
454		A	Induction	4	1	.	1	.	.	.				
455		A	Induction	5	2	.	2	.	.	.				
456		A	Induction	6	1	.	1	.	.	.				
457		A	Induction	7	2	.	2	.	.	.				
458		A	Induction	8	2	.	2	.	.	.				
459		A	Induction	9	2	.	2	.	.	.				
460		A	Induction	10	2	.	2	1.55556	.	.				
461		A	Challenge	12	.	.	.	1.55556	2	2.00	No	Yes	Yes	Yes
462		A	Challenge	13	.	.	.	1.55556	2	2.00	No	Yes	Yes	Yes
463		A	Challenge	14	.	.	.	1.55556	2	2.00	No	Yes	Yes	Yes
464		A	Challenge	15	.	.	.	1.55556	2	2.00	No	Yes	Yes	Yes
465		A	Re-Challenge	17	.	.	.	1.55556	4	3.00	No	Yes	Yes	Yes
466		A	Re-Challenge	18	.	.	.	1.55556	4	3.00	No	Yes	Yes	Yes
467		A	Re-Challenge	19	.	.	.	1.55556	2	3.00	No	Yes	Yes	Yes
468		A	Re-Challenge	20	.	.	.	1.55556	2	3.00	No	Yes	Yes	Yes
469		A	Induction	2	1	.	1	.	.	.				
470		A	Induction	3	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
471	(b) (6)	A	Induction	4	1	.	1	.	.	.				
472		A	Induction	5	1	.	1	.	.	.				
473		A	Induction	6	2	.	2	.	.	.				
474		A	Induction	7	2	.	2	.	.	.				
475		A	Induction	8	2	.	2	.	.	.				
476		A	Induction	9	2	.	2	.	.	.				
477		A	Induction	10	2	.	2	1.55556	.	.				
478		A	Challenge	12	.	.	.	1.55556	2	1.75	No	Yes	Yes	Yes
479		A	Challenge	13	.	.	.	1.55556	1	1.75	No	Yes	Yes	Yes
480		A	Challenge	14	.	.	.	1.55556	2	1.75	No	Yes	Yes	Yes
481		A	Challenge	15	.	.	.	1.55556	2	1.75	No	Yes	Yes	Yes
482		A	Re-Challenge	17	.	.	.	1.55556	4	3.00	No	Yes	Yes	Yes
483		A	Re-Challenge	18	.	.	.	1.55556	4	3.00	No	Yes	Yes	Yes
484		A	Re-Challenge	19	.	.	.	1.55556	2	3.00	No	Yes	Yes	Yes
485		A	Re-Challenge	20	.	.	.	1.55556	2	3.00	No	Yes	Yes	Yes
486		B	Induction	2	1	.	1	.	.	.				
487		B	Induction	3	1	.	1	.	.	.				
488		B	Induction	4	1	.	1	.	.	.				
489		B	Induction	5	2	.	2	.	.	.				
490		B	Induction	6	2	.	2	.	.	.				
491		B	Induction	7	2	.	2	.	.	.				
492		B	Induction	8	5	.	5	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
493	(b) (6)	B	Induction	9	4	2	5	.	.	.				
494		B	Induction	10	4	2	5	2.66667	.	.				
495		B	Challenge	12	.	.	.	2.66667	0	2.50	Yes	No	No	Yes
496		B	Challenge	13	.	.	.	2.66667	4	2.50	Yes	No	No	Yes
497		B	Challenge	14	.	.	.	2.66667	4	2.50	Yes	No	No	Yes
498		B	Challenge	15	.	.	.	2.66667	2	2.50	Yes	No	No	Yes
499		B	Re-Challenge	17	.	.	.	2.66667	7	4.75	Yes	No	No	Yes
500		B	Re-Challenge	18	.	.	.	2.66667	5	4.75	Yes	No	No	Yes
501		B	Re-Challenge	19	.	.	.	2.66667	4	4.75	Yes	No	No	Yes
502		B	Re-Challenge	20	.	.	.	2.66667	3	4.75	Yes	No	No	Yes
503		A	Induction	2	1	.	1	.	.	.				
504		A	Induction	3	1	.	1	.	.	.				
505		A	Induction	4	1	.	1	.	.	.				
506		A	Induction	5	1	.	1	.	.	.				
507		A	Induction	6	2	.	2	.	.	.				
508		A	Induction	7	2	.	2	.	.	.				
509		A	Induction	8	4	.	4	.	.	.				
510		A	Induction	9	2	1	4	.	.	.				
511		A	Induction	10	2	4	4	2.22222	.	.				
512		A	Challenge	12	.	.	.	2.22222	2	3.50	No	Yes	Yes	Yes
513		A	Challenge	13	.	.	.	2.22222	4	3.50	No	Yes	Yes	Yes
514		A	Challenge	14	.	.	.	2.22222	4	3.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
515	(b) (6)	A	Challenge	15	.	.	.	2.22222	4	3.50	No	Yes	Yes	Yes
516		A	Re-Challenge	17	.	.	.	2.22222	4	3.00	No	Yes	Yes	Yes
517		A	Re-Challenge	18	.	.	.	2.22222	4	3.00	No	Yes	Yes	Yes
518		A	Re-Challenge	19	.	.	.	2.22222	2	3.00	No	Yes	Yes	Yes
519		A	Re-Challenge	20	.	.	.	2.22222	2	3.00	No	Yes	Yes	Yes
520		B	Induction	2	1	.	1	.	.	.				
521		B	Induction	3	1	.	1	.	.	.				
522		B	Induction	4	2	.	2	.	.	.				
523		B	Induction	5	1	.	1	.	.	.				
524		B	Induction	6	2	.	2	.	.	.				
525		B	Induction	7	4	.	4	.	.	.				
526		B	Induction	8	2	1	4	.	.	.				
527		B	Induction	9	4	4	4	.	.	.				
528		B	Induction	10	3	2	4	2.55556	.	.				
529		B	Challenge	12	.	.	.	2.55556	2	3.50	No	Yes	Yes	Yes
530		B	Challenge	13	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
531		B	Challenge	14	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
532		B	Challenge	15	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
533		B	Re-Challenge	17	.	.	.	2.55556	4	3.00	No	Yes	Yes	Yes
534		B	Re-Challenge	18	.	.	.	2.55556	4	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
535	(b) (6)	B	Re-Challenge	19	.	.	.	2.55556	2	3.00	No	Yes	Yes	Yes
536		B	Re-Challenge	20	.	.	.	2.55556	2	3.00	No	Yes	Yes	Yes

List 3. Complete List of FDA's Potential Sensitization (TEST N=18 patches, RLD=9 patches) If Comparing Maximum Score between Induction and Challenge/Re-challenge Phase

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
1	(b) (6)	A	Induction	2	1	.	1	1	.	.				
2		A	Induction	3	2	.	2	2	.	.				
3		A	Induction	4	2	.	2	2	.	.				
4		A	Induction	5	2	.	2	2	.	.				
5		A	Induction	6	2	.	2	2	.	.				
6		A	Induction	7	4	.	4	4	.	.				
7		A	Induction	8	4	2	4	4	.	.				
8		A	Induction	9	2	4	4	4	.	.				
9		A	Induction	10	1	4	4	4	.	.				
10		A	Challenge	12	.	.	.	4	7	7	Yes	Yes	Yes	Yes
11		A	Challenge	13	.	.	.	4	4	7	Yes	Yes	Yes	Yes
12		A	Challenge	14	.	.	.	4	2	7	Yes	Yes	Yes	Yes
13		A	Challenge	15	.	.	.	4	4	7	Yes	Yes	Yes	Yes
14		A	Re-Challenge	17	.	.	.	4	7	7	Yes	Yes	Yes	Yes
15		A	Re-Challenge	18	.	.	.	4	7	7	Yes	Yes	Yes	Yes
16		A	Re-Challenge	19	.	.	.	4	10	10	Yes	Yes	Yes	Yes
17		A	Re-Challenge	20	.	.	.	4	7	10	Yes	Yes	Yes	Yes
18		A	Induction	2	0	.	0	0	.	.				
19		A	Induction	3	1	.	1	1	.	.				
20		A	Induction	4	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
21	(b) (6)	A	Induction	5	1	.	1	1	.	.				
22		A	Induction	6	2	.	2	2	.	.				
23		A	Induction	7	2	.	2	2	.	.				
24		A	Induction	8	2	.	2	2	.	.				
25		A	Induction	9	2	.	2	2	.	.				
26		A	Induction	10	2	.	2	2	.	.				
27		A	Challenge	12	.	.	.	2	7	7	Yes	Yes	Yes	
28		A	Challenge	13	.	.	.	2	4	7	Yes	Yes	Yes	
29		A	Challenge	14	.	.	.	2	2	7	Yes	Yes	Yes	
30		A	Challenge	15	.	.	.	2	2	7	Yes	Yes	Yes	
31		A	Induction	2	1	.	1	1	.	.				
32		A	Induction	3	1	.	1	1	.	.				
33		A	Induction	4	1	.	1	1	.	.				
34		A	Induction	5	1	.	1	1	.	.				
35		A	Induction	6	1	.	1	1	.	.				
36		A	Induction	7	4	.	4	4	.	.				
37		A	Induction	8	1	1	4	4	.	.				
38		A	Induction	9	4	4	4	4	.	.				
39		A	Induction	10	1	4	4	4	.	.				
40		A	Challenge	12	.	.	.	4	4	4	Yes	Yes	Yes	Yes
41		A	Challenge	13	.	.	.	4	4	4	Yes	Yes	Yes	Yes
42		A	Challenge	14	.	.	.	4	5	5	Yes	Yes	Yes	Yes
43		A	Challenge	15	.	.	.	4	2	5	Yes	Yes	Yes	Yes
44		A	Re-Challenge	17	.	.	.	4	7	7	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
45	(b) (6)	A	Re-Challenge	18	.	.	.	4	10	10	Yes	Yes	Yes	Yes
46		A	Re-Challenge	19	.	.	.	4	9	10	Yes	Yes	Yes	Yes
47		A	Re-Challenge	20	.	.	.	4	7	10	Yes	Yes	Yes	Yes
48		A	Induction	2	2	.	2	2	.	.				
49		A	Induction	3	1	.	1	2	.	.				
50		A	Induction	4	1	.	1	2	.	.				
51		A	Induction	5	1	.	1	2	.	.				
52		A	Induction	6	1	.	1	2	.	.				
53		A	Induction	7	1	.	1	2	.	.				
54		A	Induction	8	1	.	1	2	.	.				
55		A	Induction	9	2	.	2	2	.	.				
56		A	Induction	10	2	.	2	2	.	.				
57		A	Challenge	12	.	.	.	2	4	4	No	Yes	Yes	Yes
58		A	Challenge	13	.	.	.	2	2	4	No	Yes	Yes	Yes
59		A	Challenge	14	.	.	.	2	2	4	No	Yes	Yes	Yes
60		A	Challenge	15	.	.	.	2	2	4	No	Yes	Yes	Yes
61		A	Re-Challenge	17	.	.	.	2	4	4	No	Yes	Yes	Yes
62		A	Re-Challenge	18	.	.	.	2	4	4	No	Yes	Yes	Yes
63		A	Re-Challenge	19	.	.	.	2	2	4	No	Yes	Yes	Yes
64		A	Re-Challenge	20	.	.	.	2	2	4	No	Yes	Yes	Yes
65		A	Induction	2	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
66	(b) (6)	A	Induction	3	1	.	1	1	.	.				
67		A	Induction	4	1	.	1	1	.	.				
68		A	Induction	5	1	.	1	1	.	.				
69		A	Induction	6	1	.	1	1	.	.				
70		A	Induction	7	1	.	1	1	.	.				
71		A	Induction	8	2	.	2	2	.	.				
72		A	Induction	9	2	.	2	2	.	.				
73		A	Induction	10	2	.	2	2	.	.				
74		A	Challenge	12	.	.	.	2	4	4	No	Yes	Yes	Yes
75		A	Challenge	13	.	.	.	2	4	4	No	Yes	Yes	Yes
76		A	Challenge	14	.	.	.	2	2	4	No	Yes	Yes	Yes
77		A	Challenge	15	.	.	.	2	2	4	No	Yes	Yes	Yes
78		A	Re-Challenge	17	.	.	.	2	4	4	No	Yes	Yes	Yes
79		A	Re-Challenge	18	.	.	.	2	4	4	No	Yes	Yes	Yes
80		A	Re-Challenge	19	.	.	.	2	4	4	No	Yes	Yes	Yes
81		A	Re-Challenge	20	.	.	.	2	2	4	No	Yes	Yes	Yes
82		A	Induction	2	0	.	0	0	.	.				
83		A	Induction	3	1	.	1	1	.	.				
84		A	Induction	4	1	.	1	1	.	.				
85		A	Induction	5	1	.	1	1	.	.				
86		A	Induction	6	1	.	1	1	.	.				
87		A	Induction	7	1	.	1	1	.	.				
88		A	Induction	8	4	.	4	4	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
89	(b) (6)	A	Induction	9	4	2	4	4	.	.				
90		A	Induction	10	4	4	4	4	.	.				
91		A	Challenge	12	.	.	.	4	7	7	Yes	Yes	Yes	
92		A	Challenge	13	.	.	.	4	4	7	Yes	Yes	Yes	
93		A	Challenge	14	.	.	.	4	6	7	Yes	Yes	Yes	
94		A	Challenge	15	.	.	.	4	4	7	Yes	Yes	Yes	
95		A	Induction	2	1	.	1	1	.	.				
96		A	Induction	3	1	.	1	1	.	.				
97		A	Induction	4	1	.	1	1	.	.				
98		A	Induction	5	1	.	1	1	.	.				
99		A	Induction	6	1	.	1	1	.	.				
100		A	Induction	7	2	.	2	2	.	.				
101		A	Induction	8	2	.	2	2	.	.				
102		A	Induction	9	2	.	2	2	.	.				
103		A	Induction	10	2	.	2	2	.	.				
104		A	Challenge	12	.	.	.	2	4	4	No	Yes	Yes	Yes
105		A	Challenge	13	.	.	.	2	2	4	No	Yes	Yes	Yes
106		A	Challenge	14	.	.	.	2	2	4	No	Yes	Yes	Yes
107		A	Challenge	15	.	.	.	2	2	4	No	Yes	Yes	Yes
108		A	Re-Challenge	17	.	.	.	2	4	4	No	Yes	Yes	Yes
109		A	Re-Challenge	18	.	.	.	2	4	4	No	Yes	Yes	Yes
110		A	Re-Challenge	19	.	.	.	2	4	4	No	Yes	Yes	Yes
111		A	Re-Challenge	20	.	.	.	2	2	4	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
112	(b) (6)	A	Induction	2	1	.	1	1	.	.				
113		A	Induction	3	1	.	1	1	.	.				
114		A	Induction	4	1	.	1	1	.	.				
115		A	Induction	5	1	.	1	1	.	.				
116		A	Induction	6	1	.	1	1	.	.				
117		A	Induction	7	1	.	1	1	.	.				
118		A	Induction	8	2	.	2	2	.	.				
119		A	Induction	9	4	.	4	4	.	.				
120		A	Induction	10	4	4	4	4	.	.				
121		A	Challenge	12	.	.	.	4	4	4	Yes	Yes	Yes	Yes
122		A	Challenge	13	.	.	.	4	4	4	Yes	Yes	Yes	Yes
123		A	Challenge	14	.	.	.	4	6	6	Yes	Yes	Yes	Yes
124		A	Challenge	15	.	.	.	4	3	6	Yes	Yes	Yes	Yes
125		A	Re-Challenge	17	.	.	.	4	4	4	Yes	Yes	Yes	Yes
126		A	Re-Challenge	18	.	.	.	4	4	4	Yes	Yes	Yes	Yes
127		A	Re-Challenge	19	.	.	.	4	7	7	Yes	Yes	Yes	Yes
128		A	Re-Challenge	20	.	.	.	4	7	7	Yes	Yes	Yes	Yes
129		A	Induction	2	2	.	2	2	.	.				
130		A	Induction	3	1	.	1	2	.	.				
131		A	Induction	4	1	.	1	2	.	.				
132		A	Induction	5	1	.	1	2	.	.				
133		A	Induction	6	1	.	1	2	.	.				
134		A	Induction	7	2	.	2	2	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
135	(b) (6)	A	Induction	8	4	.	4	4	.	.				
136		A	Induction	9	4	4	4	4	.	.				
137		A	Induction	10	4	4	4	4	.	.				
138		A	Challenge	12	.	.	.	4	7	7	Yes	Yes	Yes	Yes
139		A	Challenge	13	.	.	.	4	5	7	Yes	Yes	Yes	Yes
140		A	Challenge	14	.	.	.	4	6	7	Yes	Yes	Yes	Yes
141		A	Challenge	15	.	.	.	4	4	7	Yes	Yes	Yes	Yes
142		A	Re-Challenge	17	.	.	.	4	7	7	Yes	Yes	Yes	Yes
143		A	Re-Challenge	18	.	.	.	4	5	7	Yes	Yes	Yes	Yes
144		A	Re-Challenge	19	.	.	.	4	2	7	Yes	Yes	Yes	Yes
145		A	Re-Challenge	20	.	.	.	4	5	7	Yes	Yes	Yes	Yes
146		A	Induction	2	1	.	1	1	.	.				
147		A	Induction	3	1	.	1	1	.	.				
148		A	Induction	4	1	.	1	1	.	.				
149		A	Induction	5	1	.	1	1	.	.				
150		A	Induction	6	1	.	1	1	.	.				
151		A	Induction	7	2	.	2	2	.	.				
152		A	Induction	8	2	.	2	2	.	.				
153		A	Induction	9	2	.	2	2	.	.				
154		A	Induction	10	2	.	2	2	.	.				
155		A	Challenge	12	.	.	.	2	4	4	Yes	Yes	Yes	
156		A	Challenge	13	.	.	.	2	2	4	Yes	Yes	Yes	
157		A	Challenge	14	.	.	.	2	4	4	Yes	Yes	Yes	

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
158	(b) (6)	A	Challenge	15	.	.	.	2	2	4	Yes	Yes	Yes	
159		A	Induction	2	2	.	2	2	.	.				
160		A	Induction	3	1	.	1	2	.	.				
161		A	Induction	4	1	.	1	2	.	.				
162		A	Induction	5	1	.	1	2	.	.				
163		A	Induction	6	1	.	1	2	.	.				
164		A	Induction	7	1	.	1	2	.	.				
165		A	Induction	8	2	.	2	2	.	.				
166		A	Induction	9	2	.	2	2	.	.				
167		A	Induction	10	2	.	2	2	.	.				
168		A	Challenge	12	.	.	.	2	4	4	Yes	Yes	Yes	
169		A	Challenge	13	.	.	.	2	2	4	Yes	Yes	Yes	
170		A	Challenge	14	.	.	.	2	2	4	Yes	Yes	Yes	
171		A	Challenge	15	.	.	.	2	2	4	Yes	Yes	Yes	
172		A	Induction	2	0	.	0	0	.	.				
173		A	Induction	3	1	.	1	1	.	.				
174		A	Induction	4	1	.	1	1	.	.				
175		A	Induction	5	1	.	1	1	.	.				
176		A	Induction	6	1	.	1	1	.	.				
177		A	Induction	7	2	.	2	2	.	.				
178		A	Induction	8	2	.	2	2	.	.				
179		A	Induction	9	2	.	2	2	.	.				
180		A	Induction	10	2	.	2	2	.	.				
181		A	Challenge	12	.	.	.	2	4	4	No	Yes	Yes	Yes
182		A	Challenge	13	.	.	.	2	4	4	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
183	(b) (6)	A	Challenge	14	.	.	.	2	2	4	No	Yes	Yes	Yes
184		A	Challenge	15	.	.	.	2	2	4	No	Yes	Yes	Yes
185		A	Re-Challenge	17	.	.	.	2	4	4	No	Yes	Yes	Yes
186		A	Re-Challenge	18	.	.	.	2	4	4	No	Yes	Yes	Yes
187		A	Re-Challenge	19	.	.	.	2	2	4	No	Yes	Yes	Yes
188		A	Re-Challenge	20	.	.	.	2	2	4	No	Yes	Yes	Yes
189		A	Induction	2	0	.	0	0	.	.				
190		A	Induction	3	1	.	1	1	.	.				
191		A	Induction	4	1	.	1	1	.	.				
192		A	Induction	5	1	.	1	1	.	.				
193		A	Induction	6	1	.	1	1	.	.				
194		A	Induction	7	2	.	2	2	.	.				
195		A	Induction	8	2	.	2	2	.	.				
196		A	Induction	9	2	.	2	2	.	.				
197		A	Induction	10	2	.	2	2	.	.				
198		A	Challenge	12	.	.	.	2	4	4	Yes	Yes	Yes	Yes
199		A	Challenge	13	.	.	.	2	4	4	Yes	Yes	Yes	Yes
200		A	Challenge	14	.	.	.	2	2	4	Yes	Yes	Yes	Yes
201		A	Challenge	15	.	.	.	2	2	4	Yes	Yes	Yes	Yes
202		A	Re-Challenge	17	.	.	.	2	7	7	Yes	Yes	Yes	Yes
203		A	Re-Challenge	18	.	.	.	2	7	7	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
204	(b) (6)	A	Re-Challenge	19	.	.	.	2	4	7	Yes	Yes	Yes	Yes
205		A	Re-Challenge	20	.	.	.	2	2	7	Yes	Yes	Yes	Yes
206		A	Induction	2	1	.	1	1	.	.				
207		A	Induction	3	1	.	1	1	.	.				
208		A	Induction	4	1	.	1	1	.	.				
209		A	Induction	5	1	.	1	1	.	.				
210		A	Induction	6	2	.	2	2	.	.				
211		A	Induction	7	2	.	2	2	.	.				
212		A	Induction	8	2	.	2	2	.	.				
213		A	Induction	9	2	.	2	2	.	.				
214		A	Induction	10	2	.	2	2	.	.				
215		A	Challenge	12	.	.	.	2	4	4	Yes	Yes	Yes	Yes
216		A	Challenge	13	.	.	.	2	4	4	Yes	Yes	Yes	Yes
217		A	Challenge	14	.	.	.	2	4	4	Yes	Yes	Yes	Yes
218		A	Challenge	15	.	.	.	2	2	4	Yes	Yes	Yes	Yes
219		A	Re-Challenge	17	.	.	.	2	4	4	Yes	Yes	Yes	Yes
220		A	Re-Challenge	18	.	.	.	2	4	4	Yes	Yes	Yes	Yes
221		A	Re-Challenge	19	.	.	.	2	4	4	Yes	Yes	Yes	Yes
222		A	Re-Challenge	20	.	.	.	2	2	4	Yes	Yes	Yes	Yes
223		A	Induction	2	0	.	0	0	.	.				
224		A	Induction	3	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
225	(b) (6)	A	Induction	4	1	.	1	1	.	.				
226		A	Induction	5	1	.	1	1	.	.				
227		A	Induction	6	2	.	2	2	.	.				
228		A	Induction	7	1	.	1	2	.	.				
229		A	Induction	8	2	.	2	2	.	.				
230		A	Induction	9	2	.	2	2	.	.				
231		A	Induction	10	2	.	2	2	.	.				
232		A	Challenge	12	.	.	.	2	0	0	Yes	Yes	Yes	Yes
233		A	Challenge	13	.	.	.	2	2	2	Yes	Yes	Yes	Yes
234		A	Challenge	14	.	.	.	2	4	4	Yes	Yes	Yes	Yes
235		A	Challenge	15	.	.	.	2	2	4	Yes	Yes	Yes	Yes
236		A	Re-Challenge	17	.	.	.	2	7	7	Yes	Yes	Yes	Yes
237		A	Re-Challenge	18	.	.	.	2	5	7	Yes	Yes	Yes	Yes
238		A	Re-Challenge	19	.	.	.	2	4	7	Yes	Yes	Yes	Yes
239		A	Re-Challenge	20	.	.	.	2	3	7	Yes	Yes	Yes	Yes
240		A	Induction	2	1	.	1	1	.	.				
241		A	Induction	3	1	.	1	1	.	.				
242		A	Induction	4	1	.	1	1	.	.				
243		A	Induction	5	1	.	1	1	.	.				
244		A	Induction	6	1	.	1	1	.	.				
245		A	Induction	7	2	.	2	2	.	.				
246		A	Induction	8	2	.	2	2	.	.				
247		A	Induction	9	2	.	2	2	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
248	(b) (6)	A	Induction	10	2	.	2	2	.	.				
249		A	Challenge	12	.	.	.	2	4	4	Yes	Yes	Yes	
250		A	Challenge	13	.	.	.	2	4	4	Yes	Yes	Yes	
251		A	Challenge	14	.	.	.	2	4	4	Yes	Yes	Yes	
252		A	Challenge	15	.	.	.	2	4	4	Yes	Yes	Yes	
253		A	Induction	2	1	.	1	1	.	.				
254		A	Induction	3	1	.	1	1	.	.				
255		A	Induction	4	1	.	1	1	.	.				
256		A	Induction	5	1	.	1	1	.	.				
257		A	Induction	6	1	.	1	1	.	.				
258		A	Induction	7	1	.	1	1	.	.				
259		A	Induction	8	2	.	2	2	.	.				
260		A	Induction	9	2	.	2	2	.	.				
261		A	Induction	10	2	.	2	2	.	.				
262		A	Challenge	12	.	.	.	2	2	2	Yes	Yes	Yes	Yes
263		A	Challenge	13	.	.	.	2	4	4	Yes	Yes	Yes	Yes
264		A	Challenge	14	.	.	.	2	4	4	Yes	Yes	Yes	Yes
265		A	Challenge	15	.	.	.	2	4	4	Yes	Yes	Yes	Yes
266		A	Re-Challenge	17	.	.	.	2	4	4	Yes	Yes	Yes	Yes
267		A	Re-Challenge	18	.	.	.	2	4	4	Yes	Yes	Yes	Yes
268		A	Re-Challenge	19	.	.	.	2	4	4	Yes	Yes	Yes	Yes
269		A	Re-Challenge	20	.	.	.	2	2	4	Yes	Yes	Yes	Yes
270		A	Induction	2	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
271	(b) (6)	A	Induction	3	1	.	1	1	.	.				
272		A	Induction	4	1	.	1	1	.	.				
273		A	Induction	5	1	.	1	1	.	.				
274		A	Induction	6	1	.	1	1	.	.				
275		A	Induction	7	2	.	2	2	.	.				
276		A	Induction	8	2	.	2	2	.	.				
277		A	Induction	9	2	.	2	2	.	.				
278		A	Induction	10	2	.	2	2	.	.				
279		A	Challenge	12	.	.	.	2	4	4	Yes	Yes	Yes	
280		A	Challenge	13	.	.	.	2	4	4	Yes	Yes	Yes	
281		A	Challenge	14	.	.	.	2	4	4	Yes	Yes	Yes	
282		A	Challenge	15	.	.	.	2	4	4	Yes	Yes	Yes	
283		B	Induction	2	1	.	1	1	.	.				
284		B	Induction	3	2	.	2	2	.	.				
285		B	Induction	4	2	.	2	2	.	.				
286		B	Induction	5	2	.	2	2	.	.				
287		B	Induction	6	2	.	2	2	.	.				
288		B	Induction	7	4	.	4	4	.	.				
289		B	Induction	8	4	2	4	4	.	.				
290		B	Induction	9	4	2	4	4	.	.				
291		B	Induction	10	4	4	4	4	.	.				
292		B	Challenge	12	.	.	.	4	7	7	Yes	Yes	Yes	Yes
293		B	Challenge	13	.	.	.	4	7	7	Yes	Yes	Yes	Yes
294		B	Challenge	14	.	.	.	4	4	7	Yes	Yes	Yes	Yes
295		B	Challenge	15	.	.	.	4	4	7	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
296	(b) (6)	B	Re-Challenge	17	.	.	.	4	7	7	Yes	Yes	Yes	Yes
297		B	Re-Challenge	18	.	.	.	4	10	10	Yes	Yes	Yes	Yes
298		B	Re-Challenge	19	.	.	.	4	10	10	Yes	Yes	Yes	Yes
299		B	Re-Challenge	20	.	.	.	4	7	10	Yes	Yes	Yes	Yes
300		B	Induction	2	1	.	1	1	.	.				
301		B	Induction	3	1	.	1	1	.	.				
302		B	Induction	4	1	.	1	1	.	.				
303		B	Induction	5	1	.	1	1	.	.				
304		B	Induction	6	1	.	1	1	.	.				
305		B	Induction	7	4	.	4	4	.	.				
306		B	Induction	8	4	1	4	4	.	.				
307		B	Induction	9	4	4	4	4	.	.				
308		B	Induction	10	4	5	5	5	.	.				
309		B	Challenge	12	.	.	.	5	2	2	Yes	Yes	Yes	Yes
310		B	Challenge	13	.	.	.	5	7	7	Yes	Yes	Yes	Yes
311		B	Challenge	14	.	.	.	5	4	7	Yes	Yes	Yes	Yes
312		B	Challenge	15	.	.	.	5	4	7	Yes	Yes	Yes	Yes
313		B	Re-Challenge	17	.	.	.	5	7	7	Yes	Yes	Yes	Yes
314		B	Re-Challenge	18	.	.	.	5	8	8	Yes	Yes	Yes	Yes
315		B	Re-Challenge	19	.	.	.	5	9	9	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
316	(b) (6)	B	Re-Challenge	20	.	.	.	5	4	9	Yes	Yes	Yes	Yes
317		B	Induction	2	1	.	1	1	.	.				
318		B	Induction	3	1	.	1	1	.	.				
319		B	Induction	4	1	.	1	1	.	.				
320		B	Induction	5	1	.	1	1	.	.				
321		B	Induction	6	2	.	2	2	.	.				
322		B	Induction	7	2	.	2	2	.	.				
323		B	Induction	8	2	.	2	2	.	.				
324		B	Induction	9	2	.	2	2	.	.				
325		B	Induction	10	2	.	2	2	.	.				
326		B	Challenge	12	.	.	.	2	7	7	Yes	Yes	Yes	
327		B	Challenge	13	.	.	.	2	4	7	Yes	Yes	Yes	
328		B	Challenge	14	.	.	.	2	2	7	Yes	Yes	Yes	
329		B	Challenge	15	.	.	.	2	2	7	Yes	Yes	Yes	
330		B	Induction	2	1	.	1	1	.	.				
331		B	Induction	3	1	.	1	1	.	.				
332		B	Induction	4	1	.	1	1	.	.				
333		B	Induction	5	1	.	1	1	.	.				
334		B	Induction	6	1	.	1	1	.	.				
335		B	Induction	7	4	.	4	4	.	.				
336		B	Induction	8	2	1	4	4	.	.				
337		B	Induction	9	4	4	4	4	.	.				
338		B	Induction	10	4	4	4	4	.	.				
339		B	Challenge	12	.	.	.	4	4	4	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
340	(b) (6)	B	Challenge	13	.	.	.	4	4	4	Yes	Yes	Yes	Yes
341		B	Challenge	14	.	.	.	4	5	5	Yes	Yes	Yes	Yes
342		B	Challenge	15	.	.	.	4	2	5	Yes	Yes	Yes	Yes
343		B	Re-Challenge	17	.	.	.	4	7	7	Yes	Yes	Yes	Yes
344		B	Re-Challenge	18	.	.	.	4	7	7	Yes	Yes	Yes	Yes
345		B	Re-Challenge	19	.	.	.	4	9	9	Yes	Yes	Yes	Yes
346		B	Re-Challenge	20	.	.	.	4	7	9	Yes	Yes	Yes	Yes
347		B	Induction	2	1	.	1	1	.	.				
348		B	Induction	3	1	.	1	1	.	.				
349		B	Induction	4	1	.	1	1	.	.				
350		B	Induction	5	1	.	1	1	.	.				
351		B	Induction	6	2	.	2	2	.	.				
352		B	Induction	7	2	.	2	2	.	.				
353		B	Induction	8	4	.	4	4	.	.				
354		B	Induction	9	4	2	4	4	.	.				
355		B	Induction	10	4	4	4	4	.	.				
356		B	Challenge	12	.	.	.	4	7	7	Yes	Yes	Yes	
357		B	Challenge	13	.	.	.	4	5	7	Yes	Yes	Yes	
358		B	Challenge	14	.	.	.	4	6	7	Yes	Yes	Yes	
359		B	Challenge	15	.	.	.	4	4	7	Yes	Yes	Yes	
360		B	Induction	2	1	.	1	1	.	.				
361		B	Induction	3	1	.	1	1	.	.				
362		B	Induction	4	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
363	(b) (6)	B	Induction	5	1	.	1	1	.	.				
364		B	Induction	6	2	.	2	2	.	.				
365		B	Induction	7	2	.	2	2	.	.				
366		B	Induction	8	2	.	2	2	.	.				
367		B	Induction	9	5	.	5	5	.	.				
368		B	Induction	10	4	4	5	5	.	.				
369		B	Challenge	12	.	.	.	5	10	10	Yes	Yes	Yes	Yes
370		B	Challenge	13	.	.	.	5	7	10	Yes	Yes	Yes	Yes
371		B	Challenge	14	.	.	.	5	7	10	Yes	Yes	Yes	Yes
372		B	Challenge	15	.	.	.	5	4	10	Yes	Yes	Yes	Yes
373		B	Re-Challenge	17	.	.	.	5	7	7	Yes	Yes	Yes	Yes
374		B	Re-Challenge	18	.	.	.	5	6	7	Yes	Yes	Yes	Yes
375		B	Re-Challenge	19	.	.	.	5	7	7	Yes	Yes	Yes	Yes
376		B	Re-Challenge	20	.	.	.	5	7	7	Yes	Yes	Yes	Yes
377		B	Induction	2	1	.	1	1	.	.				
378		B	Induction	3	1	.	1	1	.	.				
379		B	Induction	4	1	.	1	1	.	.				
380		B	Induction	5	1	.	1	1	.	.				
381		B	Induction	6	2	.	2	2	.	.				
382		B	Induction	7	2	.	2	2	.	.				
383		B	Induction	8	4	.	4	4	.	.				
384		B	Induction	9	4	4	4	4	.	.				
385		B	Induction	10	4	4	4	4	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
386	(b) (6)	B	Challenge	12	.	.	.	4	7	7	Yes	Yes	Yes	Yes
387		B	Challenge	13	.	.	.	4	5	7	Yes	Yes	Yes	Yes
388		B	Challenge	14	.	.	.	4	5	7	Yes	Yes	Yes	Yes
389		B	Challenge	15	.	.	.	4	4	7	Yes	Yes	Yes	Yes
390		B	Re-Challenge	17	.	.	.	4	7	7	Yes	Yes	Yes	Yes
391		B	Re-Challenge	18	.	.	.	4	5	7	Yes	Yes	Yes	Yes
392		B	Re-Challenge	19	.	.	.	4	6	7	Yes	Yes	Yes	Yes
393		B	Re-Challenge	20	.	.	.	4	4	7	Yes	Yes	Yes	Yes
394		B	Induction	2	1	.	1	1	.	.				
395		B	Induction	3	1	.	1	1	.	.				
396		B	Induction	4	1	.	1	1	.	.				
397		B	Induction	5	1	.	1	1	.	.				
398		B	Induction	6	1	.	1	1	.	.				
399		B	Induction	7	2	.	2	2	.	.				
400		B	Induction	8	2	.	2	2	.	.				
401		B	Induction	9	2	.	2	2	.	.				
402		B	Induction	10	2	.	2	2	.	.				
403		B	Challenge	12	.	.	.	2	4	4	Yes	Yes	Yes	
404		B	Challenge	13	.	.	.	2	2	4	Yes	Yes	Yes	
405		B	Challenge	14	.	.	.	2	4	4	Yes	Yes	Yes	
406		B	Challenge	15	.	.	.	2	2	4	Yes	Yes	Yes	
407		B	Induction	2	1	.	1	1	.	.				
408		B	Induction	3	1	.	1	1	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Maximum irritation Score during Induction	Sensitization Score	Max Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
409	(b) (6)	B	Induction	4	1	.	1	1	.	.				
410		B	Induction	5	1	.	1	1	.	.				
411		B	Induction	6	2	.	2	2	.	.				
412		B	Induction	7	2	.	2	2	.	.				
413		B	Induction	8	2	.	2	2	.	.				
414		B	Induction	9	2	.	2	2	.	.				
415		B	Induction	10	2	.	2	2	.	.				
416		B	Challenge	12	.	.	.	2	4	4	Yes	Yes	Yes	
417		B	Challenge	13	.	.	.	2	2	4	Yes	Yes	Yes	
418		B	Challenge	14	.	.	.	2	4	4	Yes	Yes	Yes	

List 4. Complete List of FDA's Potential Sensitization (TEST N=33 patches, RLD N=27 patches) If Comparing Mean Score between Induction and Challenge/Re-challenge Phase

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
1	(b) (6)	A	Induction	2	1	.	1	.	.	.				
2		A	Induction	3	2	.	2	.	.	.				
3		A	Induction	4	2	.	2	.	.	.				
4		A	Induction	5	2	.	2	.	.	.				
5		A	Induction	6	2	.	2	.	.	.				
6		A	Induction	7	4	.	4	.	.	.				
7		A	Induction	8	4	2	4	.	.	.				
8		A	Induction	9	2	4	4	.	.	.				
9		A	Induction	10	1	4	4	2.77778	.	.				
10		A	Challenge	12	.	.	.	2.77778	7	4.25	Yes	Yes	Yes	Yes
11		A	Challenge	13	.	.	.	2.77778	4	4.25	Yes	Yes	Yes	Yes
12		A	Challenge	14	.	.	.	2.77778	2	4.25	Yes	Yes	Yes	Yes
13		A	Challenge	15	.	.	.	2.77778	4	4.25	Yes	Yes	Yes	Yes
14		A	Re-Challenge	17	.	.	.	2.77778	7	7.75	Yes	Yes	Yes	Yes
15		A	Re-Challenge	18	.	.	.	2.77778	7	7.75	Yes	Yes	Yes	Yes
16		A	Re-Challenge	19	.	.	.	2.77778	10	7.75	Yes	Yes	Yes	Yes
17		A	Re-Challenge	20	.	.	.	2.77778	7	7.75	Yes	Yes	Yes	Yes
18		A	Induction	2	0	.	0	.	.	.				
19		A	Induction	3	1	.	1	.	.	.				
20		A	Induction	4	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
21	(b) (6)	A	Induction	5	1	.	1	.	.	.				
22		A	Induction	6	1	.	1	.	.	.				
23		A	Induction	7	1	.	1	.	.	.				
24		A	Induction	8	2	.	2	.	.	.				
25		A	Induction	9	4	.	4	.	.	.				
26		A	Induction	10	2	1	4	1.66667	.	.				
27		A	Challenge	12	.	.	.	1.66667	2	2.00	Yes	Yes	Yes	
28		A	Challenge	13	.	.	.	1.66667	2	2.00	Yes	Yes	Yes	
29		A	Challenge	14	.	.	.	1.66667	2	2.00	Yes	Yes	Yes	
30		A	Challenge	15	.	.	.	1.66667	2	2.00	Yes	Yes	Yes	
31		A	Induction	2	1	.	1	.	.	.				
32		A	Induction	3	1	.	1	.	.	.				
33		A	Induction	4	1	.	1	.	.	.				
34		A	Induction	5	1	.	1	.	.	.				
35		A	Induction	6	1	.	1	.	.	.				
36		A	Induction	7	1	.	1	.	.	.				
37		A	Induction	8	1	.	1	.	.	.				
38		A	Induction	9	2	.	2	.	.	.				
39		A	Induction	10	4	.	4	1.44444	.	.				
40		A	Challenge	12	.	.	.	1.44444	4	2.50	No	Yes	Yes	Yes
41		A	Challenge	13	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
42		A	Challenge	14	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
43		A	Challenge	15	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
44		A	Re-Challenge	17	.	.	.	1.44444	1	2.25	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
45	(b) (6)	A	Re-Challenge	18	.	.	.	1.44444	4	2.25	No	Yes	Yes	Yes
46		A	Re-Challenge	19	.	.	.	1.44444	2	2.25	No	Yes	Yes	Yes
47		A	Re-Challenge	20	.	.	.	1.44444	2	2.25	No	Yes	Yes	Yes
48		A	Induction	2	1	.	1	.	.	.				
49		A	Induction	3	0	.	0	.	.	.				
50		A	Induction	4	1	.	1	.	.	.				
51		A	Induction	5	1	.	1	.	.	.				
52		A	Induction	6	1	.	1	.	.	.				
53		A	Induction	7	1	.	1	.	.	.				
54		A	Induction	8	2	.	2	.	.	.				
55		A	Induction	9	2	.	2	.	.	.				
56		A	Induction	10	2	.	2	1.22222	.	.				
57		A	Challenge	12	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
58		A	Challenge	13	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
59		A	Challenge	14	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
60		A	Challenge	15	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
61		A	Re-Challenge	17	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
62		A	Re-Challenge	18	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
63		A	Re-Challenge	19	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
64		A	Re-Challenge	20	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
65	(b) (6)	A	Induction	2	1	.	1	.	.	.				
66		A	Induction	3	1	.	1	.	.	.				
67		A	Induction	4	1	.	1	.	.	.				
68		A	Induction	5	1	.	1	.	.	.				
69		A	Induction	6	1	.	1	.	.	.				
70		A	Induction	7	2	.	2	.	.	.				
71		A	Induction	8	2	.	2	.	.	.				
72		A	Induction	9	5	.	5	.	.	.				
73		A	Induction	10	4	4	5	2.11111	.	.				
74		A	Challenge	12	.	.	.	2.11111	4	3.00	No	Yes	Yes	Yes
75		A	Challenge	13	.	.	.	2.11111	4	3.00	No	Yes	Yes	Yes
76		A	Challenge	14	.	.	.	2.11111	2	3.00	No	Yes	Yes	Yes
77		A	Challenge	15	.	.	.	2.11111	2	3.00	No	Yes	Yes	Yes
78		A	Re-Challenge	17	.	.	.	2.11111	4	4.50	No	Yes	Yes	Yes
79		A	Re-Challenge	18	.	.	.	2.11111	4	4.50	No	Yes	Yes	Yes
80		A	Re-Challenge	19	.	.	.	2.11111	5	4.50	No	Yes	Yes	Yes
81		A	Re-Challenge	20	.	.	.	2.11111	5	4.50	No	Yes	Yes	Yes
82		A	Induction	2	1	.	1	.	.	.				
83		A	Induction	3	1	.	1	.	.	.				
84		A	Induction	4	1	.	1	.	.	.				
85		A	Induction	5	1	.	1	.	.	.				
86		A	Induction	6	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
87	(b) (6)	A	Induction	7	1	.	1	.	.	.				
88		A	Induction	8	2	.	2	.	.	.				
89		A	Induction	9	4	.	4	.	.	.				
90		A	Induction	10	5	4	5	1.88889	.	.				
91		A	Challenge	12	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
92		A	Challenge	13	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
93		A	Challenge	14	.	.	.	1.88889	2	3.50	No	Yes	Yes	Yes
94		A	Challenge	15	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
95		A	Re-Challenge	17	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
96		A	Re-Challenge	18	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
97		A	Re-Challenge	19	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
98		A	Re-Challenge	20	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
99		A	Induction	2	1	.	1	.	.	.				
100		A	Induction	3	1	.	1	.	.	.				
101		A	Induction	4	1	.	1	.	.	.				
102		A	Induction	5	1	.	1	.	.	.				
103		A	Induction	6	1	.	1	.	.	.				
104		A	Induction	7	4	.	4	.	.	.				
105		A	Induction	8	2	1	4	.	.	.				
106		A	Induction	9	4	4	4	.	.	.				
107		A	Induction	10	2	5	5	2.44444	.	.				
108		A	Challenge	12	.	.	.	2.44444	2	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
109	(b) (6)	A	Challenge	13	.	.	.	2.44444	4	3.00	No	Yes	Yes	Yes
110		A	Challenge	14	.	.	.	2.44444	4	3.00	No	Yes	Yes	Yes
111		A	Challenge	15	.	.	.	2.44444	2	3.00	No	Yes	Yes	Yes
112		A	Re-Challenge	17	.	.	.	2.44444	4	4.50	No	Yes	Yes	Yes
113		A	Re-Challenge	18	.	.	.	2.44444	6	4.50	No	Yes	Yes	Yes
114		A	Re-Challenge	19	.	.	.	2.44444	4	4.50	No	Yes	Yes	Yes
115		A	Re-Challenge	20	.	.	.	2.44444	4	4.50	No	Yes	Yes	Yes
116		A	Induction	2	0	.	0	.	.	.				
117		A	Induction	3	1	.	1	.	.	.				
118		A	Induction	4	1	.	1	.	.	.				
119		A	Induction	5	1	.	1	.	.	.				
120		A	Induction	6	2	.	2	.	.	.				
121		A	Induction	7	2	.	2	.	.	.				
122		A	Induction	8	2	.	2	.	.	.				
123		A	Induction	9	2	.	2	.	.	.				
124		A	Induction	10	2	.	2	1.44444	.	.				
125		A	Challenge	12	.	.	.	1.44444	7	3.75	Yes	Yes	Yes	
126		A	Challenge	13	.	.	.	1.44444	4	3.75	Yes	Yes	Yes	
127		A	Challenge	14	.	.	.	1.44444	2	3.75	Yes	Yes	Yes	
128		A	Challenge	15	.	.	.	1.44444	2	3.75	Yes	Yes	Yes	
129		A	Induction	2	1	.	1	.	.	.				
130		A	Induction	3	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
131	(b) (6)	A	Induction	4	1	.	1	.	.	.				
132		A	Induction	5	1	.	1	.	.	.				
133		A	Induction	6	1	.	1	.	.	.				
134		A	Induction	7	4	.	4	.	.	.				
135		A	Induction	8	1	1	4	.	.	.				
136		A	Induction	9	4	4	4	.	.	.				
137		A	Induction	10	1	4	4	2.33333	.	.				
138		A	Challenge	12	.	.	.	2.33333	4	3.75	Yes	Yes	Yes	Yes
139		A	Challenge	13	.	.	.	2.33333	4	3.75	Yes	Yes	Yes	Yes
140		A	Challenge	14	.	.	.	2.33333	5	3.75	Yes	Yes	Yes	Yes
141		A	Challenge	15	.	.	.	2.33333	2	3.75	Yes	Yes	Yes	Yes
142		A	Re-Challenge	17	.	.	.	2.33333	7	8.25	Yes	Yes	Yes	Yes
143		A	Re-Challenge	18	.	.	.	2.33333	10	8.25	Yes	Yes	Yes	Yes
144		A	Re-Challenge	19	.	.	.	2.33333	9	8.25	Yes	Yes	Yes	Yes
145		A	Re-Challenge	20	.	.	.	2.33333	7	8.25	Yes	Yes	Yes	Yes
146		A	Induction	2	2	.	2	.	.	.				
147		A	Induction	3	1	.	1	.	.	.				
148		A	Induction	4	1	.	1	.	.	.				
149		A	Induction	5	1	.	1	.	.	.				
150		A	Induction	6	1	.	1	.	.	.				
151		A	Induction	7	1	.	1	.	.	.				
152		A	Induction	8	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
	(b) (6)													
153		A	Induction	9	2	.	2	.	.	.				
154		A	Induction	10	2	.	2	1.33333	.	.				
155		A	Challenge	12	.	.	.	1.33333	4	2.50	No	Yes	Yes	Yes
156		A	Challenge	13	.	.	.	1.33333	2	2.50	No	Yes	Yes	Yes
157		A	Challenge	14	.	.	.	1.33333	2	2.50	No	Yes	Yes	Yes
158		A	Challenge	15	.	.	.	1.33333	2	2.50	No	Yes	Yes	Yes
159		A	Re-Challenge	17	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
160		A	Re-Challenge	18	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
161		A	Re-Challenge	19	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
162		A	Re-Challenge	20	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
163		A	Induction	2	1	.	1	.	.	.				
164		A	Induction	3	1	.	1	.	.	.				
165		A	Induction	4	1	.	1	.	.	.				
166		A	Induction	5	1	.	1	.	.	.				
167		A	Induction	6	1	.	1	.	.	.				
168		A	Induction	7	1	.	1	.	.	.				
169		A	Induction	8	2	.	2	.	.	.				
170		A	Induction	9	2	.	2	.	.	.				
171		A	Induction	10	2	.	2	1.33333	.	.				
172		A	Challenge	12	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
173		A	Challenge	13	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
174		A	Challenge	14	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
175	(b) (6)	A	Challenge	15	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
176		A	Re-Challenge	17	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
177		A	Re-Challenge	18	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
178		A	Re-Challenge	19	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
179		A	Re-Challenge	20	.	.	.	1.33333	2	3.50	No	Yes	Yes	Yes
180		A	Induction	2	0	.	0	.	.	.				
181		A	Induction	3	1	.	1	.	.	.				
182		A	Induction	4	1	.	1	.	.	.				
183		A	Induction	5	1	.	1	.	.	.				
184		A	Induction	6	1	.	1	.	.	.				
185		A	Induction	7	1	.	1	.	.	.				
186		A	Induction	8	4	.	4	.	.	.				
187		A	Induction	9	4	2	4	.	.	.				
188		A	Induction	10	4	4	4	1.88889	.	.				
189		A	Challenge	12	.	.	.	1.88889	7	5.25	Yes	Yes	Yes	
190		A	Challenge	13	.	.	.	1.88889	4	5.25	Yes	Yes	Yes	
191		A	Challenge	14	.	.	.	1.88889	6	5.25	Yes	Yes	Yes	
192		A	Challenge	15	.	.	.	1.88889	4	5.25	Yes	Yes	Yes	
193		A	Induction	2	1	.	1	.	.	.				
194		A	Induction	3	1	.	1	.	.	.				
195		A	Induction	4	1	.	1	.	.	.				
196		A	Induction	5	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
197	(b) (6)	A	Induction	6	1	.	1	.	.	.				
198		A	Induction	7	2	.	2	.	.	.				
199		A	Induction	8	2	.	2	.	.	.				
200		A	Induction	9	2	.	2	.	.	.				
201		A	Induction	10	2	.	2	1.44444	.	.				
202		A	Challenge	12	.	.	.	1.44444	4	2.50	No	Yes	Yes	Yes
203		A	Challenge	13	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
204		A	Challenge	14	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
205		A	Challenge	15	.	.	.	1.44444	2	2.50	No	Yes	Yes	Yes
206		A	Re-Challenge	17	.	.	.	1.44444	4	3.50	No	Yes	Yes	Yes
207		A	Re-Challenge	18	.	.	.	1.44444	4	3.50	No	Yes	Yes	Yes
208		A	Re-Challenge	19	.	.	.	1.44444	4	3.50	No	Yes	Yes	Yes
209		A	Re-Challenge	20	.	.	.	1.44444	2	3.50	No	Yes	Yes	Yes
210		A	Induction	2	0	.	0	.	.	.				
211		A	Induction	3	1	.	1	.	.	.				
212		A	Induction	4	1	.	1	.	.	.				
213		A	Induction	5	1	.	1	.	.	.				
214		A	Induction	6	1	.	1	.	.	.				
215		A	Induction	7	2	.	2	.	.	.				
216		A	Induction	8	2	.	2	.	.	.				
217		A	Induction	9	2	.	2	.	.	.				
218		A	Induction	10	2	.	2	1.33333	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
219	(b) (6)	A	Challenge	12	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
220		A	Challenge	13	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
221		A	Challenge	14	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
222		A	Challenge	15	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
223		A	Re-Challenge	17	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
224		A	Re-Challenge	18	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
225		A	Re-Challenge	19	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
226		A	Re-Challenge	20	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
227		A	Induction	2	1	.	1	.	.	.				
228		A	Induction	3	1	.	1	.	.	.				
229		A	Induction	4	1	.	1	.	.	.				
230		A	Induction	5	1	.	1	.	.	.				
231		A	Induction	6	1	.	1	.	.	.				
232		A	Induction	7	2	.	2	.	.	.				
233		A	Induction	8	2	.	2	.	.	.				
234		A	Induction	9	2	.	2	.	.	.				
235		A	Induction	10	2	.	2	1.44444	.	.				
236		A	Challenge	12	.	.	.	1.44444	2	2.00	Yes	Yes	Yes	
237		A	Challenge	13	.	.	.	1.44444	2	2.00	Yes	Yes	Yes	
238		A	Challenge	14	.	.	.	1.44444	2	2.00	Yes	Yes	Yes	
239		A	Challenge	15	.	.	.	1.44444	2	2.00	Yes	Yes	Yes	
240		A	Induction	2	0	.	0	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
241	(b) (6)	A	Induction	3	1	.	1	.	.	.				
242		A	Induction	4	1	.	1	.	.	.				
243		A	Induction	5	1	.	1	.	.	.				
244		A	Induction	6	1	.	1	.	.	.				
245		A	Induction	7	1	.	1	.	.	.				
246		A	Induction	8	2	.	2	.	.	.				
247		A	Induction	9	2	.	2	.	.	.				
248		A	Induction	10	2	.	2	1.22222	.	.				
249		A	Challenge	12	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
250		A	Challenge	13	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
251		A	Challenge	14	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
252		A	Challenge	15	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
253		A	Re-Challenge	17	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
254		A	Re-Challenge	18	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
255		A	Re-Challenge	19	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
256		A	Re-Challenge	20	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
257		A	Induction	2	1	.	1	.	.	.				
258		A	Induction	3	1	.	1	.	.	.				
259		A	Induction	4	1	.	1	.	.	.				
260		A	Induction	5	1	.	1	.	.	.				
261		A	Induction	6	1	.	1	.	.	.				
262		A	Induction	7	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
263	(b) (6)	A	Induction	8	2	.	2	.	.	.				
264		A	Induction	9	4	.	4	.	.	.				
265		A	Induction	10	4	4	4	1.77778	.	.				
266		A	Challenge	12	.	.	.	1.77778	4	4.25	Yes	Yes	Yes	Yes
267		A	Challenge	13	.	.	.	1.77778	4	4.25	Yes	Yes	Yes	Yes
268		A	Challenge	14	.	.	.	1.77778	6	4.25	Yes	Yes	Yes	Yes
269		A	Challenge	15	.	.	.	1.77778	3	4.25	Yes	Yes	Yes	Yes
270		A	Re-Challenge	17	.	.	.	1.77778	4	5.50	Yes	Yes	Yes	Yes
271		A	Re-Challenge	18	.	.	.	1.77778	4	5.50	Yes	Yes	Yes	Yes
272		A	Re-Challenge	19	.	.	.	1.77778	7	5.50	Yes	Yes	Yes	Yes
273		A	Re-Challenge	20	.	.	.	1.77778	7	5.50	Yes	Yes	Yes	Yes
274		A	Induction	2	0	.	0	.	.	.				
275		A	Induction	3	0	.	0	.	.	.				
276		A	Induction	4	1	.	1	.	.	.				
277		A	Induction	5	1	.	1	.	.	.				
278		A	Induction	6	1	.	1	.	.	.				
279		A	Induction	7	1	.	1	.	.	.				
280		A	Induction	8	1	.	1	.	.	.				
281		A	Induction	9	2	.	2	.	.	.				
282		A	Induction	10	2	.	2	1.00000	.	.				
283		A	Challenge	12	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
284		A	Challenge	13	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
285	(b) (6)	A	Challenge	14	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
286		A	Challenge	15	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
287		A	Re-Challenge	17	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
288		A	Re-Challenge	18	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
289		A	Re-Challenge	19	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
290		A	Re-Challenge	20	.	.	.	1.00000	2	2.00	No	Yes	Yes	Yes
291		A	Induction	2	2	.	2	.	.	.				
292		A	Induction	3	1	.	1	.	.	.				
293		A	Induction	4	1	.	1	.	.	.				
294		A	Induction	5	1	.	1	.	.	.				
295		A	Induction	6	1	.	1	.	.	.				
296		A	Induction	7	2	.	2	.	.	.				
297		A	Induction	8	4	.	4	.	.	.				
298		A	Induction	9	4	4	4	.	.	.				
299		A	Induction	10	4	4	4	2.22222	.	.				
300		A	Challenge	12	.	.	.	2.22222	7	5.50	Yes	Yes	Yes	Yes
301		A	Challenge	13	.	.	.	2.22222	5	5.50	Yes	Yes	Yes	Yes
302		A	Challenge	14	.	.	.	2.22222	6	5.50	Yes	Yes	Yes	Yes
303		A	Challenge	15	.	.	.	2.22222	4	5.50	Yes	Yes	Yes	Yes
304		A	Re-Challenge	17	.	.	.	2.22222	7	4.75	Yes	Yes	Yes	Yes
305		A	Re-Challenge	18	.	.	.	2.22222	5	4.75	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
306	(b) (6)	A	Re-Challenge	19	.	.	.	2.22222	2	4.75	Yes	Yes	Yes	Yes
307		A	Re-Challenge	20	.	.	.	2.22222	5	4.75	Yes	Yes	Yes	Yes
308		A	Induction	2	1	.	1	.	.	.				
309		A	Induction	3	1	.	1	.	.	.				
310		A	Induction	4	1	.	1	.	.	.				
311		A	Induction	5	1	.	1	.	.	.				
312		A	Induction	6	1	.	1	.	.	.				
313		A	Induction	7	2	.	2	.	.	.				
314		A	Induction	8	2	.	2	.	.	.				
315		A	Induction	9	2	.	2	.	.	.				
316		A	Induction	10	2	.	2	1.44444	.	.				
317		A	Challenge	12	.	.	.	1.44444	4	3.00	Yes	Yes	Yes	
318		A	Challenge	13	.	.	.	1.44444	2	3.00	Yes	Yes	Yes	
319		A	Challenge	14	.	.	.	1.44444	4	3.00	Yes	Yes	Yes	
320		A	Challenge	15	.	.	.	1.44444	2	3.00	Yes	Yes	Yes	
321		A	Induction	2	2	.	2	.	.	.				
322		A	Induction	3	1	.	1	.	.	.				
323		A	Induction	4	1	.	1	.	.	.				
324		A	Induction	5	1	.	1	.	.	.				
325		A	Induction	6	1	.	1	.	.	.				
326		A	Induction	7	1	.	1	.	.	.				
327		A	Induction	8	2	.	2	.	.	.				
328		A	Induction	9	2	.	2	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
329	(b) (6)	A	Induction	10	2	.	2	1.44444	.	.				
330		A	Challenge	12	.	.	.	1.44444	4	2.50	Yes	Yes	Yes	
331		A	Challenge	13	.	.	.	1.44444	2	2.50	Yes	Yes	Yes	
332		A	Challenge	14	.	.	.	1.44444	2	2.50	Yes	Yes	Yes	
333		A	Challenge	15	.	.	.	1.44444	2	2.50	Yes	Yes	Yes	
334		A	Induction	2	1	.	1	.	.	.				
335		A	Induction	3	1	.	1	.	.	.				
336		A	Induction	4	1	.	1	.	.	.				
337		A	Induction	5	1	.	1	.	.	.				
338		A	Induction	6	1	.	1	.	.	.				
339		A	Induction	7	1	.	1	.	.	.				
340		A	Induction	8	2	.	2	.	.	.				
341		A	Induction	9	2	.	2	.	.	.				
342		A	Induction	10	2	.	2	1.33333	.	.				
343		A	Challenge	12	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
344		A	Challenge	13	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
345		A	Challenge	14	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
346		A	Challenge	15	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
347		A	Re-Challenge	17	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
348		A	Re-Challenge	18	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
349		A	Re-Challenge	19	.	.	.	1.33333	4	3.50	No	Yes	Yes	Yes
350		A	Re-Challenge	20	.	.	.	1.33333	2	3.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
351	(b) (6)	A	Induction	2	0	.	0	.	.	.				
352		A	Induction	3	1	.	1	.	.	.				
353		A	Induction	4	1	.	1	.	.	.				
354		A	Induction	5	1	.	1	.	.	.				
355		A	Induction	6	1	.	1	.	.	.				
356		A	Induction	7	2	.	2	.	.	.				
357		A	Induction	8	2	.	2	.	.	.				
358		A	Induction	9	2	.	2	.	.	.				
359		A	Induction	10	2	.	2	1.33333	.	.				
360		A	Challenge	12	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
361		A	Challenge	13	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
362		A	Challenge	14	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
363		A	Challenge	15	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
364		A	Re-Challenge	17	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
365		A	Re-Challenge	18	.	.	.	1.33333	4	3.00	No	Yes	Yes	Yes
366		A	Re-Challenge	19	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
367		A	Re-Challenge	20	.	.	.	1.33333	2	3.00	No	Yes	Yes	Yes
368		A	Induction	2	0	.	0	.	.	.				
369		A	Induction	3	1	.	1	.	.	.				
370		A	Induction	4	1	.	1	.	.	.				
371		A	Induction	5	1	.	1	.	.	.				
372		A	Induction	6	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
	(b) (6)													
373		A	Induction	7	2	.	2	.	.	.				
374		A	Induction	8	2	.	2	.	.	.				
375		A	Induction	9	2	.	2	.	.	.				
376		A	Induction	10	2	.	2	1.33333	.	.				
377		A	Challenge	12	.	.	.	1.33333	4	3.00	Yes	Yes	Yes	Yes
378		A	Challenge	13	.	.	.	1.33333	4	3.00	Yes	Yes	Yes	Yes
379		A	Challenge	14	.	.	.	1.33333	2	3.00	Yes	Yes	Yes	Yes
380		A	Challenge	15	.	.	.	1.33333	2	3.00	Yes	Yes	Yes	Yes
381		A	Re-Challenge	17	.	.	.	1.33333	7	5.00	Yes	Yes	Yes	Yes
382		A	Re-Challenge	18	.	.	.	1.33333	7	5.00	Yes	Yes	Yes	Yes
383		A	Re-Challenge	19	.	.	.	1.33333	4	5.00	Yes	Yes	Yes	Yes
384		A	Re-Challenge	20	.	.	.	1.33333	2	5.00	Yes	Yes	Yes	Yes
385		A	Induction	2	1	.	1	.	.	.				
386		A	Induction	3	1	.	1	.	.	.				
387		A	Induction	4	1	.	1	.	.	.				
388		A	Induction	5	1	.	1	.	.	.				
389		A	Induction	6	1	.	1	.	.	.				
390		A	Induction	7	4	.	4	.	.	.				
391		A	Induction	8	4	1	4	.	.	.				
392		A	Induction	9	4	4	4	.	.	.				
393		A	Induction	10	4	4	4	2.33333	.	.				
394		A	Challenge	12	.	.	.	2.33333	4	3.50	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
395	(b) (6)	A	Challenge	13	.	.	.	2.33333	4	3.50	Yes	Yes	Yes	Yes
396		A	Challenge	14	.	.	.	2.33333	4	3.50	Yes	Yes	Yes	Yes
397		A	Challenge	15	.	.	.	2.33333	2	3.50	Yes	Yes	Yes	Yes
398		A	Re-Challenge	17	.	.	.	2.33333	7	5.75	Yes	Yes	Yes	Yes
399		A	Re-Challenge	18	.	.	.	2.33333	4	5.75	Yes	Yes	Yes	Yes
400		A	Re-Challenge	19	.	.	.	2.33333	7	5.75	Yes	Yes	Yes	Yes
401		A	Re-Challenge	20	.	.	.	2.33333	5	5.75	Yes	Yes	Yes	Yes
402		A	Induction	2	1	.	1	.	.	.				
403		A	Induction	3	1	.	1	.	.	.				
404		A	Induction	4	1	.	1	.	.	.				
405		A	Induction	5	2	.	2	.	.	.				
406		A	Induction	6	1	.	1	.	.	.				
407		A	Induction	7	2	.	2	.	.	.				
408		A	Induction	8	2	.	2	.	.	.				
409		A	Induction	9	2	.	2	.	.	.				
410		A	Induction	10	2	.	2	1.55556	.	.				
411		A	Challenge	12	.	.	.	1.55556	2	2.00	No	Yes	Yes	Yes
412		A	Challenge	13	.	.	.	1.55556	2	2.00	No	Yes	Yes	Yes
413		A	Challenge	14	.	.	.	1.55556	2	2.00	No	Yes	Yes	Yes
414		A	Challenge	15	.	.	.	1.55556	2	2.00	No	Yes	Yes	Yes
415		A	Re-Challenge	17	.	.	.	1.55556	4	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
416	(b) (6)	A	Re-Challenge	18	.	.	.	1.55556	4	3.00	No	Yes	Yes	Yes
417		A	Re-Challenge	19	.	.	.	1.55556	2	3.00	No	Yes	Yes	Yes
418		A	Re-Challenge	20	.	.	.	1.55556	2	3.00	No	Yes	Yes	Yes
419		A	Induction	2	1	.	1	.	.	.				
420		A	Induction	3	1	.	1	.	.	.				
421		A	Induction	4	1	.	1	.	.	.				
422		A	Induction	5	1	.	1	.	.	.				
423		A	Induction	6	2	.	2	.	.	.				
424		A	Induction	7	2	.	2	.	.	.				
425		A	Induction	8	2	.	2	.	.	.				
426		A	Induction	9	2	.	2	.	.	.				
427		A	Induction	10	2	.	2	1.55556	.	.				
428		A	Challenge	12	.	.	.	1.55556	4	3.50	Yes	Yes	Yes	Yes
429		A	Challenge	13	.	.	.	1.55556	4	3.50	Yes	Yes	Yes	Yes
430		A	Challenge	14	.	.	.	1.55556	4	3.50	Yes	Yes	Yes	Yes
431		A	Challenge	15	.	.	.	1.55556	2	3.50	Yes	Yes	Yes	Yes
432		A	Re-Challenge	17	.	.	.	1.55556	4	3.50	Yes	Yes	Yes	Yes
433		A	Re-Challenge	18	.	.	.	1.55556	4	3.50	Yes	Yes	Yes	Yes
434		A	Re-Challenge	19	.	.	.	1.55556	4	3.50	Yes	Yes	Yes	Yes
435		A	Re-Challenge	20	.	.	.	1.55556	2	3.50	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
436	(b) (6)	A	Induction	2	1	.	1	.	.	.				
437		A	Induction	3	1	.	1	.	.	.				
438		A	Induction	4	1	.	1	.	.	.				
439		A	Induction	5	1	.	1	.	.	.				
440		A	Induction	6	2	.	2	.	.	.				
441		A	Induction	7	2	.	2	.	.	.				
442		A	Induction	8	2	.	2	.	.	.				
443		A	Induction	9	2	.	2	.	.	.				
444		A	Induction	10	2	.	2	1.55556	.	.				
445		A	Challenge	12	.	.	.	1.55556	2	1.75	No	Yes	Yes	Yes
446		A	Challenge	13	.	.	.	1.55556	1	1.75	No	Yes	Yes	Yes
447		A	Challenge	14	.	.	.	1.55556	2	1.75	No	Yes	Yes	Yes
448		A	Challenge	15	.	.	.	1.55556	2	1.75	No	Yes	Yes	Yes
449		A	Re-Challenge	17	.	.	.	1.55556	4	3.00	No	Yes	Yes	Yes
450		A	Re-Challenge	18	.	.	.	1.55556	4	3.00	No	Yes	Yes	Yes
451		A	Re-Challenge	19	.	.	.	1.55556	2	3.00	No	Yes	Yes	Yes
452		A	Re-Challenge	20	.	.	.	1.55556	2	3.00	No	Yes	Yes	Yes
453		A	Induction	2	0	.	0	.	.	.				
454		A	Induction	3	1	.	1	.	.	.				
455		A	Induction	4	1	.	1	.	.	.				
456		A	Induction	5	1	.	1	.	.	.				
457		A	Induction	6	2	.	2	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
458	(b) (6)	A	Induction	7	1	.	1	.	.	.				
459		A	Induction	8	2	.	2	.	.	.				
460		A	Induction	9	2	.	2	.	.	.				
461		A	Induction	10	2	.	2	1.33333	.	.				
462		A	Challenge	12	.	.	.	1.33333	0	2.00	Yes	Yes	Yes	Yes
463		A	Challenge	13	.	.	.	1.33333	2	2.00	Yes	Yes	Yes	Yes
464		A	Challenge	14	.	.	.	1.33333	4	2.00	Yes	Yes	Yes	Yes
465		A	Challenge	15	.	.	.	1.33333	2	2.00	Yes	Yes	Yes	Yes
466		A	Re-Challenge	17	.	.	.	1.33333	7	4.75	Yes	Yes	Yes	Yes
467		A	Re-Challenge	18	.	.	.	1.33333	5	4.75	Yes	Yes	Yes	Yes
468		A	Re-Challenge	19	.	.	.	1.33333	4	4.75	Yes	Yes	Yes	Yes
469		A	Re-Challenge	20	.	.	.	1.33333	3	4.75	Yes	Yes	Yes	Yes
470		A	Induction	2	1	.	1	.	.	.				
471		A	Induction	3	1	.	1	.	.	.				
472		A	Induction	4	1	.	1	.	.	.				
473		A	Induction	5	1	.	1	.	.	.				
474		A	Induction	6	2	.	2	.	.	.				
475		A	Induction	7	2	.	2	.	.	.				
476		A	Induction	8	4	.	4	.	.	.				
477		A	Induction	9	2	1	4	.	.	.				
478		A	Induction	10	2	4	4	2.22222	.	.				
479		A	Challenge	12	.	.	.	2.22222	2	3.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
480	(b) (6)	A	Challenge	13	.	.	.	2.22222	4	3.50	No	Yes	Yes	Yes
481		A	Challenge	14	.	.	.	2.22222	4	3.50	No	Yes	Yes	Yes
482		A	Challenge	15	.	.	.	2.22222	4	3.50	No	Yes	Yes	Yes
483		A	Re-Challenge	17	.	.	.	2.22222	4	3.00	No	Yes	Yes	Yes
484		A	Re-Challenge	18	.	.	.	2.22222	4	3.00	No	Yes	Yes	Yes
485		A	Re-Challenge	19	.	.	.	2.22222	2	3.00	No	Yes	Yes	Yes
486		A	Re-Challenge	20	.	.	.	2.22222	2	3.00	No	Yes	Yes	Yes
487		A	Induction	2	1	.	1	.	.	.				
488		A	Induction	3	1	.	1	.	.	.				
489		A	Induction	4	1	.	1	.	.	.				
490		A	Induction	5	1	.	1	.	.	.				
491		A	Induction	6	1	.	1	.	.	.				
492		A	Induction	7	2	.	2	.	.	.				
493		A	Induction	8	2	.	2	.	.	.				
494		A	Induction	9	2	.	2	.	.	.				
495		A	Induction	10	2	.	2	1.44444	.	.				
496		A	Challenge	12	.	.	.	1.44444	4	4.00	Yes	Yes	Yes	
497		A	Challenge	13	.	.	.	1.44444	4	4.00	Yes	Yes	Yes	
498		A	Challenge	14	.	.	.	1.44444	4	4.00	Yes	Yes	Yes	
499		A	Challenge	15	.	.	.	1.44444	4	4.00	Yes	Yes	Yes	
500		A	Induction	2	1	.	1	.	.	.				
501		A	Induction	3	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
	(b) (6)													
502		A	Induction	4	1	.	1	.	.	.				
503		A	Induction	5	1	.	1	.	.	.				
504		A	Induction	6	1	.	1	.	.	.				
505		A	Induction	7	1	.	1	.	.	.				
506		A	Induction	8	2	.	2	.	.	.				
507		A	Induction	9	2	.	2	.	.	.				
508		A	Induction	10	2	.	2	1.33333	.	.				
509		A	Challenge	12	.	.	.	1.33333	2	3.50	Yes	Yes	Yes	Yes
510		A	Challenge	13	.	.	.	1.33333	4	3.50	Yes	Yes	Yes	Yes
511		A	Challenge	14	.	.	.	1.33333	4	3.50	Yes	Yes	Yes	Yes
512		A	Challenge	15	.	.	.	1.33333	4	3.50	Yes	Yes	Yes	Yes
513		A	Re-Challenge	17	.	.	.	1.33333	4	3.50	Yes	Yes	Yes	Yes
514		A	Re-Challenge	18	.	.	.	1.33333	4	3.50	Yes	Yes	Yes	Yes
515		A	Re-Challenge	19	.	.	.	1.33333	4	3.50	Yes	Yes	Yes	Yes
516		A	Re-Challenge	20	.	.	.	1.33333	2	3.50	Yes	Yes	Yes	Yes
517		A	Induction	2	1	.	1	.	.	.				
518		A	Induction	3	1	.	1	.	.	.				
519		A	Induction	4	1	.	1	.	.	.				
520		A	Induction	5	1	.	1	.	.	.				
521		A	Induction	6	1	.	1	.	.	.				
522		A	Induction	7	2	.	2	.	.	.				
523		A	Induction	8	2	.	2	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
524	(b) (6)	A	Induction	9	2	.	2	.	.	.				
525		A	Induction	10	2	.	2	1.44444	.	.				
526		A	Challenge	12	.	.	.	1.44444	4	4.00	Yes	Yes	Yes	
527		A	Challenge	13	.	.	.	1.44444	4	4.00	Yes	Yes	Yes	
528		A	Challenge	14	.	.	.	1.44444	4	4.00	Yes	Yes	Yes	
529		A	Challenge	15	.	.	.	1.44444	4	4.00	Yes	Yes	Yes	
530		B	Induction	2	1	.	1	.	.	.				
531		B	Induction	3	2	.	2	.	.	.				
532		B	Induction	4	2	.	2	.	.	.				
533		B	Induction	5	2	.	2	.	.	.				
534		B	Induction	6	2	.	2	.	.	.				
535		B	Induction	7	4	.	4	.	.	.				
536		B	Induction	8	4	2	4	.	.	.				
537		B	Induction	9	4	2	4	.	.	.				
538		B	Induction	10	4	4	4	2.77778	.	.				
539		B	Challenge	12	.	.	.	2.77778	7	5.50	Yes	Yes	Yes	Yes
540		B	Challenge	13	.	.	.	2.77778	7	5.50	Yes	Yes	Yes	Yes
541		B	Challenge	14	.	.	.	2.77778	4	5.50	Yes	Yes	Yes	Yes
542		B	Challenge	15	.	.	.	2.77778	4	5.50	Yes	Yes	Yes	Yes
543		B	Re-Challenge	17	.	.	.	2.77778	7	8.50	Yes	Yes	Yes	Yes
544		B	Re-Challenge	18	.	.	.	2.77778	10	8.50	Yes	Yes	Yes	Yes
545		B	Re-Challenge	19	.	.	.	2.77778	10	8.50	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
546	(b) (6)	B	Re-Challenge	20	.	.	.	2.77778	7	8.50	Yes	Yes	Yes	Yes
547		B	Induction	2	1	.	1	.	.	.				
548		B	Induction	3	1	.	1	.	.	.				
549		B	Induction	4	1	.	1	.	.	.				
550		B	Induction	5	1	.	1	.	.	.				
551		B	Induction	6	2	.	2	.	.	.				
552		B	Induction	7	1	.	1	.	.	.				
553		B	Induction	8	2	.	2	.	.	.				
554		B	Induction	9	2	.	2	.	.	.				
555		B	Induction	10	4	.	4	1.66667	.	.				
556		B	Challenge	12	.	.	.	1.66667	4	2.50	No	Yes	Yes	Yes
557		B	Challenge	13	.	.	.	1.66667	2	2.50	No	Yes	Yes	Yes
558		B	Challenge	14	.	.	.	1.66667	2	2.50	No	Yes	Yes	Yes
559		B	Challenge	15	.	.	.	1.66667	2	2.50	No	Yes	Yes	Yes
560		B	Re-Challenge	17	.	.	.	1.66667	4	3.75	No	Yes	Yes	Yes
561		B	Re-Challenge	18	.	.	.	1.66667	7	3.75	No	Yes	Yes	Yes
562		B	Re-Challenge	19	.	.	.	1.66667	2	3.75	No	Yes	Yes	Yes
563		B	Re-Challenge	20	.	.	.	1.66667	2	3.75	No	Yes	Yes	Yes
564		B	Induction	2	1	.	1	.	.	.				
565		B	Induction	3	1	.	1	.	.	.				
566		B	Induction	4	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
567	(b) (6)	B	Induction	5	1	.	1	.	.	.				
568		B	Induction	6	1	.	1	.	.	.				
569		B	Induction	7	1	.	1	.	.	.				
570		B	Induction	8	2	.	2	.	.	.				
571		B	Induction	9	2	.	2	.	.	.				
572		B	Induction	10	2	.	2	1.33333	.	.				
573		B	Challenge	12	.	.	.	1.33333	1	1.75	No	Yes	Yes	Yes
574		B	Challenge	13	.	.	.	1.33333	2	1.75	No	Yes	Yes	Yes
575		B	Challenge	14	.	.	.	1.33333	2	1.75	No	Yes	Yes	Yes
576		B	Challenge	15	.	.	.	1.33333	2	1.75	No	Yes	Yes	Yes
577		B	Re-Challenge	17	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
578		B	Re-Challenge	18	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
579		B	Re-Challenge	19	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
580		B	Re-Challenge	20	.	.	.	1.33333	2	2.00	No	Yes	Yes	Yes
581		B	Induction	2	1	.	1	.	.	.				
582		B	Induction	3	1	.	1	.	.	.				
583		B	Induction	4	1	.	1	.	.	.				
584		B	Induction	5	1	.	1	.	.	.				
585		B	Induction	6	1	.	1	.	.	.				
586		B	Induction	7	4	.	4	.	.	.				
587		B	Induction	8	4	1	4	.	.	.				
588		B	Induction	9	4	4	4	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
589	(b) (6)	B	Induction	10	4	5	7	2.66667	.	.				
590		B	Challenge	12	.	.	.	2.66667	4	4.50	No	Yes	Yes	Yes
591		B	Challenge	13	.	.	.	2.66667	6	4.50	No	Yes	Yes	Yes
592		B	Challenge	14	.	.	.	2.66667	4	4.50	No	Yes	Yes	Yes
593		B	Challenge	15	.	.	.	2.66667	4	4.50	No	Yes	Yes	Yes
594		B	Re-Challenge	17	.	.	.	2.66667	4	4.00	No	Yes	Yes	Yes
595		B	Re-Challenge	18	.	.	.	2.66667	4	4.00	No	Yes	Yes	Yes
596		B	Re-Challenge	19	.	.	.	2.66667	2	4.00	No	Yes	Yes	Yes
597		B	Re-Challenge	20	.	.	.	2.66667	6	4.00	No	Yes	Yes	Yes
598		B	Induction	2	1	.	1	.	.	.				
599		B	Induction	3	1	.	1	.	.	.				
600		B	Induction	4	1	.	1	.	.	.				
601		B	Induction	5	1	.	1	.	.	.				
602		B	Induction	6	1	.	1	.	.	.				
603		B	Induction	7	4	.	4	.	.	.				
604		B	Induction	8	4	1	4	.	.	.				
605		B	Induction	9	4	4	4	.	.	.				
606		B	Induction	10	4	5	5	2.44444	.	.				
607		B	Challenge	12	.	.	.	2.44444	2	4.25	Yes	Yes	Yes	Yes
608		B	Challenge	13	.	.	.	2.44444	7	4.25	Yes	Yes	Yes	Yes
609		B	Challenge	14	.	.	.	2.44444	4	4.25	Yes	Yes	Yes	Yes
610		B	Challenge	15	.	.	.	2.44444	4	4.25	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
611	(b) (6)	B	Re-Challenge	17	.	.	.	2.44444	7	7.00	Yes	Yes	Yes	Yes
612		B	Re-Challenge	18	.	.	.	2.44444	8	7.00	Yes	Yes	Yes	Yes
613		B	Re-Challenge	19	.	.	.	2.44444	9	7.00	Yes	Yes	Yes	Yes
614		B	Re-Challenge	20	.	.	.	2.44444	4	7.00	Yes	Yes	Yes	Yes
615		B	Induction	2	1	.	1	.	.	.				
616		B	Induction	3	1	.	1	.	.	.				
617		B	Induction	4	1	.	1	.	.	.				
618		B	Induction	5	1	.	1	.	.	.				
619		B	Induction	6	2	.	2	.	.	.				
620		B	Induction	7	2	.	2	.	.	.				
621		B	Induction	8	2	.	2	.	.	.				
622		B	Induction	9	2	.	2	.	.	.				
623		B	Induction	10	2	.	2	1.55556	.	.				
624		B	Challenge	12	.	.	.	1.55556	7	3.75	Yes	Yes	Yes	
625		B	Challenge	13	.	.	.	1.55556	4	3.75	Yes	Yes	Yes	
626		B	Challenge	14	.	.	.	1.55556	2	3.75	Yes	Yes	Yes	
627		B	Challenge	15	.	.	.	1.55556	2	3.75	Yes	Yes	Yes	
628		B	Induction	2	1	.	1	.	.	.				
629		B	Induction	3	1	.	1	.	.	.				
630		B	Induction	4	1	.	1	.	.	.				
631		B	Induction	5	1	.	1	.	.	.				
632		B	Induction	6	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
633	(b) (6)	B	Induction	7	4	.	4	.	.	.				
634		B	Induction	8	2	1	4	.	.	.				
635		B	Induction	9	4	4	4	.	.	.				
636		B	Induction	10	4	4	4	2.33333	.	.				
637		B	Challenge	12	.	.	.	2.33333	4	3.75	Yes	Yes	Yes	Yes
638		B	Challenge	13	.	.	.	2.33333	4	3.75	Yes	Yes	Yes	Yes
639		B	Challenge	14	.	.	.	2.33333	5	3.75	Yes	Yes	Yes	Yes
640		B	Challenge	15	.	.	.	2.33333	2	3.75	Yes	Yes	Yes	Yes
641		B	Re-Challenge	17	.	.	.	2.33333	7	7.50	Yes	Yes	Yes	Yes
642		B	Re-Challenge	18	.	.	.	2.33333	7	7.50	Yes	Yes	Yes	Yes
643		B	Re-Challenge	19	.	.	.	2.33333	9	7.50	Yes	Yes	Yes	Yes
644		B	Re-Challenge	20	.	.	.	2.33333	7	7.50	Yes	Yes	Yes	Yes
645		B	Induction	2	1	.	1	.	.	.				
646		B	Induction	3	1	.	1	.	.	.				
647		B	Induction	4	1	.	1	.	.	.				
648		B	Induction	5	1	.	1	.	.	.				
649		B	Induction	6	2	.	2	.	.	.				
650		B	Induction	7	4	.	4	.	.	.				
651		B	Induction	8	4	2	4	.	.	.				
652		B	Induction	9	4	2	4	.	.	.				
653		B	Induction	10	4	5	5	2.55556	.	.				
654		B	Challenge	12	.	.	.	2.55556	4	4.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
655	(b) (6)	B	Challenge	13	.	.	.	2.55556	4	4.50	No	Yes	Yes	Yes
656		B	Challenge	14	.	.	.	2.55556	6	4.50	No	Yes	Yes	Yes
657		B	Challenge	15	.	.	.	2.55556	4	4.50	No	Yes	Yes	Yes
658		B	Re-Challenge	17	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
659		B	Re-Challenge	18	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
660		B	Re-Challenge	19	.	.	.	2.55556	2	3.50	No	Yes	Yes	Yes
661		B	Re-Challenge	20	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
662		B	Induction	2	0	.	0	.	.	.				
663		B	Induction	3	1	.	1	.	.	.				
664		B	Induction	4	1	.	1	.	.	.				
665		B	Induction	5	1	.	1	.	.	.				
666		B	Induction	6	2	.	2	.	.	.				
667		B	Induction	7	2	.	2	.	.	.				
668		B	Induction	8	2	.	2	.	.	.				
669		B	Induction	9	4	.	4	.	.	.				
670		B	Induction	10	4	2	4	1.88889	.	.				
671		B	Challenge	12	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
672		B	Challenge	13	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
673		B	Challenge	14	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
674		B	Challenge	15	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
675		B	Re-Challenge	17	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
676	(b) (6)	B	Re-Challenge	18	.	.	.	1.88889	4	3.00	No	Yes	Yes	Yes
677		B	Re-Challenge	19	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
678		B	Re-Challenge	20	.	.	.	1.88889	2	3.00	No	Yes	Yes	Yes
679		B	Induction	2	1	.	1	.	.	.				
680		B	Induction	3	1	.	1	.	.	.				
681		B	Induction	4	1	.	1	.	.	.				
682		B	Induction	5	1	.	1	.	.	.				
683		B	Induction	6	2	.	2	.	.	.				
684		B	Induction	7	2	.	2	.	.	.				
685		B	Induction	8	4	.	4	.	.	.				
686		B	Induction	9	4	2	4	.	.	.				
687		B	Induction	10	4	4	4	2.22222	.	.				
688		B	Challenge	12	.	.	.	2.22222	7	5.50	Yes	Yes	Yes	
689		B	Challenge	13	.	.	.	2.22222	5	5.50	Yes	Yes	Yes	
690		B	Challenge	14	.	.	.	2.22222	6	5.50	Yes	Yes	Yes	
691		B	Challenge	15	.	.	.	2.22222	4	5.50	Yes	Yes	Yes	
692		B	Induction	2	2	.	2	.	.	.				
693		B	Induction	3	1	.	1	.	.	.				
694		B	Induction	4	1	.	1	.	.	.				
695		B	Induction	5	1	.	1	.	.	.				
696		B	Induction	6	2	.	2	.	.	.				
697		B	Induction	7	2	.	2	.	.	.				
698		B	Induction	8	4	.	4	.	.	.				

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	(b) (6)													
699		B	Induction	9	4	2	4	.	.	.				
700		B	Induction	10	4	4	4	2.33333	.	.				
701		B	Challenge	12	.	.	.	2.33333	4	2.50	No	Yes	Yes	Yes
702		B	Challenge	13	.	.	.	2.33333	2	2.50	No	Yes	Yes	Yes
703		B	Challenge	14	.	.	.	2.33333	2	2.50	No	Yes	Yes	Yes
704		B	Challenge	15	.	.	.	2.33333	2	2.50	No	Yes	Yes	Yes
705		B	Re-Challenge	17	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
706		B	Re-Challenge	18	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
707		B	Re-Challenge	19	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
708		B	Re-Challenge	20	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
709		B	Induction	2	0	.	0	.	.	.				
710		B	Induction	3	1	.	1	.	.	.				
711		B	Induction	4	1	.	1	.	.	.				
712		B	Induction	5	1	.	1	.	.	.				
713		B	Induction	6	1	.	1	.	.	.				
714		B	Induction	7	1	.	1	.	.	.				
715		B	Induction	8	2	.	2	.	.	.				
716		B	Induction	9	2	.	2	.	.	.				
717		B	Induction	10	2	.	2	1.22222	.	.				
718		B	Challenge	12	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
719		B	Challenge	13	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
720		B	Challenge	14	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
721	(b) (6)	B	Challenge	15	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
722		B	Re-Challenge	17	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
723		B	Re-Challenge	18	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
724		B	Re-Challenge	19	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
725		B	Re-Challenge	20	.	.	.	1.22222	2	2.00	No	Yes	Yes	Yes
726		B	Induction	2	1	.	1	.	.	.				
727		B	Induction	3	1	.	1	.	.	.				
728		B	Induction	4	1	.	1	.	.	.				
729		B	Induction	5	1	.	1	.	.	.				
730		B	Induction	6	2	.	2	.	.	.				
731		B	Induction	7	2	.	2	.	.	.				
732		B	Induction	8	2	.	2	.	.	.				
733		B	Induction	9	5	.	5	.	.	.				
734		B	Induction	10	4	4	5	2.22222	.	.				
735		B	Challenge	12	.	.	.	2.22222	10	7.00	Yes	Yes	Yes	Yes
736		B	Challenge	13	.	.	.	2.22222	7	7.00	Yes	Yes	Yes	Yes
737		B	Challenge	14	.	.	.	2.22222	7	7.00	Yes	Yes	Yes	Yes
738		B	Challenge	15	.	.	.	2.22222	4	7.00	Yes	Yes	Yes	Yes
739		B	Re-Challenge	17	.	.	.	2.22222	7	6.75	Yes	Yes	Yes	Yes
740		B	Re-Challenge	18	.	.	.	2.22222	6	6.75	Yes	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
741	(b) (6)	B	Re-Challenge	19	.	.	.	2.22222	7	6.75	Yes	Yes	Yes	Yes
742		B	Re-Challenge	20	.	.	.	2.22222	7	6.75	Yes	Yes	Yes	Yes
743		B	Induction	2	1	.	1	.	.	.				
744		B	Induction	3	1	.	1	.	.	.				
745		B	Induction	4	2	.	2	.	.	.				
746		B	Induction	5	1	.	1	.	.	.				
747		B	Induction	6	1	.	1	.	.	.				
748		B	Induction	7	2	.	2	.	.	.				
749		B	Induction	8	2	.	2	.	.	.				
750		B	Induction	9	2	.	2	.	.	.				
751		B	Induction	10	4	.	4	1.77778	.	.				
752		B	Challenge	12	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
753		B	Challenge	13	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
754		B	Challenge	14	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
755		B	Challenge	15	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
756		B	Re-Challenge	17	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
757		B	Re-Challenge	18	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
758		B	Re-Challenge	19	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
759		B	Re-Challenge	20	.	.	.	1.77778	2	2.00	No	Yes	Yes	Yes
760		B	Induction	2	1	.	1	.	.	.				
761		B	Induction	3	1	.	1	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
	(b) (6)													
762		B	Induction	4	1	.	1	.	.	.				
763		B	Induction	5	2	.	2	.	.	.				
764		B	Induction	6	2	.	2	.	.	.				
765		B	Induction	7	2	.	2	.	.	.				
766		B	Induction	8	2	.	2	.	.	.				
767		B	Induction	9	4	.	4	.	.	.				
768		B	Induction	10	4	2	4	2.11111	.	.				
769		B	Challenge	12	.	.	.	2.11111	4	2.50	No	Yes	Yes	Yes
770		B	Challenge	13	.	.	.	2.11111	2	2.50	No	Yes	Yes	Yes
771		B	Challenge	14	.	.	.	2.11111	2	2.50	No	Yes	Yes	Yes
772		B	Challenge	15	.	.	.	2.11111	2	2.50	No	Yes	Yes	Yes
773		B	Re-Challenge	17	.	.	.	2.11111	4	3.00	No	Yes	Yes	Yes
774		B	Re-Challenge	18	.	.	.	2.11111	4	3.00	No	Yes	Yes	Yes
775		B	Re-Challenge	19	.	.	.	2.11111	2	3.00	No	Yes	Yes	Yes
776		B	Re-Challenge	20	.	.	.	2.11111	2	3.00	No	Yes	Yes	Yes
777		B	Induction	2	1	.	1	.	.	.				
778		B	Induction	3	1	.	1	.	.	.				
779		B	Induction	4	1	.	1	.	.	.				
780		B	Induction	5	1	.	1	.	.	.				
781		B	Induction	6	2	.	2	.	.	.				
782		B	Induction	7	2	.	2	.	.	.				
783		B	Induction	8	4	.	4	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
784	(b) (6)	B	Induction	9	4	4	4	.	.	.				
785		B	Induction	10	4	4	4	2.22222	.	.				
786		B	Challenge	12	.	.	.	2.22222	7	5.25	Yes	Yes	Yes	Yes
787		B	Challenge	13	.	.	.	2.22222	5	5.25	Yes	Yes	Yes	Yes
788		B	Challenge	14	.	.	.	2.22222	5	5.25	Yes	Yes	Yes	Yes
789		B	Challenge	15	.	.	.	2.22222	4	5.25	Yes	Yes	Yes	Yes
790		B	Re-Challenge	17	.	.	.	2.22222	7	5.50	Yes	Yes	Yes	Yes
791		B	Re-Challenge	18	.	.	.	2.22222	5	5.50	Yes	Yes	Yes	Yes
792		B	Re-Challenge	19	.	.	.	2.22222	6	5.50	Yes	Yes	Yes	Yes
793		B	Re-Challenge	20	.	.	.	2.22222	4	5.50	Yes	Yes	Yes	Yes
794		B	Induction	2	1	.	1	.	.	.				
795		B	Induction	3	1	.	1	.	.	.				
796		B	Induction	4	1	.	1	.	.	.				
797		B	Induction	5	1	.	1	.	.	.				
798		B	Induction	6	1	.	1	.	.	.				
799		B	Induction	7	2	.	2	.	.	.				
800		B	Induction	8	2	.	2	.	.	.				
801		B	Induction	9	2	.	2	.	.	.				
802		B	Induction	10	2	.	2	1.44444	.	.				
803		B	Challenge	12	.	.	.	1.44444	4	3.00	Yes	Yes	Yes	
804		B	Challenge	13	.	.	.	1.44444	2	3.00	Yes	Yes	Yes	
805		B	Challenge	14	.	.	.	1.44444	4	3.00	Yes	Yes	Yes	

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
806	(b) (6)	B	Challenge	15	.	.	.	1.44444	2	3.00	Yes	Yes	Yes	
807		B	Induction	2	1	.	1	.	.	.				
808		B	Induction	3	1	.	1	.	.	.				
809		B	Induction	4	1	.	1	.	.	.				
810		B	Induction	5	1	.	1	.	.	.				
811		B	Induction	6	2	.	2	.	.	.				
812		B	Induction	7	2	.	2	.	.	.				
813		B	Induction	8	2	.	2	.	.	.				
814		B	Induction	9	2	.	2	.	.	.				
815		B	Induction	10	2	.	2	1.55556	.	.				
816		B	Challenge	12	.	.	.	1.55556	4	3.00	Yes	Yes	Yes	
817		B	Challenge	13	.	.	.	1.55556	2	3.00	Yes	Yes	Yes	
818		B	Challenge	14	.	.	.	1.55556	4	3.00	Yes	Yes	Yes	
819		B	Challenge	15	.	.	.	1.55556	2	3.00	Yes	Yes	Yes	
820		B	Induction	2	1	.	1	.	.	.				
821		B	Induction	3	1	.	1	.	.	.				
822		B	Induction	4	1	.	1	.	.	.				
823		B	Induction	5	1	.	1	.	.	.				
824		B	Induction	6	1	.	1	.	.	.				
825		B	Induction	7	2	.	2	.	.	.				
826		B	Induction	8	2	.	2	.	.	.				
827		B	Induction	9	4	.	4	.	.	.				
828		B	Induction	10	4	4	4	1.88889	.	.				
829		B	Challenge	12	.	.	.	1.88889	4	2.50	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
830	(b) (6)	B	Challenge	13	.	.	.	1.88889	2	2.50	No	Yes	Yes	Yes
831		B	Challenge	14	.	.	.	1.88889	2	2.50	No	Yes	Yes	Yes
832		B	Challenge	15	.	.	.	1.88889	2	2.50	No	Yes	Yes	Yes
833		B	Re-Challenge	17	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
834		B	Re-Challenge	18	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
835		B	Re-Challenge	19	.	.	.	1.88889	4	3.50	No	Yes	Yes	Yes
836		B	Re-Challenge	20	.	.	.	1.88889	2	3.50	No	Yes	Yes	Yes
837		B	Induction	2	1	.	1	.	.	.				
838		B	Induction	3	1	.	1	.	.	.				
839		B	Induction	4	1	.	1	.	.	.				
840		B	Induction	5	2	.	2	.	.	.				
841		B	Induction	6	2	.	2	.	.	.				
842		B	Induction	7	2	.	2	.	.	.				
843		B	Induction	8	4	.	4	.	.	.				
844		B	Induction	9	4	2	4	.	.	.				
845		B	Induction	10	4	4	4	2.33333	.	.				
846		B	Challenge	12	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
847		B	Challenge	13	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
848		B	Challenge	14	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
849		B	Challenge	15	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
850		B	Re-Challenge	17	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
851	(b) (6)	B	Re-Challenge	18	.	.	.	2.33333	4	3.00	No	Yes	Yes	Yes
852		B	Re-Challenge	19	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
853		B	Re-Challenge	20	.	.	.	2.33333	2	3.00	No	Yes	Yes	Yes
854		B	Induction	2	1	.	1	.	.	.				
855		B	Induction	3	1	.	1	.	.	.				
856		B	Induction	4	2	.	2	.	.	.				
857		B	Induction	5	1	.	1	.	.	.				
858		B	Induction	6	2	.	2	.	.	.				
859		B	Induction	7	6	.	6	.	.	.				
860		B	Induction	8	4	1	6	.	.	.				
861		B	Induction	9	4	4	6	.	.	.				
862		B	Induction	10	4	4	6	3.44444	.	.				
863		B	Challenge	12	.	.	.	3.44444	4	3.50	Yes	Yes	Yes	Yes
864		B	Challenge	13	.	.	.	3.44444	4	3.50	Yes	Yes	Yes	Yes
865		B	Challenge	14	.	.	.	3.44444	4	3.50	Yes	Yes	Yes	Yes
866		B	Challenge	15	.	.	.	3.44444	2	3.50	Yes	Yes	Yes	Yes
867		B	Re-Challenge	17	.	.	.	3.44444	7	5.25	Yes	Yes	Yes	Yes
868		B	Re-Challenge	18	.	.	.	3.44444	4	5.25	Yes	Yes	Yes	Yes
869		B	Re-Challenge	19	.	.	.	3.44444	5	5.25	Yes	Yes	Yes	Yes
870		B	Re-Challenge	20	.	.	.	3.44444	5	5.25	Yes	Yes	Yes	Yes

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871	(b) (6)	B	Induction	2	1	.	1	.	.	.				
872		B	Induction	3	1	.	1	.	.	.				
873		B	Induction	4	1	.	1	.	.	.				
874		B	Induction	5	1	.	1	.	.	.				
875		B	Induction	6	2	.	2	.	.	.				
876		B	Induction	7	2	.	2	.	.	.				
877		B	Induction	8	5	.	5	.	.	.				
878		B	Induction	9	4	2	5	.	.	.				
879		B	Induction	10	4	2	5	2.55556	.	.				
880		B	Challenge	12	.	.	.	2.55556	4	3.50	Yes	Yes	Yes	Yes
881		B	Challenge	13	.	.	.	2.55556	4	3.50	Yes	Yes	Yes	Yes
882		B	Challenge	14	.	.	.	2.55556	4	3.50	Yes	Yes	Yes	Yes
883		B	Challenge	15	.	.	.	2.55556	2	3.50	Yes	Yes	Yes	Yes
884		B	Re-Challenge	17	.	.	.	2.55556	4	3.50	Yes	Yes	Yes	Yes
885		B	Re-Challenge	18	.	.	.	2.55556	4	3.50	Yes	Yes	Yes	Yes
886		B	Re-Challenge	19	.	.	.	2.55556	4	3.50	Yes	Yes	Yes	Yes
887		B	Re-Challenge	20	.	.	.	2.55556	2	3.50	Yes	Yes	Yes	Yes
888		B	Induction	2	1	.	1	.	.	.				
889		B	Induction	3	1	.	1	.	.	.				
890		B	Induction	4	2	.	2	.	.	.				
891		B	Induction	5	1	.	1	.	.	.				
892		B	Induction	6	2	.	2	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
893	(b) (6)	B	Induction	7	4	.	4	.	.	.				
894		B	Induction	8	2	1	4	.	.	.				
895		B	Induction	9	4	4	4	.	.	.				
896		B	Induction	10	3	2	4	2.55556	.	.				
897		B	Challenge	12	.	.	.	2.55556	2	3.50	No	Yes	Yes	Yes
898		B	Challenge	13	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
899		B	Challenge	14	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
900		B	Challenge	15	.	.	.	2.55556	4	3.50	No	Yes	Yes	Yes
901		B	Re-Challenge	17	.	.	.	2.55556	4	3.00	No	Yes	Yes	Yes
902		B	Re-Challenge	18	.	.	.	2.55556	4	3.00	No	Yes	Yes	Yes
903		B	Re-Challenge	19	.	.	.	2.55556	2	3.00	No	Yes	Yes	Yes
904		B	Re-Challenge	20	.	.	.	2.55556	2	3.00	No	Yes	Yes	Yes
905		B	Induction	2	1	.	1	.	.	.				
906		B	Induction	3	1	.	1	.	.	.				
907		B	Induction	4	1	.	1	.	.	.				
908		B	Induction	5	1	.	1	.	.	.				
909		B	Induction	6	1	.	1	.	.	.				
910		B	Induction	7	2	.	2	.	.	.				
911		B	Induction	8	2	.	2	.	.	.				
912		B	Induction	9	2	.	2	.	.	.				
913		B	Induction	10	4	.	4	1.66667	.	.				
914		B	Challenge	12	.	.	.	1.66667	2	3.50	Yes	Yes	Yes	

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
915	(b) (6)	B	Challenge	13	.	.	.	1.66667	4	3.50	Yes	Yes	Yes	
916		B	Challenge	14	.	.	.	1.66667	4	3.50	Yes	Yes	Yes	
917		B	Challenge	15	.	.	.	1.66667	4	3.50	Yes	Yes	Yes	
918		B	Induction	2	1	.	1	.	.	.				
919		B	Induction	3	1	.	1	.	.	.				
920		B	Induction	4	1	.	1	.	.	.				
921		B	Induction	5	2	.	2	.	.	.				
922		B	Induction	6	2	.	2	.	.	.				
923		B	Induction	7	2	.	2	.	.	.				
924		B	Induction	8	5	.	5	.	.	.				
925		B	Induction	9	4	2	5	.	.	.				
926		B	Induction	10	4	2	5	2.66667	.	.				
927		B	Challenge	12	.	.	.	2.66667	2	3.50	Yes	Yes	Yes	Yes
928		B	Challenge	13	.	.	.	2.66667	4	3.50	Yes	Yes	Yes	Yes
929		B	Challenge	14	.	.	.	2.66667	4	3.50	Yes	Yes	Yes	Yes
930		B	Challenge	15	.	.	.	2.66667	4	3.50	Yes	Yes	Yes	Yes
931		B	Re-Challenge	17	.	.	.	2.66667	4	3.50	Yes	Yes	Yes	Yes
932		B	Re-Challenge	18	.	.	.	2.66667	4	3.50	Yes	Yes	Yes	Yes
933		B	Re-Challenge	19	.	.	.	2.66667	4	3.50	Yes	Yes	Yes	Yes
934		B	Re-Challenge	20	.	.	.	2.66667	2	3.50	Yes	Yes	Yes	Yes
935		B	Induction	2	1	.	1	.	.	.				
936		B	Induction	3	2	.	2	.	.	.				

Obs	Subject Identifier	Treatment	Study Phase (c)	Visit Number (n)	1st Patch Original Irritation Score in Induction	2nd Patch Original Irritation Score in Induction	Irritation Score after LOCF in Induction	Mean irritation (after LOCF) score across visits	Sensitization Score	Mean Sensitization Score in Challenge/Rechallenge	Mylan's Final Potential Sensitization in Summary.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge	FDA's Potential Sensitization in ReChallenge
937	(b) (6)	B	Induction	4	1	.	1	.	.	.				
938		B	Induction	5	1	.	1	.	.	.				
939		B	Induction	6	2	.	2	.	.	.				
940		B	Induction	7	2	.	2	.	.	.				
941		B	Induction	8	5	.	5	.	.	.				
942		B	Induction	9	4	2	5	.	.	.				
943		B	Induction	10	2	4	5	2.66667	.	.				
944		B	Challenge	12	.	.	.	2.66667	4	4.00	Yes	Yes	Yes	
945		B	Challenge	13	.	.	.	2.66667	4	4.00	Yes	Yes	Yes	
946		B	Challenge	14	.	.	.	2.66667	4	4.00	Yes	Yes	Yes	
947		B	Challenge	15	.	.	.	2.66667	4	4.00	Yes	Yes	Yes	
948		B	Induction	2	1	.	1	.	.	.				
949		B	Induction	3	2	.	2	.	.	.				
950		B	Induction	4	1	.	1	.	.	.				
951		B	Induction	5	2	.	2	.	.	.				
952		B	Induction	6	2	.	2	.	.	.				
953		B	Induction	7	1	.	1	.	.	.				
954		B	Induction	8	2	.	2	.	.	.				
955		B	Induction	9	2	.	2	.	.	.				
956		B	Induction	10	2	.	2	1.66667	.	.				
957		B	Challenge	12	.	.	.	1.66667	2	2.00	Yes	Yes	Yes	
958		B	Challenge	13	.	.	.	1.66667	2	2.00	Yes	Yes	Yes	
959		B	Challenge	14	.	.	.	1.66667	2	2.00	Yes	Yes	Yes	
960		B	Challenge	15	.	.	.	1.66667	2	2.00	Yes	Yes	Yes	


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Yu-Te Wu

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Wanjie Sun

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM TO REVIEW COMPLETED IN JAN 2016

ANDA/Serial Number:	206497
Drug Name:	Methylphenidate Transdermal System 10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
Reference Listed Drug:	Daytrana Transdermal System, 3.3 mg/hr
Applicant:	Mylan Pharmaceuticals Inc
Date(s):	Originally Submitted on 12/13/2013 Response to ECD request on 2/18/2016
Biometrics Division:	DBVIII
Statistical Reviewer:	Wanjie Sun, Ph.D.
Concurring Reviewers:	Yu-te Wu, Ph.D.
Medical Division:	Division of Clinical Review in OGD/OPS/CDER
Clinical Team:	Sunny Tse, Ph.D. Ying Fan, Ph.D.
Keywords:	Sensitization, non-inferiority, matched paired analysis

1 EXECUTIVE SUMMARY

In the original statistical review of A206497, FDA had a very different result in sensitization from the sponsor. Division of Clinical Review sent an ECD request to the sponsor on 2/11/2016 and requested more details about the sensitization analysis. The sponsor submitted a post-hoc sensitization re-analysis on 2/18/2016. The results of post-hoc analyses were different from those of the original submission. FDA and the sponsor had different interpretations regarding one of the criteria used to define sensitization in the FDA guidance of Methylphenidate. The criterion stated that the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were ***generally higher*** than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction. Based on the sponsor's listing of potential sensitization (mptp-12130-statistical-1.pdf), the sponsor interpreted 'generally higher' as the average irritation score from the challenge/re-challenge phase being higher than the average irritation score from the induction phase. However, FDA's clinical and statistical review team interpret 'generally higher' as the maximum irritation score from the challenge/re-challenge phase being higher than all irritation scores from the induction phase. FDA has used this definition on other ANDAs of transdermal systems as well. The purpose of this addendum review is to re-evaluate sensitization data using sponsor's interpretation of 'generally higher' and to compare the results to those of FDA's original analyses.

Conclusions and Recommendations

Sensitization

MPTP 12130:

Using the sponsor's interpretation of 'generally higher' (i.e., in average irritation score):

Among the 66 subjects of FDA's per-protocol population for sensitization (FPPSEN) in Study MPTP 12130, TEST has 9.1 more percentage point of subjects with potential sensitization than RLD (P_T=50.0%, P_R= 40.9%), with the one-sided 95% upper bound of 18.5% for the proportion difference between TEST and RLD: $P_T - P_R$.

Using the FDA's interpretation of 'generally higher' (i.e., in maximum irritation score):

Among the 66 subjects of FDA's per-protocol population for sensitization (FPPSEN) in Study MPTP 12130, TEST has 13.7 more percentage point of subjects with potential sensitization than RLD (P_T=27.3%, P_R= 13.6%), with the one-sided 95% upper bound of 23.7% for the proportion difference between TEST and RLD: $P_T - P_R$.

2 STATISTICAL EVALUATION OF SENSITIZATION STUDY MPTP-12130

2.1 STUDY ENDPOINTS

Primary Endpoint: Potential Sensitization

A) Sponsor's Definition

The sponsor did not provide an explicit definition of potential sensitization in their ECD response submitted on 2/18/2016. However, based on the sponsor's listing (mptp-12130-statistical-1.pdf), the sponsor seemed to have considered a subject to be potentially sensitized if all of the following criteria were met:

a. The subject had at least 1 evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
b. The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were generally higher ***(in average irritation scores)*** than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.
d. If the subject completed a Re-Challenge Phase, the above 3 criteria were met during ***either*** the Challenge Phase ***or*** the Re-Challenge Phase.
e. Scores that resolved before 48 hours were generally considered to be due to irritation instead of sensitization.

B) FDA's Definition by Using the Sponsor's Interpretation of "Generally Higher" (Average Score)

The FDA's definition of 'potential sensitization' by using the sponsor's interpretation of 'Generally higher' is that a subject is considered to be potentially sensitized if all of the following criteria were met:

a. The subject had at least 1 evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
b. The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were generally higher ***(in average irritation scores)*** than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.
d. If the subject completed a Re-Challenge Phase, the above 3 criteria were met during ***both*** the Challenge Phase ***and*** the Re-Challenge Phase.
e. Scores that resolved before 48 hours were generally considered to be due to irritation instead of sensitization.

After the FDA adopted the sponsor's interpretation of 'generally higher', the definitions of the sponsor and the FDA still differ in Criterion d. If a subject completed a re-challenge phase, the sponsor requires criteria a), b) and c) to be met during ***either*** the challenge phase ***o***r the re-challenge phase; whereas the

FDA requires those criteria to be met during ***both*** the challenge phase ***and*** the re-challenge phase, according to the FDA guidance for methylphenidate.

2.2 STATISTICAL METHOD

Sponsor (Post-hoc):

1) The sponsor listed descriptive statistics for the proportion of subjects with potential sensitization (primary endpoint) in each treatment group with no statistical analysis.

2) The sponsor also tested whether the mean irritation score of the test product (TEST) is non-inferior to that of the reference listed drug (RLD) during the challenge phase and the re-challenge phase, respectively. The non-inferiority hypotheses are as follows:

$$H_0: \frac{U_T}{U_R} > 1.25 \text{ (Inferior)}$$

$$H_1: \frac{U_T}{U_R} \leq 1.25 \text{ (Non-inferior)},$$

where U_T and U_R are the mean irritation scores for TEST and RLD during the challenge or re-challenge phase, and 1.25 is a pre-specified non-inferiority margin. The significance level for the NI test of patch irritation is 0.05. Non-inferiority is established if the upper bound (UB) of the one-sided 95% confidence interval of $U_T - 1.25U_R$ is less than or equal to 0.

FDA:

The FDA compared the proportion of subjects with potential sensitization (primary endpoint) between TEST and RLD. Since there are sufficient number of potential sensitization in this study, upper bound (UB) of the one-sided 95% confidence interval of $P_T - P_R$ is provided to aid the clinical reviewers in making a decision on sensitization of this test product.

2.3 SUBJECT DISPOSITION

Per-Protocol (PP) Patch Population for Sensitization (PPSEN):
PPSEN stays the same as in the original statistical review. 66 subjects were included in the PPSEN by both the FDA and the sponsor. Of the 66 subjects, 31 subjects entered the re-challenge phase.

3 STATISTICAL RESULTS

Primary Endpoint: Potential Sensitization

Sponsor's primary endpoint:

In the sponsor's ECD submission (mptp-12130-statistical-1.pdf), 36 TEST (54.6%) vs. 32 RLD (48.5%) out of 66 sponsor's PPSEN subjects had potential sensitization (Table 2).

FDA's primary endpoint:

According to FDA's re-analysis by using the sponsor's interpretation of 'generally higher' (Table 1), 33 TEST (50%) vs. 27 RLD (40.9%) out of 66 FDA's PPSEN subjects had potential sensitization (Table 1). A list of 3 TEST and 5 RLD patches with discrepant results between the sponsor and the FDA's re-analysis is shown in Appendix A.

Among the 66 subjects in the FDA's PPSEN population, 56 (84.9%) subjects had concordant scores (diagonal) between TEST and RLD, and 10 (15.1%) subjects had discordant (off-diagonal) scores. TEST had 33 (P_T =0.50) patches with potential sensitization, and RLD had 27 (P_R = 0.409) patches with potential sensitization. The point estimate of $P_T - P_R$ was 0.091 (Table 2). The one-sided 95% upper bound for $P_T - P_R$ was 0.185. Based on the 95% upper confidence bound for the difference in proportions, the TEST patch might exceed the RLD patch in the proportion of subjects with potential sensitization by at most 18.5 percentage points.

Table 1 Proportion of Subjects with Potential Sensitization (PS) by TEST and RLD in the FDA's PPSEN Population in the Challenge Phase of Study MPTP-12130

	TEST PS		
RLD PS	No	Yes	Total
No	31 (47.0%)	8 (12.1%)	39 (59.1%)
Yes	2 (3.0%)	25 (37.9%)	27 (40.9%)
Total	33 (50.0%)	33 (50.0%)	66 (100%)

Table 2 Non-Inferiority Test for Proportion of Subjects with Potential Sensitization (PS) in the FPPSEN Population in the Challenge Phase of Study MPTP-12130

	Sponsor (mptp-12130-statistical-1.pdf)			**FDA**			
Hypothesis	**P (TEST PS)** P_T **(N=66)**	**P (RLD PS)** P_R **(N=66)**	$P_T - P_R$	**P (TEST PS)** P_T **(N=66)**	**P (RLD PS)** P_R **(N=66)**	$P_T - P_R$	**95%UB of** $P_T - P_R$
H0: $P_T - P_R > \delta$ (Inferior) H1: $P_T - P_R \leq \delta$ (Non-inferior)	54.6%	48.5%	6.1%	50.0%	40.9%	9.1%	18.5%

In summary, if using the sponsor's interpretation of 'generally higher' (i.e., average irritation score rather than maximum irritation score), among the 66 subjects of FDA's PPSEN in Study MPTP 12130, TEST has 9.1 more percentage point of subjects with potential sensitization than RLD (P_T=50.0%, P_R= 40.9%), with the one-sided 95% upper bound of 18.5% for $P_T - P_R$.

COMMENTS ON SPONSOR'S POST-HOC ANALYSIS

The FDA statistical reviewers have the following concerns over the sponsor's post-hoc sensitization analysis:

1) Post-hoc analyses are generally not acceptable. Post hoc analysis consists of choosing statistical methods and looking at the data - after the study has concluded – for patterns that are not specified a priori. The concern is that each time a pattern in the data is considered, a statistical test is effectively performed. This greatly inflates the total number of statistical tests and increases the likelihood that any finding is due to chance alone. A related concern is that once the data have been examined, analysis methods may then be chosen based on known properties of the methods that are more likely to give favorable results with the data values observed.

2) Although the FDA guidance did not explicitly interpret 'generally higher', it did clearly specify that "*If the subject completed a re-challenge phase, the above 3 criteria met during **both** the challenge **and** the re-challenge phases".* Based on the sponsor's listing of potential sensitization (mptp-12130-statistical-1.pdf), the sponsor used a criterion of "*3 criteria met during **either** the challenge **or** the re-challenge phases"*, which does not follow the FDA's guidance for methylphenidate.

3) The sponsor's post hoc statistical analysis tested whether the mean irritation score of the test product (TEST) is non-inferior to that of the reference listed drug (RLD) during the challenge phase and the re-challenge phase, respectively. However, in the FDA guidance, the primary endpoint is potential sensitization rather than the mean irritation score. NI tests of TEST vs RLD in the mean irritation score during the challenge and re-challenge phases do not address whether the TEST is no more sensitizing than the RLD. Therefore, the sponsor's statistical analysis is not appropriate by using a primary endpoint which does not follow the FDA guidance for methylphenidate.

Conclusions and Recommendations

Sensitization

MPTP 12130:

Using the sponsor's interpretation of 'generally higher' (i.e., average irritation score):

Among the 66 subjects of FDA's per-protocol population for sensitization (FPPSEN) in Study MPTP 12130, TEST has 9.1 more percentage point of subjects with potential sensitization than RLD (P_T=50.0%, P_R= 40.9%), with the one-sided 95% upper bound of 18.5% for the proportion difference between TEST and RLD: $P_T - P_R$.

Using the FDA's interpretation of 'generally higher' (i.e., maximum irritation score):

Among the 66 subjects of FDA's per-protocol population for sensitization (FPPSEN) in Study MPTP 12130, TEST has 13.7 more percentage point of subjects with potential sensitization than RLD (P_T=27.3%, P_R= 13.6%), with the one-sided 95% upper bound of 23.7% for the proportion difference between TEST and RLD: $P_T - P_R$.

Appendix A.

Subjects with Discrepant Result of Potential Sensitization between the sponsor and FDA Using the Sponsor's Interpretation of 'Generally Higher'

Obs	Treatment A (TEST) / B (RLD)	Subject Identifier	Study Phase (c)	Visit Number (n)	Irritation Score during Challenge or Rechallenge	Last Irritation Score during Challenge or Rechallenge	Mean irritation score across visits in Challenge	Mean irritation score in Induction	Sponsor's Final Potential Sensitization	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge Phase	FDA's Potential Sensitization in ReChallenge Phase
1	A	(b) (6)	Challenge	12	4	1	2.25000	2.44444	Yes	No	No	
2	A		Challenge	13	2	1	2.25000	2.44444			No	
3	A		Challenge	14	2	1	2.25000	2.44444			No	
4	A		Challenge	15	1	1	2.25000	2.44444			No	
5	A		Re-Challenge	17	4	2	3.50000	2.44444				Yes
6	A		Re-Challenge	18	4	2	3.50000	2.44444				Yes
7	A		Re-Challenge	19	4	2	3.50000	2.44444				Yes
8	A		Re-Challenge	20	2	2	3.50000	2.44444				Yes
9	A		Challenge	12	2	2	2.00000	2.77778	Yes	No	No	
10	A		Challenge	13	2	2	2.00000	2.77778			No	
11	A		Challenge	14	2	2	2.00000	2.77778			No	
12	A		Challenge	15	2	2	2.00000	2.77778			No	
13	A		Re-Challenge	17	4	2	3.50000	2.77778				Yes
14	A		Re-Challenge	18	4	2	3.50000	2.77778				Yes
15	A		Re-Challenge	19	4	2	3.50000	2.77778				Yes
16	A		Re-Challenge	20	2	2	3.50000	2.77778				Yes
17	A		Challenge	12	2	2	2.00000	2.22222	Yes	No	No	
18	A		Challenge	13	2	2	2.00000	2.22222			No	

Obs	Treatment A (TEST) / B (RLD)	Subject Identifier	Study Phase (c)	Visit Number (n)	Irritation Score during Challenge or Rechallenge	Last Irritation Score during Challenge or Rechallenge	Mean irritation score across visits in Challenge	Mean irritation score in Induction	Sponsor's Final Potential Sensitization	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge Phase	FDA's Potential Sensitization in ReChallenge Phase
19	A	(b) (6)	Challenge	14	2	2	2.00000	2.22222			No	
20	A		Challenge	15	2	2	2.00000	2.22222			No	
21	A		Re-Challenge	17	2	2	2.66667	2.22222				Yes
22	A		Re-Challenge	18	4	2	2.66667	2.22222				Yes
23	A		Re-Challenge	19	.	2	2.66667	2.22222				Yes
24	A		Re-Challenge	20	2	2	2.66667	2.22222				Yes
25	B		Challenge	12	2	2	2.00000	2.44444	Yes	No	No	
26	B		Challenge	13	2	2	2.00000	2.44444			No	
27	B		Challenge	14	2	2	2.00000	2.44444			No	
28	B		Challenge	15	2	2	2.00000	2.44444			No	
29	B		Re-Challenge	17	4	2	3.00000	2.44444				Yes
30	B		Re-Challenge	18	4	2	3.00000	2.44444				Yes
31	B		Re-Challenge	19	2	2	3.00000	2.44444				Yes
32	B		Re-Challenge	20	2	2	3.00000	2.44444				Yes
33	B		Challenge	12	2	2	2.00000	2.77778	Yes	No	No	
34	B		Challenge	13	2	2	2.00000	2.77778			No	
35	B		Challenge	14	2	2	2.00000	2.77778			No	
36	B		Challenge	15	2	2	2.00000	2.77778			No	
37	B		Re-Challenge	17	4	2	3.50000	2.77778				Yes

Obs	Treatment A (TEST) / B (RLD)	Subject Identifier	Study Phase (c)	Visit Number (n)	Irritation Score during Challenge or Rechallenge	Last Irritation Score during Challenge or Rechallenge	Mean irritation score across visits in Challenge	Mean irritation score in Induction	Sponsor's Final Potential Sensitization	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge Phase	FDA's Potential Sensitization in ReChallenge Phase
38	B	(b) (6)	Re-Challenge	18	4	2	3.50000	2.77778				Yes
39	B		Re-Challenge	19	4	2	3.50000	2.77778				Yes
40	B		Re-Challenge	20	2	2	3.50000	2.77778				Yes
41	B		Challenge	12	4	2	3.00000	3.11111	Yes	No	No	
42	B		Challenge	13	4	2	3.00000	3.11111			No	
43	B		Challenge	14	2	2	3.00000	3.11111			No	
44	B		Challenge	15	2	2	3.00000	3.11111			No	
45	B		Re-Challenge	17	7	2	5.00000	3.11111				Yes
46	B		Re-Challenge	18	7	2	5.00000	3.11111				Yes
47	B		Re-Challenge	19	4	2	5.00000	3.11111				Yes
48	B		Re-Challenge	20	2	2	5.00000	3.11111				Yes
49	B		Challenge	12	2	2	1.75000	2.11111	Yes	No	No	
50	B		Challenge	13	2	2	1.75000	2.11111			No	
51	B		Challenge	14	1	2	1.75000	2.11111			No	
52	B		Challenge	15	2	2	1.75000	2.11111			No	
53	B		Re-Challenge	17	4	2	2.50000	2.11111				Yes
54	B		Re-Challenge	18	2	2	2.50000	2.11111				Yes
55	B		Re-Challenge	19	2	2	2.50000	2.11111				Yes

Obs	Treatment A (TEST) / B (RLD)	Subject Identifier	Study Phase (c)	Visit Number (n)	Irritation Score during Challenge or Rechallenge	Last Irritation Score during Challenge or Rechallenge	Mean irritation score across visits in Challenge	Mean irritation score in Induction	Sponsor's Final Potential Sensitization	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge Phase	FDA's Potential Sensitization in ReChallenge Phase
56	B	(b) (6)	Re-Challenge	20	2	2	2.50000	2.11111				Yes
57	B		Challenge	12	0	2	2.50000	2.66667	Yes	No	No	
58	B		Challenge	13	4	2	2.50000	2.66667			No	
59	B		Challenge	14	4	2	2.50000	2.66667			No	
60	B		Challenge	15	2	2	2.50000	2.66667			No	
61	B		Re-Challenge	17	7	3	4.75000	2.66667				Yes
62	B		Re-Challenge	18	5	3	4.75000	2.66667				Yes
63	B		Re-Challenge	19	4	3	4.75000	2.66667				Yes
64	B		Re-Challenge	20	3	3	4.75000	2.66667				Yes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number:	206497
Drug Name:	Methylphenidate Transdermal System 10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
Reference Listed Drug:	Daytrana Transdermal System, 3.3 mg/hr
Applicant:	Mylan Pharmaceuticals Inc
Date(s):	Submitted on 12/13/2013
Biometrics Division:	DBVIII
Statistical Reviewer:	Wanjie Sun, Ph.D.
Concurring Reviewers:	Yu-te Wu, Ph.D.
Medical Division:	Division of Clinical Review in OGD/OPS/CDER
Clinical Team:	Sunny Tse, Ph.D. Ying Fan, Ph.D.
Keywords:	Adhesion, irritation, sensitization, non-inferiority, matched paired analysis

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List of Tables

1 EXECUTIVE SUMMARY

The purpose of this review is to evaluate that the adhesion performance of the intended duration of wear for Methylphenidate Transdermal System, 10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr) (TEST, manufactured by Mylan Technologies Inc.) was at least as good as the reference listed product (RLD: Daytrana Transdermal System, 3.3 mg/hr manufactured by Noven Pharms Inc.); and to evaluate that TEST was no more irritating or sensitizing than RLD. The sponsor conducted one pilot irritation study (MPTP-11007), three PK adhesion study (MPTP-11030, MPTP-11125, MPTP-12012), and two combined adhesion, irritation, and sensitization studies (MPTP-12046, and MPTP-12130) to support this application. Among the six studies, only one study (MPTP-12130) was reviewed and the other five studies are not reviewed as suggested by the clinical primary reviewer (Table 1).

Study MPTP-12130 is the study that was reviewed by the statistical reviewer. It was an irritation evaluator blinded, multiple-dose, randomized, one-period, two-treatment cumulative irritation study conducted at PRACS Institute in Fargo, ND. The primary objectives of this study were to evaluate the cumulative irritation and sensitization potential of a single formulation of Mylan's Methylphenidate Transdermal Systems 10mg/9hours compared to Noven's Daytrana 10 mg (releasing 10mg/9hours) in healthy adult male and female volunteers. In addition, the adhesive quality of Mylan's Methylphenidate Transdermal System was compared to Noven's Daytrana in all enrolled subjects during the first patch application. One hundred subjects were utilized in the assessment of patch adhesion. Ninety-three (out of 100) healthy, non-tobacco using male and female subjects between the ages of 18 and 45 completed MPTP-12130. Sixty-six subjects underwent challenge phase and 31 subjects completed the re-challenge phase.

Table 1. Five Studies Not Reviewered in this Report, recommended by DCR

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
MPTP-11030 - Single-Dose Pilot Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fed BE	(b) (4)
MPTP-11007 - Comparative Evaluation of the Cumulative Irritation of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) following a 48 to 72 hour Wear in Healthy Adult Volunteers	Cumulative Irritation Study (n=32)	(b) (4)

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
MPTP-11125 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fasting Bioequivalence	Overlay is allowed
MPTP-12012 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fasting Bioequivalence	The applicant evaluated irritation. However, the study duration is only for 9 hours.
MPTP-12046 - Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Shire) in Healthy Adult Volunteers	Cumulative Irritation and Sensitization (n=100)	The sponsor noted data integrity issue and deficiencies in procedure by Novum Pharmaceutical Research Service. Due to data integrity issue, not recommended for the review.

Conclusions and Recommendations

Adhesion:

Study 12130: The non-inferiority of the test product (TEST: Methylphenidate Transdermal Systems 10mg/9 hours manufactured by Mylan Pharmaceutical Inc.) versus the reference listed product (RLD: Daytrana 10 mg/9 hours manufactured by Noven Pharms Inc.) was established in adhesion based on the primary endpoint – mean adhesion score across visits, among the FDA's Per Protocol Population for adhesion (FPPPA: N=100) in Study MPTP 12130.

The statistical review and evaluation of the data submitted for ANDA 206497 Study MPTP 12130 support approval for adhesion.

Irritation:

MPTP 12130: The non-inferiority of the test product (TEST: Methylphenidate Transdermal Systems 10mg/9 hours manufactured by Mylan Pharmaceutical Inc.) versus the reference listed product (RLD: Daytrana 10 mg/9 hours manufactured by Noven Pharms Inc.) was established in irritation using the primary endpoint – mean irritation score across visits, based on the FDA's Per Protocol Population for irritation (FPPIRR, N=92) in Study MPTP 12130.

The statistical review and evaluation of the data submitted for ANDA 206497 Study MPTP 12130 support approval for irritation.

Sensitization

MPTP 12130: Among the 66 subjects of FDA's per-protocol population for sensitization (FPPSEN) in Study MPTP 12130, TEST has 13.7 more percentage point of subjects with potential sensitization than RLD (P_T =27.3%, P_R = 13.6%), with the one-sided 95% upper bound of 23.7% for the proportion difference between TEST and RLD: $P_T - P_R$.

2 INTRODUCTION

Overview

Methylphenidate is a CNS stimulant. Its mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known, but methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space. Mylan's Methylphenidate Transdermal System is a generic version of Daytrana® (methylphenidate transdermal system), which is approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Reference Drug

Daytrana® (Methylphenidate Transdermal System, MTDS) is an adhesive based matrix transdermal system or patch that is applied to intact skin. Daytrana (manufactured by Noven Pharms Inc), NDA 021514, was originally approved by FDA on April 6th, 2006. The approved indications are as follows:

Daytrana is a CNS stimuland indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).
Children (ages 6-12): the efficacy of Daytrana in ADHD was established in two 7-week controlled trials in children.
Adolescents (ages 13-17): the efficacy of Daytrana in ADHD was established in one 7-week, controlled study in adolescents.

Data Sources

The data were submitted electronically and the data files are located in DARRTS and Generic Drug Review Platform under ANDA # 206497:
\\cdsesub1\evsprod\ANDA206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets

3 STATISTICAL METHODOLOGY

3.1 Continuous Data

Continuous data includes the mean adhesion or irritation score across visits for each treatment arm. The objective is to test a non-inferiority (NI) hypothesis as follows:

$$H_0: \frac{U_T}{U_R} > 1.25 \text{ (Inferior)}$$

$$H_1: \frac{U_T}{U_R} \leq 1.25 \text{ (Non-inferior)},$$

where U_T and U_R are the mean adhesion or irritation scores for TEST and RLD, and 1.25 is a pre-specified non-inferiority margin. The significance level for the NI test of patch adhesion or irritation is 0.05. Non-inferiority is established if the upper bound (UB) of the one-sided 95% confidence interval of $U_T - 1.25U_R$ is less than or equal to 0.

In cross-over and matched parallel studies, continuous data from the two treatment arms are correlated. Therefore, a Linear Mixed Model, which can incorporate the intra-class correlation, is used to model the mean adhesion or irritation score. The statistical literature shows that the fixed effects in linear mixed models are robust to mis-specification of error distribution (Jacqmin-Gadda et al 2007) or random-effect distribution (Verbeke et al 1997).

For the *k*th treatment arm of *i*th subject, the mean adhesion or irritation score across visits $\bar{y}_{ki}$ is modeled as follows:

$$\bar{y}_{ki} = U + \beta_T x_{Ti} + \beta_R x_{Ri} + \gamma^T W_i + \varepsilon_{ki},$$

where U is the intercept, x_{Ti} and x_{Ri} are the indicators of TEST and RLD treatment arms for subject i, and β_T and β_R are the treatment effect for TEST and RLD, W_i is the vector of values of covariates like design variables, γ is the vector of parameters for W_i, and ε_{ki} is the measurement error for the *k*th treatment arm of *i*th subject. The residual variance covariance matrix is assumed to be no-diagonal factor analytic (FA0). The upper bound of $U_T - 1.25U_R$ can be derived from a linear contrast based on the linear mixed model.

3.2 Binary Data

Binary data includes the proportion of clinically significant detachment or irritation or sensitization ("event") for each treatment arm. The objective is to test a non-inferiority hypothesis as follows:

$$H_0: P_T - P_R > \delta \text{ (Inferior)}$$

$$H_1: P_T - P_R \leq \delta \text{ (Non-inferior)},$$

where P_T and P_R are the proportions of "event" for TEST and RLD , and δ is a pre-specified non-inferiority margin. The significance level is 0.05. Non-inferiority is established if the upper bound (UB) of the one-sided 95% confidence interval of $P_T - P_R$ is less than or equal to δ. The tabulation of event/non-event for TEST and RLD is as follows.

Total n=a+b+c+d		TEST	
		Non-Event	Event
RLD	Non-Event	a	b
	Event	c	d

The matched proportion difference $P_T - P_R$ can be estimated by the quantity $\frac{b-c}{n}$ after a simple derivation. There are different ways to calculate the upper bound of the matched proportion difference $P_T - P_R$. A common way is to use the McNemar method (McNemar 1947) based on normal approximation under the law of large numbers. The UB is calculated as follows:

$$UB = \frac{b-c}{n} + 1.645\frac{1}{n}\sqrt{b+c-\frac{(b-c)^2}{n}}$$

Schuirmann (2008) proposed a different way of normal approximation by combining Nam (1997) and Liu et al (2002)'s approaches. Based on the simulation results, Schuirmann (2008) recommended an optimal normal approximation which worked the best in various simulated scenarios.

$$\text{Let } Z = \frac{\hat{\delta} + cc - \delta}{\sqrt{\frac{\xi^* - \delta^2}{n}}},$$

where $\hat{\delta} = \frac{b-c}{n}$, the continuity correction, $cc = \frac{1}{n}$, $\xi^* = \max(\hat{\delta}, |\delta|)$.

The one-sided 95% upper bound (UB) for the matched proportion difference, $P_T - P_R$, is the value of δ that makes $Z = Z_{0\,05} = -1.64$. Schuirmann's method was used in this statistical report. For any given non-inferiority bound δ, the null hypothesis H_0 may be rejected if this 95% upper confidence bound for the quantity $P_T - P_R$ is less than or equal to δ, that is:
$U \leq \delta$. Rejection of the null hypothesis H_0 supports the conclusion of non-inferiority of the test to the comparator. The non-inferiority standard δ is not yet specified in the guidance for this product.

4 STATISTICAL EVALUATION

4.1 ADHESION: Study MPTP-12130

4.1.1 STUDY DESIGN

Study MPTP-12130 was an irritation evaluator blinded, multiple-dose, randomized, one-period, two-treatment cumulative irritation study conducted at the PRACS Institute in Fargo, ND. The primary objectives of this study was to evaluate the cumulative irritation and sensitization potential of a single formulation of Mylan's Methylphenidate Transdermal Systems 10mg/9hours compared to Noven's Daytrana 10 mg (releasing 10mg/9hours) in healthy adult male and female volunteers. In addition, the adhesive quality of Mylan's Methylphenidate Transdermal System was compared to Noven's Daytrana in all enrolled subjects during the first patch application. Ninety-three (out of 100) healthy, non-tobacco using male and female subjects between the ages of 18 and 45 completed the irritation study. One hundred subjects completed the adhesion study. Sixty-six subjects underwent challenge phase and 31 subjects completed the re-challenge phase.

Each subject received Mylan's Methylphenidate Transdermal System, 10 mg/9 hours and Noven's Daytrana® 10 mg and applied to a clean, dry area of the skin on the right or left side of the hip according to the randomization scheme. Subjects wore each treatment for 48-72 hours. Patches were re-applied to the same skin site every 48-72 hours for 21 consecutive days (for a total of 9 patch applications per treatment). Adhesion was assessed for the first 9 hours of the 1st application at the following times 1, 3, 5, 7, and 9 hours post patch application. For the Challenge and Re-Challenge Phases of the study, an irritation evaluation occurred 30 to 45 minutes after patch removal and at 24, 48, and 72 hours after patch removal.

Treatment was implemented in three groups as follows:

Group 1 (b) (6)
Induction Phase: (b) (6)
Challenge Phase: (b) (6)
Re-Challenge Phase: (b) (6)

Group 2 (b) (6)
Induction Phase: (b) (6)
Challenge Phase: (b) (6)
Re-Challenge Phase: (b) (6)

Group 3 (b) (6)
Induction Phase: (b) (6)
Challenge Phase: (b) (6)
Re-Challenge Phase: (b) (6)

Treatments

TEST: Methylphenidate 10mg/9hrs
Manufactured for Mylan Pharmaceuticals Inc by Mylan Technologies Inc. (Mylan)

RLD: Daytrana® 10mg/9hrs
Manufactured by Noven Pharmaceuticals Inc for Noven Therapeutics LLC (Noven)

Comment: The study design follows the recommendation of the FDA's guidance on methylphenidate[1] in general. There was only one site involved in the study, but the guidance recommended the study to be conducted in multiple centers with different climate condition.

4.1.2 ADHESION ASSESSMENT

Sponsor's Adhesion Scale

The sponsor used a 12-point scale for adhesion assessment, where a score of '100' indicated 100% adhered to the skin, while a score of '0' indicated the transdermal system was completely detached from the skin.

FDA's Adhesion Scale

FDA used a 5-point scale for adhesion assessment as recommended by the FDA guidance[1] as follows:

0 = 90-100% adhered (essentially no lift off the skin)
1 = 75% to <90% adhered (some edges only lifting off of the skin)
2 = 50% to <75% adhered (less than half of the system lifting off the skin)
3 = >0% to <50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
4 = 0% adhered - patch detached (patch completely off the skin)

FDA's Adhesion Conversion Table from 12-point to 5-point Scale

Statistical reviewer converted the sponsor's 12-point scale to the FDA's 5-point scale with confirmation from the clinical reviewers, per an email communication dated 12/3/2015.

Table 2: FDA Conversion of Sponsor's Adhesion Scoring from 12-point to 5-point Scale

Sponsor's Score	Description	FDA's Score
100	Adhesion: 100%	0
95	Adhesion: >90% to <100%	0
85	Adhesion: >80% to 90%	1
75	Adhesion: >70% to 80%	1
65	Adhesion: >60% to 70%	2
55	Adhesion: >50% to 60%	2
45	Adhesion: >40% to 50%	3
35	Adhesion: >30% to 40%	3
25	Adhesion: >20% to 30%	3
15	Adhesion: >10% to 20%	3

5	Adhesion: >0% to 10%	3
0	Adhesion: 0%	4

4.1.3 STUDY ENDPOINTS

Primary Endpoint

Sponsor's primary endpoint was the mean adhesion score over the five visits (1, 3, 5, 7, 9 hour), using Mylan's 12-point adhesion scale.

FDA's primary endpoint was the mean adhesion score over the five visits (1, 3, 5, 7, 9 hour), which was confirmed by clinical reviewers per an email communication dated 12/08/2015), using the FDA's 5-point adhesion scale.

Other Endpoints

Other endpoints suggested by the FDA guidance included:

1) proportion of subjects with a meaningful degree of detachment for each product. In this report, we define a meaningful degree of detachment as having at least one adhesion score greater than or equal to 3.
2) time from patch application until complete detachment (score=4) or partial detachment (score ≥ 3, i.e., ≥50% of detachment) during patch wear.

4.1.4 SUBJECT DISPOSITION

Per-Protocol (PP) Patch Population for Adhesion (PPPA) :

Sponsor's PPPA (SPPPA): All of the 100 randomized subjects had valid adhesion scores and were included in the statistical analysis of adhesion.

FDA's PPPA (FPPPA): FPPPA includes all subjects except those with patches removed early for unacceptable irritation or those subjects who dropped out of the study before the end of the first application.

A total of 100 subjects were enrolled in Study MPTP-12130 (Table 3). FDA's reviewers agreed with the sponsor for the inclusion of subjects in the FPPPA population. All of these 100 subjects were included in both the FDA's and the sponsor's PPPA.

Table 3: Number of Subjects in Sponsor's and FDA's PP Population for Adhesion (PPPA) in Adhesion Study MPTP-12130

	Sponsor's PPPA			FDA's PPPA		
	TEST	**RLD**	**Total N of Subjects**	**TEST**	**RLD**	**Total N of Subjects**
Randomized	100	100	100	100	100	100
Total PP Population for Adhesion	100	100	100	100	100	100
Total Exclusion from PPPA	0	0	0	0	0	0

4.1.5 MISSING DATA AND IMPUTATION

Sponsor's Imputation:

No imputation was done for the adhesion data by the sponsor.

FDA's Imputation:

The worst (highest) adhesion value was carried forward for patches with improved adhesion scores recorded across visits given that adhesion score should not improve unless being reinforced. No complete detachment (score = 4) was observed in this study. There was no missing intermittent adhesion score in this study.

In details, among the 100 subjects randomized in Adhesion Study of MPTP-12130 (Table 4), eight (8%) out of 100 TEST patches and 25 (25%) out of 100 RLD patches had improved adhesion scores across visits, and were applied worst case carried forward imputation.

Table 4: Number of Patches with Imputed Adhesion Scores in the FDA's PPPA (FPPPA) Population in Adhesion Study MPTP-12130

	TEST	**RLD**
Randomized		
N of patches	100	100
Discontinued due to patch fell off, N (%)	0 (0%)	0 (0%)
FDA's PP for Adhesion		
N of patches	100	100
Total N of patches with worst observation carried forward due to improved adhesion score recorded, N (%)	8 (8%)	25 (25%)

4.1.6 DEMOGRAPHICS

Table 5 shows the distribution of the demographic characteristics in the FPPPA population in Adhesion Study of MPTP-12130. Among the 100 subjects in the FPPPA population, 62% were females, 93% were white, and the average age was 27.2 years old.

Table 5: Demographics in the FDA's PPPA (FPPPA) Population in Adhesion Study MPTP-12130

Characteristics	FPPPA (N=100)
Age (years)	
Mean (STD)	27.2 (7.2)
Female n (%)	62 (62.0%)
Race n (%)	
White	93 (93.0%)
Other	7 (7%)

4.1.7 STATISTICAL RESULTS

4.1.7.1 Tabulation of Adhesion Score

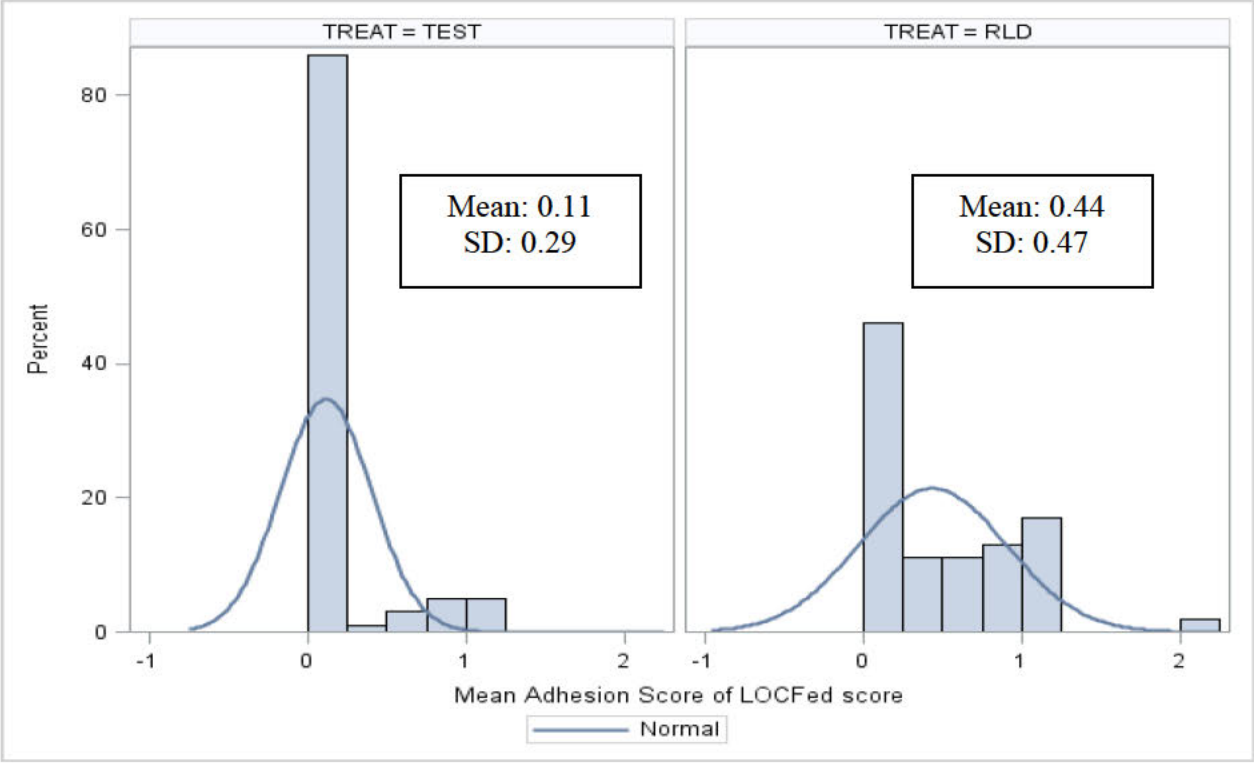
Table 6 summarizes the frequency of adhesion scores at each time point by TEST and RLD among the 100 subjects in the FPPPA population. Figure 1 shows the distribution of the mean adhesion score (± standard deviation) across visits (TEST: 0.11±0.29; RLD: 0.44±0.47).

Table 6: Frequency of Adhesion Scores at Each Time Point for TEST and RLD in the FPPPA Population in Adhesion Study MPTP-12130

Hr	TEST (N=100) n (%)						RLD (N=100) n (%)					
	Score 0	Score 1	Score 2	Score 3	Score 4	Mean	Score 0	Score 1	Score 2	Score 3	Score 4	Mean
1	95 (95)	5 (5)	0 (0)	0 (0)	0 (0)	0.05	82 (82)	16 (16)	2 (2)	0 (0)	0 (0)	0.20
3	90 (90)	10 (10)	0 (0)	0 (0)	0 (0)	0.10	68 (68)	30 (30)	2 (2)	0 (0)	0 (0)	0.34
5	87 (87)	13 (13)	0 (0)	0 (0)	0 (0)	0.13	57 (57)	41 (41)	2 (2)	0 (0)	0 (0)	0.45
7	86 (86)	14 (14)	0 (0)	0 (0)	0 (0)	0.14	46 (46)	51 (51)	3 (3)	0 (0)	0 (0)	0.57
9	85 (85)	15 (15)	0 (0)	0 (0)	0 (0)	0.15	42 (42)	55 (55)	2 (2)	1 (1)	0 (0)	0.62

Hr	TEST (N=100) n (%)						RLD (N=100) n (%)					
	Score 0	Score 1	Score 2	Score 3	Score 4	Mean	Score 0	Score 1	Score 2	Score 3	Score 4	Mean
All	443 (88.6)	57 (11.4)	0 (0)	0 (0)	0 (0)	0.11	295 (59.0)	193 (38.6)	11 (2.2)	1 (0.2)	0 (0)	0.44

Figure 1 Distribution of Mean Adhesion Score by TEST and RLD in the FPPPA Population (N=100) in Study MPTP-12130



4.1.7.2 Primary Endpoint: Mean Adhesion Score

Sponsor:

The sponsor used a 12-point adhesion score as described in 4.1.2 where a higher score indicates better adhesion. A one-sided hypothesis was used to determine if the adhesion score of Mylan's Methylphenidate Transdermal System (TEST) was equivalent to or better than that of RLD. For the mean adhesion score, the null and alternative hypothesis were: H_0: $U_T/U_R < 0.8$ and H_1: $U_T/U_R \geq 0.8$. The null hypothesis H_0 was rejected when the lower limit of the 90% confidence interval (that is the 95% lower confidence bound) for the quantity $U_T - 0.8U_R$ was ≥ 0.

Based on the sponsor's analysis (Table 7), the one-sided 95% lower bound of $U_T - 0.8U_R$ was 22.1, which was greater than 0. Therefore, the sponsor established NI for adhesion.

FDA:

The FDA used a 5-point adhesion score as described in 4.1.2 where a lower score indicates better adhesion. A one-sided hypothesis was used to determine if the adhesion score of Mylan's Methylphenidate Transdermal System (TEST) was non-inferior to RLD. For the mean adhesion score across visits, the null and alternative hypothesis were: H_0: $U_T/U_R > 1.25$ and H_1: $U_T/U_R \leq 1.25$. The Linear Mixed Model as described in the 3.1 Statistical Methods for continuous data was used. For Study MPTP-12130, since treatment was implemented in three groups (b) (6) at different time, group was adjusted in the model as a design variable. Subjects were also randomized such that TEST and RLD were applied to left + right hip or right + left hip, therefore, patch application site (left or right hip) was also adjusted in the model as another design variable. The null hypothesis H_0 was rejected when the upper limit of the 90% confidence interval (that is the 95% one-sided upper confidence bound) for the linear contrast $U_T - 1.25U_R$ was ≤ 0.

Based on the FDA's analysis (Table 7), the least square mean (± standard error) was 0.087 ± 0.025 for the TEST arm and 0.409 ± 0.042 for the RLD arm among the 100 subjects in the FPPPA population. The one-sided 95% upper bound of $U_T - 1.25U_R$ was -0.5173, which was less than 0. Therefore, based on the FDA's analysis, non-inferiority of TEST vs. RLD in adhesion passed using the primary endpoint – mean adhesion score across visits.

Table 7: Sponsor's and FDA's Non-inferiority Test for Mean Adhesion Score in Adhesion Study MPTP-12130

Sponsor (N=100)*				**FDA (N=100)**			
NI Hypothesis	**LSmean**	**95%LB of $U_T - 0.8U_R$**	**Pass or Fail NI**	**NI Hypothesis**	**LSmean (std error)**	**95%UB of $U_T - 1.25U$**	**Pass or Fail NI**
H_0 (Inferior): $\frac{U_T}{U_R} < 0.8$ H_1(NonInferior) $\frac{U_T}{U_R} \geq 0.8$	TEST: 95.1 RLD: 91.2	22.1 (>0)	**Pass NI**	H_0 (Inferior): $\frac{U_T}{U_R} > 1.25$ H_1 (NonInferior): $\frac{U_T}{U_R} \leq 1.25$	TEST: 0.087 (0.025) RLD: 0.409 (0.042)	-0.5173 (<0)	**Pass NI**

*Source: Table 14.9 on page 78 in the sponsor's study report MPTP-12130.

4.1.7.3 Other Endpoint: Proportion of Subjects with a Meaningful Degree of Detachment (Adhesion Score ≥3)

Table 8 shows the proportion of subjects by treatment with adhesion score of 3 or greater at any time, which was used to denote a meaningful degree of detachment in this report.

Among the 100 subjects in the FPPPA population, 99 (99%) subjects had concordant scores (diagonal) between TEST and RLD, and only 1 (1%) subject had discordant (off-diagonal) scores. TEST had zero (P_T=0%) patch with adhesion score ≥ 3 at any time, and RLD had 1 (P_R=1%) patch with adhesion score ≥ 3 at any time. The point estimate of $P_T - P_R$ was -1.0% (Table 9). The one-sided 95% upper bound for $P_T - P_R$ was 2.6%. Based on the 95% upper confidence bound for the difference in proportions, the TEST patch might exceed the RLD patch by at most 2.6 percentage points in the proportion of subjects with a meaningful degree of detachment.

Table 8: Proportion of Subjects with A Meaningful Degree of Detachment by TEST and RLD in the FPPPA Population in Adhesion Study of MPTP-12130

Table 8	**TEST**		
RLD	Maximum Score < 3	Maximum Score ≥ 3	Total
Maximum Score < 3	99 (99%)	0 (0%)	99 (99%)
Maximum Score ≥ 3	1 (1%)	0 (0%)	1 (1%)
Total	100 (100%)	0 (0%)	100 (100%)

Table 9: Non-Inferiority Test for Proportion of Subjects with a Meaningful Degree of Detachment in the FPPPA Population in Adhesion Study of MPTP-12130

Hypothesis	**P (TEST score ≥ 3)** P_T	**P (RLD score ≥ 3)** P_R	**Point Estimate of** $P_T - P_R$	**95%UB of** $P_T - P_R$
H_0: $P_T - P_R > \delta$ (Inferior) H_1: $P_T - P_R \leq \delta$ (Non-inferior)	0%	1.0%	-1.0%	2.6%

4.1.7.4 Other Endpoint: Time from Patch Application until Patch Complete or Partial Detachment

Patch Complete Detachment (Score = 4)

No TEST or RLD patches had complete detachment at any time.

Patch Partial Detachment (Score ≥ 3)

One RLD vs. zero TEST patches had partial detachment (score ≥ 3 or detachment ≥ 50%). The one RLD patch with partial detachment started detachment ≥ 50% at Hour 9.

Table 10: Time from Patch Application until Patch Complete or Partial Detachment in the FPPPA Population in Adhesion Study of MPTP-12130

Treatment	Hour from Patch Application to Detachment				
	1	3	5	7	9
Patch Complete Detachment (Score ≥ 3)					
TEST (N=0)	0	0	0	0	0
RLD (N=1)	0	0	0	0	1

In summary, the non-inferiority of Methylphenidate Transdermal System (10 mg/9 hours) manufactured by Mylan (TEST) vs. Daytrana (10 mg/9 hours) manufactured by Noven (RLD) was established in adhesion for the adhesion study of MPTP-12130 using the primary endpoint – mean adhesion score based on the FDA's 5-point scale based on the 100 subjects in the FPPPA population.

4.2 Irritation Study of MPTP-12130

4.2.1 STUDY DESIGN

Same as Section 4.1.1.

4.2.2 IRRITATION ASSESSMENT

Both the sponsor and the FDA used the following two scales to evaluate and score the skin reactions.

Scale 1: Dermal Response

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; or minimal edema; or minimal popular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test (i.e., application) site	7

Scale 2: Other Effects

Observation	Score (numeric equivalent)
Slightly glazed appearance	A(0)
Marked glazed appearance	B(1)
Glazing with peeling and cracking	C(2)
Glazing with fissures	F(3)
Film of dried serous exudates covering all or part of the patch site	G(3)
Small petechial erosions and/or scabs	H(3)

Comments: The study design and the scale for irritation assessment follow the recommendation of the FDA's guidance on Methylphenidate [1], therefore, they are adequate.

4.2.3 STUDY ENDPOINTS

Primary Endpoint

Sponsor's primary endpoint was the mean cumulative irritation, which was defined for each subject as the sum of all 9 individual irritation scores obtained at 0.5 hours after patch removal divided by 9.

FDA's primary endpoint was the mean cumulative irritation score calculated as the sum of all combined "Dermal Response" and "Other Effects" scores observed at each observation (i.e., 9 observations) divided by the total number of observations (i.e., 9).

Comments: The definition of primary efficacy endpoint follows the recommendation of the FDA's guidance on Methylphenidate, therefore, it is adequate.

Other Endpoints

Other endpoints suggested by the FDA guidance included:

1) Proportion of subjects with a meaningful degree of irritation for each product.
2) Total number of observations with a combined "Dermal Response" and "Other Effects" irritation score of 3 or more for each test article.

3) Number of patches that were moved or removed due to an unacceptable degree of irritation.
4) Number of days from patch application until patch removal due to excessive irritation.

4.2.4 SUBJECT DISPOSITION

Per-Protocol (PP) Patch Population for Irritation (PPIRR) :

Sponsor's PPIRR (SPPIRR): Subjects must have had 7 valid irritation scores recorded to be included in the irritation analysis. Cumulative Irritation Study Report for MPTP-12130 (page 49) indicated, "Ninety-two subjects completed the Irritation (induction) phase of the study with 93 subjects (includes Subject (b) (6) utilized in the cumulative irritation analysis". According to the sponsor's data define file (12130define.pdf), 7 subjects were excluded from the SPPIRR due to fewer than 7 valid irritation scores out of 9 measurements (Subjects (b) (6)

FDA's PPIRR (FPPIRR): The test articles need to be applied sequentially to the same site for the entire 21 day induction phase (without any period of detachment longer than 24 hours) to be evaluated for the cumulative irritation effect OR if a patch is moved or removed due to excessive irritation, it should be included using Last Observation Carried Forward (LOCF).

A total of 100 subjects were enrolled in the Study MPTP-12130 (Table 11). According to the FDA's analysis, 92 subjects were included in the FDA's PPIRR. Besides the 7 subjects the sponsor excluded from PPIRR, one more subject (Subject (b) (6) was excluded from FDA's PPIRR. This is because Subject (b) (6) withdrew from the study after visit 9 (day 19) and was detached for more than 24 hours during the 21 day induction.

Table 11: Number of Subjects in Sponsor's and FDA's PP Population for Irritation (PPIRR) in Irritation Study MPTP-12130

	Sponsor's PPIRR			FDA's PPIRR		
	TEST	**RLD**	**Total N of Subjects**	**TEST**	**RLD**	**Total N of Subjects**
Randomized	100	100	100	100	100	100
Total PP population for Irritation	93	93	93	92	92	92
Total Exclusion from PPIRR due to early withdraw (detachment > 24 hours)	7	7	7	8	8	8
Subject ID	(b) (6)					

4.2.5 MISSING DATA AND IMPUTATION

Sponsor's Imputation:

For any missing score, the previous score was carried forward.

FDA's Imputation:

For subjects who experience irritation consistent with a combined score of ≥ 3, or who experience symptomatic intolerable irritation, the patch may be moved to a new site in order to complete the 21-day Induction Phase. In this circumstance, the highest score observed (not truncated to 3) prior to discontinuation of a patch site should be carried forward for the remaining observations unless a higher score is observed at the new location if applicable in the induction phase.

Among the 92 FPPIRR, 39 (42.4%) subjects had TEST patches moved and 62 (67.4%) subjects had RLD patches moved due to excessive irritation (score ≥ 3) and were applied the highest score prior to removal and carried forward for all remaining observations unless a higher score is observed at the new location if applicable in the irritation study.

Table 12: Number of Patches with Imputed Irritation Scores in the FDA's PPIRR (FPPIRR) Population in Irritation Study MPTP-12130

	TEST	SLS
Randomized		
N	100	100
FDA's PP for Irritation		
N	92	92
Patch removed due to excessive irritation in Induction Phase, and worst observation prior to removal carried forward, N (%)	39 (42.4%)	62 (67.4%)

4.2.6 DEMOGRAPHICS

Table 13 shows the distribution of the demographic characteristics in the FPPIRR population. The 92 subjects in the FPPIRR population were 62% females, 93.5% white, 6.5% of other races, and were on average 27.3 years old.

Table 13: Demographics in the FDA's PPIRR (FPPIRR) Population in Irritation Study MPTP-12130

Characteristics	FPPIRR (N=92)
Age (years)	
Mean (STD)	27.3 (7.1)
Female n (%)	57 (62.0%)
Race n (%)	
White	86 (93.5%)
Other	6 (6.5%)

4.2.7 STATISTICAL RESULTS

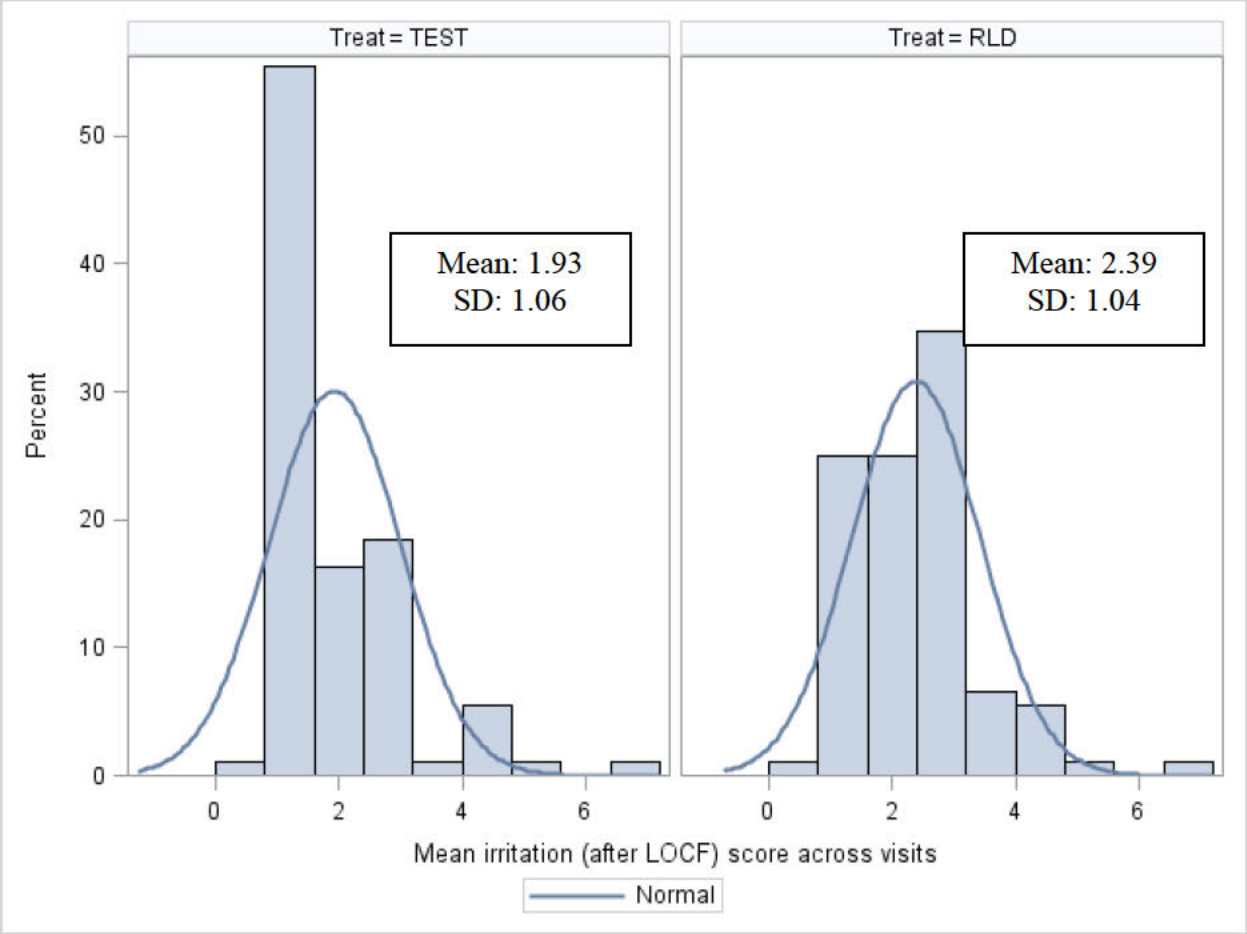
4.2.7.1 Tabulation of Irritation Score

Table 14 summarizes the frequency of the irritation scores at each time point and across all time points by TEST and RLD among the 92 subjects in the FPPIRR population. Figure 2 shows the distribution and the mean (± standard deviation) of irritation scores across visits for TEST (1.93±1.06) and RLD (2.39±1.04).

Table 14: Frequency of Irritation Scores at Each Time Point for TEST and RLD in the FPPIRR Population in Irritation Study MPTP-12130

Visit	TEST (N=92) n (%)									RLD (N=92) n (%)								
	0	1	2	3	4	5	6	7	Mean	0	1	2	3	4	5	6	7	Mean
2	23 (25)	62 (67.4)	6 (6.5)	0	0	0	0	1 (1.1)	0.88	12 (13)	72 (78.3)	7 (7.6)	0	0	0	0	1 (1.1)	1.01
3	5 (5.4)	84 (91.3)	2 (2.2)	0	0	0	0	1 (1.1)	1.03	2 (2.2)	77 (83.7)	12 (13.0)	0	0	0	0	1 (1.1)	1.17
4	1 (1.1)	85 (92.4)	5 (5.4)	0	0	0	0	1 (1.1)	1.11	3 (3.3)	71 (77.2)	17 (18.5)	0	0	0	0	1 (1.1)	1.22
5	0	80 (87.0)	6 (6.5)	0	4 (4.4)	0	0	2 (2.2)	1.33	1 (1.1)	54 (58.7)	30 (32.6)	0	5 (5.4)	0	0	2 (2.2)	1.61
6	0	58 (63.0)	15 (16.3)	0	15 (16.3)	0	0	4 (4.4)	1.91	0	34 (37.0)	33 (35.9)	1 (1.1)	20 (21.7)	0	0	4 (4.4)	2.29
7	0	41 (44.6)	22 (23.9)	0	23 (25.0)	0	0	6 (6.5)	2.38	0	22 (23.9)	32 (34.8)	0	29 (31.5)	0	2 (2.2)	7 (7.6)	2.86
8	0	22 (23.9)	37 (40.2)	0	25 (27.2)	0	1 (1.1)	7 (7.6)	2.73	1 (1.1)	9 (9.8)	30 (32.6)	1 (1.1)	31 (33.7)	7 (7.6)	4 (4.4)	9 (9.8)	3.46
9	0	18 (19.6)	35 (38.0)	0	28 (30.4)	3 (3.3)	1 (1.1)	7 (7.6)	2.93	1 (1.1)	4 (4.4)	25 (27.2)	0	34 (37.0)	13 (14.1)	5 (5.4)	10 (10.9)	3.86
10	0	20 (21.7)	30 (32.6)	0	28 (30.4)	5 (5.4)	1 (1.1)	8 (8.7)	3.03	0	8 (8.7)	19 (20.7)	0	34 (37.0)	14 (15.2)	4 (4.4)	13 (14.1)	3.99
All	29 (3.5)	470 (56.8)	158 (19.1)	0	123 (14.9)	8 (1.0)	3 (0.4)	37 (4.5)	1.93 (1.06)	20 (2.4)	351 (42.4)	205 (24.8)	2 (0.2)	153 (18.5)	34 (4.1)	15 (1.8)	48 (5.8)	2.39 (1.04)

Figure 2. Distribution of Mean Irritation Score by TEST and RLD in the FPPIRR Population in Irritation Study MPTP 12130



4.2.7.2 Primary Endpoint: Mean Irritation Score across Visits

Sponsor:

These mean scores were evaluated by Analysis of Variance using Proc GLM of SAS 9.1 (or higher) with a statistical model incorporating terms for sequence, subject-nested-within-sequence, treatment, and patch application site. A one-sided hypothesis test was to be used to determine if the response of the Mylan's Methylphenidate Transdermal System, 10 mg/9 hr was equivalent to or better than the Noven's Daytrana 10 mg. For the mean irritation scores, the null and alternative hypotheses are: H_0: $U_T/U_R > 1.25$ and H_1: $U_T/U_R \leq 1.25$. The null hypothesis H_0 will be rejected when the upper limit of the 90% confidence interval (that is the 95% upper confidence bound) for the quantity $U_T - 1.25U_R$ was ≤ 0.

Based on the Sponsor's analysis (Table 15), the one-sided 95% upper bound of $U_T - 1.25U_R$ was -0.94, which was less than 0. Therefore, the Sponsor established NI for irritation.

FDA:

A one-sided hypothesis was used to determine if the mean irritation score of Mylan's Methylphenidate Transdermal System (TEST) was non-inferior to that of Noven's Daytrana . For the mean irritation score across visits, the null and alternative hypothesis were: H_0: $U_T/U_R > 1.25$ and H_1: $U_T/U_R \leq 1.25$. The Linear Mixed Model as described in Section 3.1 Statistical Methods for continuous data was applied. For Study MPTP-12130, since treatment was implemented in three groups (b) (6) at different time, group was adjusted in the model as a design variable. Subjects were also randomized such that TEST and RLD were applied to left + right hip or right + left hip, therefore, patch application site (left or right hip) was also adjusted in the model as another design variable. The null hypothesis H_0 was rejected when the upper limit of the 90% confidence interval (that is the 95% one-sided upper confidence bound) for the linear contrast $U_T - 1.25U_R$ was ≤ 0.

Based on the FDA's analysis (Table 15), the Least Squares Mean (± standard error) was 1.99 ± 0.12 for TEST and 2.45 ± 0.12 for RLD in the FPPIRR population. The one-sided 95% upper bound of $U_T - 1.25U_R$ was -0.96, which was less than zero. Therefore, the non-inferiority test of Mylan's Methylphenidate Transdermal System (TEST) vs. Noven's Daytrana passed using the primary endpoint – mean irritation score across visits.

Table 15: Sponsor's and FDA's Non-inferiority Test for Mean Irritation Score in Irritation Study MPTP-12130

Sponsor* (Sponsor's PPIRR N=93)				**FDA (FDA's PPIRR N=92)**			
NI Hypothesis	**LSmean**	**95%UB of $U_T - 1.25U_R$**	**Pass or Fail NI**	**NI Hypothesis**	**LSmean (std error)**	**95%UB of $U_T - 1.25U$**	**Pass or Fail NI**
H_0 (Inferior): $\frac{U_T}{U_R} > 1.25$ H_1(Non-Inferior) $\frac{U_T}{U_R} \leq 1.25$	TEST: 1.874 RLD: 2.324	-0.94 (<0)	**Pass NI**	H_0 (Inferior): $\frac{U_T}{U_R} > 1.25$ H_1 (Non-Inferior): $\frac{U_T}{U_R} \leq 1.25$	TEST: 1.99 (0.12) RLD: 2.45 (0.12)	-0.96 (<0)	**Pass NI**

*Source: Table 14.6 on page 76 in the sponsor's study report MPTP-12130

4.2.7.3 Other Endpoints: Proportion of Subjects with a Meaningful Degree of Irritation (Irritation Score ≥ 3)

Table 16 shows the proportion of subjects by treatment with irritation score greater than or equal to 3 at any time, which was used to denote a meaningful degree of irritation in this report.

Among the 92 subjects in the FPPIRR population, 69 (75 %) subjects had concordant scores (diagonal) between TEST and RLD, and 23 (25.0%) subjects had discordant (off-diagonal) scores. TEST had 42 (P_T =45.7%) patches with at least one irritation score ≥ 3, while RLD had 65 (P_R =70.7%) patches with irritation score ≥ 3 at any time. Therefore, TEST has 25 less percentage point of meaningful degree of irritation than RLD (The point estimate of $P_T - P_R$ was –25.0%, Table 17). The one-sided 95% upper bound for $P_T - P_R$ was -15.8%, which is less than 0. This confirms the result from the primary analysis (Section 4.2.7.2)

Table 16: Proportion of Subjects with At Least One Irritation Score ≥ 3 by TEST and RLD in the FPPIRR Population in Irritation Study MPTP-12130

	TEST		
RLD	Maximum Score < 3	Maximum Score ≥ 3	Total
Maximum Score < 3	27 (29.3%)	0 (0%)	27 (29.3%)
Maximum Score ≥ 3	23 (25.0%)	42 (45.7%)	65 (70.7%)
Total	50 (54.3%)	42 (45.7%)	92 (100%)

Table 17: Non-Inferiority Test for Proportion of Subjects with a Meaningful Degree of Irritation (Irritation Score ≥ 3) in the FPPIRR Population in Irritation Study MPTP-12130

Hypothesis	**P (TEST score ≥ 3)** P_T **(N=92)**	**P (RLD score ≥ 3)** P_R **(N=92)**	**Point Estimate of** $P_T - P_R$	**95%UB of** $P_T - P_R$
H_0: $P_T - P_R > \delta$ (Inferior) H_1: $P_T - P_R \leq \delta$ (Non-inferior)	45.7%	70.7%	-25.0%	-15.8%

4.2.7.4 Other Endpoint: Number of Patches Moved or Removed Due to an Unacceptable Degree of Irritation (irritation score ≥ 3)

Among the 92 subjects in the FPPIRR population, 39 (42.4%) patches in the TEST arm and 62 (67.4%) patches in the RLD arm were removed due to an unacceptable degree of irritation (irritation score ≥ 3).

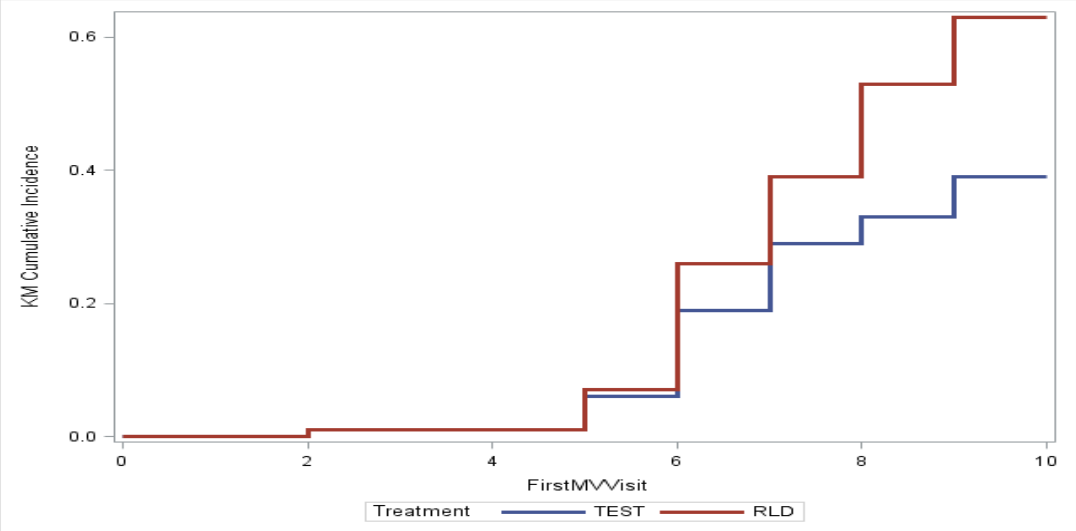
4.2.7.5 Other Endpoint: Days from Patch Application Until Patch Removal due to Excessive Irritation

Table 18 shows the day from patch application to patch removal due to excessive irritation (≥ 3) among the 92 subjects in the FPPIRR population. Thirty-nine of the TEST patches vs 62 of the RLD patches were removed due to excessive irritation. Among the 39 TEST patch removals, 1 patch removal occurred on Day 3 (Visit 2), 5 removals occurred on Day 10 (Visit 5), 13 removals occurred on Day 12 (Visit 6), 10 removals occurred on Day 15 (Visit 7), 4 occurred on Day 17 (Visit 8), and 6 occurred on Day 19 (Visit 9). Among the 62 RLD patch removals, 1 patch removal occurred on Day 3 (Visit 2), 6 occurred on Day 10 (Visit 5), 18 removals occurred on Day 12 (Visit 6), 13 removals occurred on Day 15 (Visit 7), 14 occurred on Day 17 (Visit 8), and 10 occurred on Day 19 (Visit 9). Figure 3 shows the Kaplan-Meier cumulative incidence of patch removal due to excessive irritation by treatment group, which intuitively shows that TEST had patch removal (event) later than RLD in general. This analysis also supports the non-inferiority result of TEST vs. RLD based on the primary endpoint – cumulative mean irritation score in MPTP 12130.

Table 18: Number of Days until Patch Removal Due to Excessive Irritation in the FPPIRR Population (N=92) in Irritation Study MPTP-12130

Treatment	Visit of First Patch Removal due to Excessive Irritation							
	2 (Day 3)	3 (Day 5)	4 (Day 8)	5 (Day 10)	6 (Day 12)	7 (Day 15)	8 (Day 17)	9 (Day 19)
TEST (N=39)	1	0	0	5	13	10	4	6
RLD (N=62)	1	0	0	6	18	13	14	10

Figure 3. Kaplan Meier Cumulative Incidence of Patch Removal due to Excessive Irritation in the FPPIRR Population in Study MPTP-12130



In summary, the non-inferiority of the Mylan's Methylphenidate Transdermal System, 10 mg/9 hr (TEST) vs. Noven's Daytrana 10 mg (RLD) was established in irritation using the primary endpoint – mean irritation score across visits for the irritation study MPTP-12130. Analyses for the other endpoints also support the result based on the primary endpoint.

4.3 Sensitization Study MPTP-12130

4.3.1 STUDY DESIGN

Same as Section 4.1.1.

4.3.2 STUDY ENDPOINTS

Primary Endpoint: Potential Sensitization

Sponsor's definition: A subject was considered to be potentially sensitized if all of the following criteria were met:

a. The subject had at least 1 evaluation occurring at more than 24 hours (eg, at 48 or 72 hours) after the removal of the Challenge Phase patch.
b. The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.
d. If the subject completed a Re-Challenge Phase, the above 3 criteria were met during both the Challenge Phase and the Re-Challenge Phase.
e. Scores that resolved before 48 hours were generally considered to be due to irritation instead of sensitization.

FDA's definition is the same as the sponsor's definition, which is based on the FDA's guidance for Methylphenidate. For Criteria *c*, if the maximum score in the challenge or re-challenge phase is higher than the maximum score in the induction phase, this is considered as " numeric scores obtained during the Challenge Phase evaluations generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase".

4.3.3 SUBJECT DISPOSITION

Per-Protocol (PP) Patch Population for Sensitization (PPSEN):

Sponsor's PPSEN (SPPSEN):

To be included in the sensitization analysis as SPPSEN, a treatment should have been worn for the entire 21-day Induction Phase AND for the entire 48-hour Challenge Phase AND the subject must have returned for at least one of the scheduled evaluations at 48 or 72 hours after removal of the Challenge Phase application. If a treatment is removed prior to the end of the 48-hour

Challenge Phase due to an intolerable reaction, the application site was evaluated at 24, 48 and 72 hours after the patch removal and is included in the analysis using LOCF.

For those subjects demonstrating a sensitization reaction following the Challenge Phase of the study, a Re-Challenge Phase was conducted 4 to 8 weeks after the conclusion of the Challenge Phase Procedures.

Sixty-six subjects completed the Challenge phase and were included in SPPSEN. Among the 66 subjects, 31 subjects completed the Re-challenge phase.

FDA's PPSEN (FPPSEN): FDA's PPSEN is defined the same way as the sponsor's SPPSEN, which is based on the FDA's guidance for Methylphenidate.

FDA agreed with the sponsor's SPPSEN population: 66 subjects during the challenge phase, and 31 subjects during the re-challenge phase.

Table 19: Number of Subjects in Sponsor's and FDA's PP Population for Sensitization (PPSEN) in Irritation/Sensitization Study MPTP- 12130

	Sponsor's PPSEN			FDA's PPSEN		
	TEST	**RLD**	**Total N of Subjects**	**TEST**	**SLS**	**Total N of Subjects**
Randomized	100	100	100	100	100	100
PP Population for Sensitization during the Challenge Phase	**66**	**66**	**66**	**66**	**66**	**66**
Total Exclusion from PPSEN	34	34	34	34	34	34
Due to incomplete study	34	34	34	34	34	34
PP Population for Sensitization during the ReChallenge Phase	**31**	**31**	**31**	**31**	**31**	**31**

4.3.4 MISSING DATA AND IMPUTATION

Sponsor's Imputation:

No imputation was done because no patch was removed during the challenge phase.

FDA's Imputation:

Likewise, no imputation was done because no patch was removed during the challenge phase.

4.3.5 DEMOGRAPHICS

Table 20 shows the distribution of the demographic characteristics in the FPPSEN population during the challenge phase (N=66) and re-challenge phase (N=31). The 66 subjects in the FPPSEN population during the challenge were 60.6% females, 97.0% white, and had a mean age of 27.5 years old. The 31 subjects in the FPPSEN population during the re-challenge were 61.3% females, 96.8% white, and had a mean age of 29.0 years old.

Table 20: Demographics in the FDA's PPSEN (FPPSEN) Population in Challenge (N=66) and Re-Challenge (N=31) Phase of Study MPTP-12130

Phase	**Challenge**	**Re-Challenge**
Characteristics	**FPPSEN (N=66)**	**FPPSEN (N=31)**
Age (years)		
Mean (STD)	27.5 (7.6)	29.0 (8.0)
Female n (%)	40 (60.6%)	19 (61.3%)
Race n (%)		
White	64 (97.0%)	30 (96.8%)
Other	2 (3.0%)	1 (3.2%)

4.3.6 STATISTICAL RESULTS

Table 21 summarizes the frequency of irritation scores at each time point for TEST and RLD among the 66 FPPSEN subjects in the challenge phase and 31 subjects in the re-challenge phase.

Primary Endpoint: Potential Sensitization

Sponsor's Potential Sensitization:

In the sponsor's study report for MPTP 12130 (Table 14.7 of mptp-12130—study-report-body.pdf) and in the submitted SAS data set - Summary.xpt, 17 TEST vs. 19 RLD out of 66 SPPSEN subjects had potential sensitization (Table 22). If breaking down to the challenge and re-challenge phases (according to sponsor's submitted irritation/sensitization data: Irriraw.xpt), 37 TEST vs. 40 RLD had potential sensitization out of 66 SPPSEN subjects during the challenge phase (Table 22). Of the 66, 31 subjects entered the re-challenge phase. Of the 31 subjects, 9 TEST vs. 10 RLD had potential sensitization during the re-challenge phase (Table 22). Those who were potentially sensitized in both the challenge and re-challenge phases were classified as final potential sensitization: 17 TEST and 19 RLD.

FDA's Potential Sensitization:

According to FDA's analysis (Table 22), during the challenge phase, 19 TEST vs. 10 RLD patches had potential sensitization out of 66 FPPSEN subjects. During the re-challenge phase, 18 TEST vs. 8 RLD had potential sensitization out of 31 FPPSEN subjects. Both are different from the sponsor's results (in the data set Irriraw.xpt).
Combining the challenge and re-challenge phases, 18 TEST vs. 9 RLD patches (Table 23) have final potential sensitization, which is different from the sponsor's result in the study report (17 TEST vs. 19 RLD).A list of the 7 TEST and 10 RLD patches with discrepant results between the sponsor and the FDA's analysis is shown in Appendix A.

Table 21. Frequency of Irritation Scores at Each Time Point during the Challenge (N=66) and Re-Challenge (N=31) Phase of Study MPTP-12130 in the FPPSEN Population

Challenge Hour	TEST (N=66) n (%)										RLD (N=66) n (%)										
	0	1	2	3	4	5	6	7	9	10	0	1	2	3	4	5	6	7	8	9	10
0.5 (n=66)	7 (10.6)	16 (24.2)	21 (31.8)	0	18 (27.3)	0	0	4 (6.1)	0	0	7 (10.6)	14 (21.2)	23 (34.9)	0	17 (25.8)	0	0	4 (6.1)	0	0	1 (1.5)
24 (n=66)	20 (30.3)	10 (15.2)	18 (27.3)	0	17 (25.8)	1 (1.5)	0	0	0	0	17 (25.8)	10 (15.2)	18 (27.3)	0	15 (22.7)	2 (3.0)	1 (1.5)	3 (4.6)	0	0	0
48 (n=66)	16 (24.2)	11 (16.7)	26 (39.4)	0	9 (13.6)	1 (1.5)	3 (4.5)	0	0	0	12 (18.2)	14 (21.2)	23 (34.9)	0	12 (18.2)	2 (3.0)	2 (3.0)	1 (1.5)	0	0	0
72 (n=66)	22 (33.3)	7 (10.6)	27 (40.9)	1 (1.5)	9 (13.6)	0	0	0	0	0	19 (28.8)	7 (10.6)	27 (40.9)	0	13 (19.7)	0	0	0	0	0	0
Total (n=66)	65 (24.6)	44 (16.7)	92 (34.9)	1 (0.4)	53 (20.1)	2 (0.8)	3 (1.1)	4 (1.5)	0	0	55 (20.8)	45 (17.1)	91 (34.5)	0	57 (21.6)	4 (1.5)	3 (1.1)	8 (3.0)	0	0	1 (0.4)
Re-Challenge Hour	TEST (N=31) n (%)										RLD (N=31) n (%)										
	0	1	2	3	4	5	6	7	9	10	0	1	2	3	4	5	6	7	8	9	10
0.5 (n=31)	0	4 (12.9)	4 (12.9)	0	17 (54.8)	0	0	6 (19.4)	0	0	0	2 (6.5)	5 (16.1)	0	16 (51.6)	0	0	8 (25.8)	0	0	0
24 (n=31)	1 (3.2)	1 (3.2)	4 (12.9)	0	19 (61.3)	2 (6.5)	1 (3.2)	2 (6.4)	0	1 (3.2)	1 (3.2)	0	5 (16.1)	0	17 (54.8)	2 (6.5)	1 (3.2)	3 (9.7)	1 (3.2)	0	1 (3.2)
48 (n=30)	1 (3.3)	1 (3.3)	13 (43.3)	0	10 (33.3)	1 (3.3)	0	2 (6.7)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	16 (53.3)	0	6 (20.0)	1 (3.3)	1 (3.3)	1 (3.3)	0	2 (6.7)	1 (3.3)
72 (n=31)	1 (3.2)	2 (6.5)	20 (64.5)	1 (3.2)	1 (3.2)	3 (9.7)	0	3 (9.7)	0	0	1 (3.2)	2 (6.5)	19 (61.3)	1 (3.2)	3 (9.7)	1 (3.2)	1 (3.2)	3 (9.7)	0	0	0
Total	3 (2.4)	8 (6.5)	41 (33.3)	1 (0.8)	47 (38.2)	6 (4.9)	1 (0.8)	13 (10.6)	1 (0.8)	2 (1.6)	3 (2.4)	5 (4.1)	45 (36.6)	1 (0.8)	42 (34.2)	4 (3.3)	3 (2.4)	15 (12.2)	1 (0.8)	2 (1.6)	2 (1.6)

Table 22. Frequency of Potential Sensitization during the Challenge and Re-Challenge Phase of Study MPTP-12130 Based on Sponsor's IrriRaw.xpt and FDA

Sponsor's Potential Sensitization based on IrriRaw.xpt				**FDA's Potential Sensitization**			
Challenge Phase	**Potential Sensitization**			**Challenge Phase**	**Potential Sensitization**		
Treatment	**No**	**Yes**	**Total**	**Treatment**	**No**	**Yes**	**Total**
TEST	29 (43.9%)	37 (56.1%)	66 (100%)	**TEST**	47 (71.2%)	19 (28.8%)	66 (100%)
RLD	26 (39.4%)	40 (60.6%)	66 (100%)	**RLD**	56 (84.8%)	10 (15.2%)	66 (100%)
Total	55	77	132	**Total**	103	29	132
Re-Challenge Phase	**Potential Sensitization**			**Re-Challenge Phase**	**Potential Sensitization**		
Treatment	**No**	**Yes**	**Total**	**Treatment**	**No**	**Yes**	**Total**
TEST	22 (71.0%)	9 (29.0%)	31 (100%)	**TEST**	13 (41.9%)	18 (58.1%)	31 (100%)
RLD	21 (67.7%)	10 (32.3%)	31 (100%)	**RLD**	23 (74.2%)	8 (25.8%)	31 (100%)
Total	43	19	62	**Total**	36	26	62

Table 23 Frequency of Final Potential Sensitization Combining Challenge and Re-Challenge Phase of MPTP 12130 Among the 66 FPPSEN Subjects based on Sponsor's Study Report and FDA

Sponsor's Potential Sensitization based on Study Report				FDA's Potential Sensitization			
	Potential Sensitization				Potential Sensitization		
Treatment	No	Yes	Total	Treatment	No	Yes	Total
TEST	49 (74.2%)	17 (25.8%)	66 (100%)	TEST	48 (72.7%)	18 (27.3%)	66 (100%)
RLD	47 (71.2%)	19 (28.8%)	66 (100%)	RLD	57 (86.4%)	9 (13.6%)	66 (100%)
Total	96	36	132	Total	105	27	132

Since there are sufficient number of events with potential sensitization in study MPTP-12130, proportion of subjects with potential sensitization was compared between TEST and RLD (Table 24) using the method described in Section 3.2. The objective is to test a non-inferiority hypothesis as follows: H_0: $P_T - P_R > \delta$ (Inferior); H_1: $P_T - P_R \leq \delta$ (Non-inferior).

Among the 66 subjects in the FPPSEN population, 55 (83.3%) subjects had concordant scores (diagonal) between TEST and RLD, and 11 (16.7%) subject had discordant (off-diagonal) scores. TEST had 18 (P_T=0.273) patches with potential sensitization, and RLD had 9 (P_R= 0.136) patches with potential sensitization. The point estimate of $P_T - P_R$ was 0.137 (Table 25). The one-sided 95% upper bound for $P_T - P_R$ was 0.237. Based on the 95% upper confidence bound for the difference in proportions, the TEST patch might exceed the RLD patch in the proportion of subjects with potential sensitization by at most 23.7 percentage points.

Table 24 Proportion of Subjects with Potential Sensitization (PS) by TEST and RLD in the FPPSEN Population in the Challenge Phase of Study MPTP-12130

	TEST PS		
RLD PS	No	Yes	Total
No	47 (71.2%)	10 (15.2%)	57 (86.4%)
Yes	1 (1.5%)	8 (12.1%)	9 (13.6%)
Total	48 (72.7%)	18 (27.3%)	66 (100%)

Table 25 Non-Inferiority Test for Proportion of Subjects with Potential Sensitization (PS) in the FPPSEN Population in the Challenge Phase of Study MPTP-12130

Hypothesis	**P (TEST PS) P_T (N=66)**	**P (RLD PS) P_R (N=66)**	**Point Estimate of $P_T - P_R$**	**95%UB of $P_T - P_R$**
H_0: $P_T - P_R > \delta$ (Inferior) H_1: $P_T - P_R \leq \delta$ (Non-inferior)	27.3%	13.6%	13.7%	23.7%

In summary, among the 66 subjects of FPPSEN in Study MPTP 12130, TEST has 13.7 more percentage point of subjects with potential sensitization than RLD (P_T=27.3%, P_R= 13.6%), with the one-sided 95% upper bound of 23.7% for $P_T - P_R$.

5. SUMMARY AND CONCLUSIONS

5.1 Comments on Sponsor's Analysis

For sensitization, although the sponsor used the same definition as what is recommended in the FDA guidance, their number of subjects with potential sensitization for each treatment group did not agree with FDA's result, which leads to different sensitization results. According to the FDA, TEST has 13.7% more subjects with potential sensitization than RLD (P_T=27.3%, P_R= 13.6%), with the one-sided 95% upper bound of 23.7% for $P_T - P_R$ (Tables 24 and 25). According to the sponsor, TEST has 3% less subjects with potential sensitization than RLD (P_T=25.8%, P_R= 28.8%). A list of subjects (7 TEST and 10 RLD) with discrepant results between the sponsor and FDA is provided in Appendix A.

5.2 Summary and Conclusions

5.2.1 ADHESION

Study MPTP 12130:

Primary Endpoint: Cumulative Mean Adhesion Score:

The Least Square Mean (± standard error) was 0.087 ± 0.025 for the TEST arm and 0.409 ± 0.042 for the RLD arm among the 100 subjects in the FPPPA. The one-sided 95% upper bound of $U_T - 1.25U_R$ was -0.517, which was less than 0. Therefore, the non-inferiority of TEST vs. RLD in adhesion was established using the primary endpoint – mean adhesion score across visits for study MPTP-12130.

Other Endpoint: Proportion of Subjects with a Meaningful Degree of Detachment

In this report, a meaningful degree of detachment is defined as having at least one adhesion score ≥3.

In the FDA's Per Protocol Population for adhesion (FPPPA, n=100), no TEST (P_T=0) versus 1% of RLD (P_R) had a meaningful degree of detachment. The point estimate of $P_T - P_R$ was -1.0%, and the one-sided 95% upper bound for $P_T - P_R$ was 2.6%.

In summary, the non-inferiority of the test product (TEST: Methylphenidate Transdermal Systems 10mg/9 hours (3.3 mg/hr) manufactured by Mylan Technologies Inc.) versus the reference listed product (RLD: Daytrana Transdermal System, 3.3 mg/hr manufactured by Noven Pharms Inc.) was established in adhesion based on the primary endpoint – mean adhesion score across visits, among the 100 FPPPA subjects in Study MPTP 12130.

5.2.2 IRRITATION

Study MPTP 12130:

Primary Endpoint: Cumulative Mean Irritation Score:

The Least Squares Mean (± standard error) was 1.99 ± 0.12 for TEST and 2.45 ± 0.12 for RLD in the FPPIRR (n=92) population. The one-sided 95% upper bound of $U_T - 1.25U_R$ was -0.96, which was less than zero. Therefore, the non-inferiority of Mylan's Methylphenidate Transdermal System (TEST) vs. Noven's Daytrana Transdermal System (RLD) was established in irritation using the primary endpoint – mean irritation score across visits, among the 92 FPPIRR subjects for Study MPTP 12130.

Other Endpoint: Proportion of Subjects with a Meaningful Degree of Irritation

In the FPPIRR (n=92), 45.7% of TEST (P_T) versus 70.7% of RLD (P_R) had at least one irritation score greater than or equal to 3. The point estimate of $P_T - P_R$ was -25%, and the one-sided 95% upper bound for $P_T - P_R$ was -15.8%.

In summary, the non-inferiority of the test product (TEST: Methylphenidate Transdermal Systems 10mg/9 hours (3.3 mg/hr) manufactured by Mylan Technologies Inc.) versus the reference listed product (RLD: Daytrana Transdermal System, 3.3 mg/hr manufactured by Noven Pharms Inc.) was established in irritation based on the primary endpoint – mean irritation score across visits, among the 92 FPPIRR subjects in Study MPTP 12130.

5.2.3 SENSITIZATION

Study MPTP 12130:

In summary, among the 66 subjects of FPPSEN in Study MPTP 12130, TEST has 13.7 more percentage point of subjects with potential sensitization than RLD (P_T =27.3%, P_R = 13.6%), with the one-sided 95% upper bound of 23.7% for the proportion difference between TEST and RLD: $P_T - P_R$.

REFERENCES

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4. McNemar Q, Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika* 1947; 12(2): 153-157.

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Appendix A.

Subjects with Discrepant Result of Potential Sensitization between the sponsor and FDA

Obs	Treatment A (TEST) / B (RLD)	Subject Identifier	Study Phase (c)	Visit Number (n)	Irritation Score during Challenge or Rechallenge	Last Irritation Score during Challenge or Rechallenge	Maximum Irritation Score during Challenge or Rechallenge	Maximum Irritation Score during Induction Phase	Sponsor's Final Potential Sensitization in Study Report and Summary.xpt	Sponsor's Potential Sensitization in Challenge or Rechallenge IrriRaw.xpt	FDA's Final Potential Sensitization	FDA's Potential Sensitization in Challenge Phase	FDA's Potential Sensitization in ReChallenge Phase
1	A	(b) (6)	Challenge	12	2	2	2	4	Yes	Yes	No	No	
2	A		Challenge	13	2	2	2	4	Yes	Yes	No	No	
3	A		Challenge	14	2	2	2	4	Yes	Yes	No	No	
4	A		Challenge	15	2	2	2	4	Yes	Yes	No	No	
5	A		Challenge	12	4	2	4	2	No	Yes	Yes	Yes	
6	A		Challenge	13	2	2	4	2	No	Yes	Yes	Yes	
7	A		Challenge	14	2	2	4	2	No	Yes	Yes	Yes	
8	A		Challenge	15	2	2	4	2	No	Yes	Yes	Yes	
9	A		Re-Challenge	17	4	2	4	2	No	No	Yes		Yes
10	A		Re-Challenge	18	4	2	4	2	No	No	Yes		Yes
11	A		Re-Challenge	19	2	2	4	2	No	No	Yes		Yes
12	A		Re-Challenge	20	2	2	4	2	No	No	Yes		Yes
13	A		Challenge	12	4	2	4	2	No	Yes	Yes	Yes	
14	A		Challenge	13	4	2	4	2	No	Yes	Yes	Yes	
15	A		Challenge	14	2	2	4	2	No	Yes	Yes	Yes	
16	A		Challenge	15	2	2	4	2	No	Yes	Yes	Yes	
17	A		Re-Challenge	17	4	2	4	2	No	No	Yes		Yes

18	A	(b) (6)	Re-Challenge	18	4	2	4	2	No	No	Yes		Yes
19	A		Re-Challenge	19	4	2	4	2	No	No	Yes		Yes
20	A		Re-Challenge	20	2	2	4	2	No	No	Yes		Yes
21	A		Challenge	12	4	2	4	2	No	Yes	Yes	Yes	
22	A		Challenge	13	2	2	4	2	No	Yes	Yes	Yes	
23	A		Challenge	14	2	2	4	2	No	Yes	Yes	Yes	
24	A		Challenge	15	2	2	4	2	No	Yes	Yes	Yes	
25	A		Re-Challenge	17	4	2	4	2	No	No	Yes		Yes
26	A		Re-Challenge	18	4	2	4	2	No	No	Yes		Yes
27	A		Re-Challenge	19	4	2	4	2	No	No	Yes		Yes
28	A		Re-Challenge	20	2	2	4	2	No	No	Yes		Yes
29	A		Challenge	12	2	2	2	2	Yes	Yes	No	No	
30	A		Challenge	13	2	2	2	2	Yes	Yes	No	No	
31	A		Challenge	14	2	2	2	2	Yes	Yes	No	No	
32	A		Challenge	15	2	2	2	2	Yes	Yes	No	No	
33	A		Challenge	12	4	2	4	2	No	Yes	Yes	Yes	
34	A		Challenge	13	4	2	4	2	No	Yes	Yes	Yes	
35	A		Challenge	14	2	2	4	2	No	Yes	Yes	Yes	
36	A		Challenge	15	2	2	4	2	No	Yes	Yes	Yes	
37	A		Re-Challenge	17	4	2	4	2	No	No	Yes		Yes
38	A		Re-Challenge	18	4	2	4	2	No	No	Yes		Yes

39	A	(b) (6)	Re-Challenge	19	2	2	4	2	No	No	Yes		Yes
40	A		Re-Challenge	20	2	2	4	2	No	No	Yes		Yes
41	A		Challenge	12	4	2	4	4	Yes	Yes	No	No	
42	A		Challenge	13	4	2	4	4	Yes	Yes	No	No	
43	A		Challenge	14	4	2	4	4	Yes	Yes	No	No	
44	A		Challenge	15	2	2	4	4	Yes	Yes	No	No	
45	A		Re-Challenge	17	7	5	7	4	Yes	Yes	No		Yes
46	A		Re-Challenge	18	4	5	7	4	Yes	Yes	No		Yes
47	A		Re-Challenge	19	7	5	7	4	Yes	Yes	No		Yes
48	A		Re-Challenge	20	5	5	7	4	Yes	Yes	No		Yes
49	B		Challenge	12	2	2	2	6	Yes	Yes	No	No	
50	B		Challenge	13	2	2	2	6	Yes	Yes	No	No	
51	B		Challenge	14	2	2	2	6	Yes	Yes	No	No	
52	B		Challenge	15	2	2	2	6	Yes	Yes	No	No	
53	B		Challenge	12	2	2	2	4	Yes	Yes	No	No	
54	B		Challenge	13	2	2	2	4	Yes	Yes	No	No	
55	B		Challenge	14	2	2	2	4	Yes	Yes	No	No	
56	B		Challenge	15	2	2	2	4	Yes	Yes	No	No	
57	B		Challenge	12	4	2	4	7	Yes	Yes	No	No	
58	B		Challenge	13	4	2	4	7	Yes	Yes	No	No	
59	B		Challenge	14	2	2	4	7	Yes	Yes	No	No	
60	B		Challenge	15	2	2	4	7	Yes	Yes	No	No	
61	B		Re-Challenge	17	7	2	7	7	Yes	Yes	No		No

62	B	(b) (6)	Re-Challenge	18	7	2	7	7	Yes	Yes	No		No
63	B		Re-Challenge	19	4	2	7	7	Yes	Yes	No		No
64	B		Re-Challenge	20	2	2	7	7	Yes	Yes	No		No
65	B		Challenge	12	4	2	4	6	Yes	Yes	No	No	
66	B		Challenge	13	4	2	4	6	Yes	Yes	No	No	
67	B		Challenge	14	4	2	4	6	Yes	Yes	No	No	
68	B		Challenge	15	2	2	4	6	Yes	Yes	No	No	
69	B		Re-Challenge	17	7	5	7	6	Yes	Yes	No		Yes
70	B		Re-Challenge	18	4	5	7	6	Yes	Yes	No		Yes
71	B		Re-Challenge	19	5	5	7	6	Yes	Yes	No		Yes
72	B		Re-Challenge	20	5	5	7	6	Yes	Yes	No		Yes
73	B		Challenge	12	4	2	4	5	Yes	Yes	No	No	
74	B		Challenge	13	4	2	4	5	Yes	Yes	No	No	
75	B		Challenge	14	4	2	4	5	Yes	Yes	No	No	
76	B		Challenge	15	2	2	4	5	Yes	Yes	No	No	
77	B		Re-Challenge	17	4	2	4	5	Yes	Yes	No		No
78	B		Re-Challenge	18	4	2	4	5	Yes	Yes	No		No
79	B		Re-Challenge	19	4	2	4	5	Yes	Yes	No		No
80	B		Re-Challenge	20	2	2	4	5	Yes	Yes	No		No
81	B		Challenge	12	0	2	0	5	Yes	Yes	No	No	

82	B	(b) (6)	Challenge	13	4	2	4	5	Yes	Yes	No	No	
83	B		Challenge	14	4	2	4	5	Yes	Yes	No	No	
84	B		Challenge	15	2	2	4	5	Yes	Yes	No	No	
85	B		Re-Challenge	17	7	3	7	5	Yes	Yes	No		Yes
86	B		Re-Challenge	18	5	3	7	5	Yes	Yes	No		Yes
87	B		Re-Challenge	19	4	3	7	5	Yes	Yes	No		Yes
88	B		Re-Challenge	20	3	3	7	5	Yes	Yes	No		Yes
89	B		Challenge	12	2	4	2	4	Yes	Yes	No	No	
90	B		Challenge	13	4	4	4	4	Yes	Yes	No	No	
91	B		Challenge	14	4	4	4	4	Yes	Yes	No	No	
92	B		Challenge	15	4	4	4	4	Yes	Yes	No	No	
93	B		Challenge	12	2	4	2	5	Yes	Yes	No	No	
94	B		Challenge	13	4	4	4	5	Yes	Yes	No	No	
95	B		Challenge	14	4	4	4	5	Yes	Yes	No	No	
96	B		Challenge	15	4	4	4	5	Yes	Yes	No	No	
97	B		Re-Challenge	17	4	2	4	5	Yes	Yes	No		No
98	B		Re-Challenge	18	4	2	4	5	Yes	Yes	No		No
99	B		Re-Challenge	19	4	2	4	5	Yes	Yes	No		No
100	B		Re-Challenge	20	2	2	4	5	Yes	Yes	No		No
101	B		Challenge	12	4	4	4	5	Yes	Yes	No	No	
102	B		Challenge	13	4	4	4	5	Yes	Yes	No	No	
103	B		Challenge	14	4	4	4	5	Yes	Yes	No	No	

104	B	(b) (6)	Challenge	15	4	4	4	5	Yes	Yes	No	No
105	B		Challenge	12	2	2	2	2	Yes	Yes	No	No
106	B		Challenge	13	2	2	2	2	Yes	Yes	No	No
107	B		Challenge	14	2	2	2	2	Yes	Yes	No	No
108	B		Challenge	15	2	2	2	2	Yes	Yes	No	No

STATISTICAL FILLING REVIEW AMENDMENT

ANDA	**206497**
DRUG NAME	**Methylphenidate**
APPLICANT NAME	**Mylan Technologies Inc.**
REFERENCE LISTED DRUG (RLD)	**Daytrana® 10mg (releasing 10 mg/9 hours), Noven Pharmaceuticals Inc**
***Primary* REVIEWER**	**Guoying Sun**
***Secondary* REVIEWER**	**Stella Grosser**
DATE	9/12/2014

RECOMMENDATION TO DCR FROM A STATISTICAL PERSPECTIVE	
ACCEPTABLE	X
NOT ACCEPTABLE	

Reviewed by:

Guoying Sun, Ph.D.
Primary Reviewer Generic Team, DBVI/OB/OTS/CDER

Stella Grosser, Ph.D., Team Leader
Secondary Reviewer Generic Team, DBVI/OB/OTS/CDER

Reference ID: 3628052

Reason for the Refuse to File (RTF):

From Department of Clinical Review perspective, the data from a skin irritation/sensitization/adhesion study (MPTP-12130) and the adhesion study (MPTP-11030) were not acceptable for receiving the ANDA. The submission was incomplete.

DBVI/OB Response to Sponsor's Resubmission after Refuse to Receive:

The adhesion data from study MPTP-11030 is acceptable.

As indicated in the original filing review, the data from study MPTP-12130 are acceptable for statistical review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUOYING SUN
09/15/2014

STELLA C GROSSER
09/16/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

OTHER REVIEWS

Addendum to Review of Skin Irritation, Sensitization and Adhesion Studies Following OSIS Inspection Report for ANDA 206497

ANDA number	206497
Drug Product	Methylphenidate Transdermal System
Strength(s)	10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
Applicant Name	Mylan Technologies, Inc.
Treatment Indication	treatment of Attention Deficit Hyperactivity Disorder
Reference Listed Drug (RLD)	Daytrana® Transdermal System, 3.3 mg/hr
NDA number for RLD	NDA 021514
RLD Applicant Name	Noven Pharmaceuticals, Inc.
Original Submission Date	12/13/2013
Materials Reviewed	(b) (4) ANDA 204403 OSIS inspection report 07/21/2015 ANDA 206497 OSIS inspection report 07/15/2016 Draft Product-Specific Guidance recommended in Jul 2010
Primary Reviewer	Sunny Tse, PhD Clinical Reviewer Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office Generic Drugs (OGD)
Secondary Reviewer	Ying Fan, PhD Acting Team Leader, ANDA Team DCR, OB, OGD
Tertiary Reviewer	Daiva Shetty, MD Acting Director DCR, OB, OGD
Date of Completion	07/20/2016
DCR Conclusion	The Division of Clinical Review concludes that the skin irritation/sensitization/adhesion study (MPTP-12130) is NOT adequate to support approval of the application. OSIS inspection finding is acceptable. However, acceptable inspection findings do not change DCR's original conclusion.

Table of Contents

Addendum to Review of Skin Irritation, Sensitization and Adhesion Studies Following OSIS Inspection Report for ANDA 206497

1 Executive Summary

1.1 Approval Recommendation

The Division of Clinical Review concludes that the skin irritation/sensitization/adhesion study (MPTP-12130) is NOT adequate to support approval of the application. Based on Office of Study Integrity and Surveillance (OSIS) inspection findings, the clinical data from the skin irritation/sensitization/adhesion study (MPTP-12130) are acceptable. However, acceptable inspection findings do not change DCR's original conclusion.

1.2 Summary of Clinical Findings

This is an addendum to the original DCR review dated 03/28/2016 which was completed prior to OSIS inspection results. The original DCR review dated 03/28/2016 reviewed skin irritation/sensitization/adhesion study (MPTP-12130). The applicant's Methylphenidate Transdermal System (test product) was shown to be non-inferior to the Daytrana® Transdermal System (reference) with regard to irritation, with substantial potential for sensitization. The data demonstrated non-inferiority of the test product compared to the reference with regard to adhesion.

The OSIS review for ANDA 206497 dated 07/15/2016 was not taken into consideration by DCR as it addressed study MPHP-11007, (b) (4) According to OSIS reviews for (b) (4) ANDA 204403 (Rivastigmine Transdermal System, 4.6 mg/24 hours, 9.5 mg/24 hours, and 13.3 mg/24 hours) dated 07/21/2015, OSIS concluded that no action was indicated (NAI) for both ANDAs at the Cetero Research 4801 Amber Valley Pkwy S., Fargo, ND 58104 clinical site. This particular clinical site is the same as the one for the current submission for skin irritation/sensitization/adhesion study (MPTP-12130). Therefore, the clinical data from the skin irritation/sensitization/adhesion study (MPTP-12130) are acceptable.

2 Additional Clinical Review

2.1 Review of the Office of Study Integrity and Surveillance (OSIS) Inspection Reports (07/21/2015, 02/22/2016, and 07/15/2016)

OSIS had considered all sites submitted by the applicant and had corresponding clinical site inspection histories except for the study MPHP-11007 clinical site. Given this, the study MPHP-11007 clinical site was selected for inspection. DCR did not take into consideration the 07/15/2016 ANDA 206497 OSIS report as study MPHP-11007 (b) (4) OSIS had inspected the MPTP-12130 clinical site and the review was submitted under ANDAs (b) (4) and 204403. Therefore inspection was not conducted for study MPTP-12130 for this current ANDA. This clinical site had prior acceptable inspection history. See below for details.

ANDA 206497 Clinical Site Inspection History

STUDY	PRINCIPAL INVESTIGATOR / CLINICAL SITE	HAS PRIOR INSPECTION HISTORY	Comment
skin irritation/sensitization/adhesion study (MPTP-12130)	Alan K. Copa, PharmD Cetero Research 4801 Amber Valley Pkwy S., Fargo, ND 58104	(b) (4) NAI on 07/21/2015 for ANDA 204403	Data acceptable based on acceptable OSIS inspection history.

Per OSIS findings of acceptable inspectional history, DCR concludes that clinical data from the skin irritation/sensitization/adhesion study (MPTP-12130) are acceptable for the review.

2.2 Conclusion and Recommendation

2.2.1 Conclusion

Based on acceptable OSIS inspection findings, the clinical data from the skin irritation/sensitization/adhesion study (MPTP-12130) are acceptable. However, acceptable inspection findings do not change DCR's original conclusion. The clinical data are NOT adequate to demonstrate that sensitization potential of the proposed generic methylphenidate transdermal system is no worse than the reference listed drug product. Therefore, the DCR concludes that the submitted evaluable skin irritation/sensitization/adhesion study (Study MPTP-12130) is not adequate to support approval of this application.

2.2.2 Recommendations

From the DCR perspective, skin irritation/sensitization/adhesion study (MPTP-12130) is inadequate to support approval of this application, contingent on approval recommendations from the other disciplines on the review team.

CLINICAL COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has completed its review and the following major deficiencies have been identified for Skin irritation/Sensitization/Adhesion study (Study MPTP-12130):

Study MPTP-12130 did not provide adequate data to ensure that the sensitization potential of the proposed generic methylphenidate transdermal system 10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr) (test) is no worse than that of the reference product.

We do not agree with your numbers of subjects sensitized or potentially sensitized to each product. When we applied the four criteria described in the FDA product-specific bioequivalence guidance to your data,[1] of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the reference product, respectively, with 100% more test sites than reference sites showing potential sensitization.

We noted that you interpreted the term *generally higher* in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we considered it reasonable and reevaluated your data using your interpretation. Using your interpretation of *generally higher*, 33 test versus 27 reference product skin sites showed potential sensitization. The proportions are 50% for test versus 40.9% for reference product, with 22% more test sites than reference product sites showing sensitization.

The point estimate for the proportion of skin sites showing potential sensitization was higher for the test product compared with the reference product regardless of which interpretation of *generally higher* we used.

We note that there are several formulation differences between your test product and the reference product, which makes a difference in potential sensitization biologically plausible.

[1] Draft Guidance on Methylphenidate Film, Extended Release/Transdermal *Recommended Jul 2010* http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm220196.pdf

Daiva Shetty

Digitally signed by Daiva Shetty
Date: 7/25/2016 09:23:51AM
GUID: 5081924f00008b85e43df3f5824475e5

Sunny Tse

Digitally signed by Sunny Tse
Date: 7/25/2016 09:25:24AM
GUID: 508da6ff0002855c7da84880bd716ed2

Recommendation to FDA statistician from DCR (12/17/2015)
Methylphenidate Transdermal System, 10mg/9hrs, 15mg/9hrs, 20mg/9hrs & 30mg/9hrs

ANDA #	Study #	PP subject adjustment requested (yes/no)	Subject number	Reason for inclusion/exclusion	Comments
206497	MPTP-12130	yes; remove from irritation PP population and sensitization PP population	(b) (6)	Subject (b) (6) Visit 10 irritation data was missing, so the subject test and reference patches were absent for 2 days in induction.	This combined irritation, sensitization, and adhesion study is requested for statistics review.

DCR recommends not to perform detailed reviews on the following studies:

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
MPTP-11030 - Single-Dose Pilot Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fed BE	(b) (4)
MPTP-11007 - Comparative Evaluation of the Cumulative Irritation of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) following a 48 to 72 hour Wear in Healthy Adult Volunteers	Cumulative Irritation Study (n=32)	(b) (4)
MPTP-11125 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult	Fasting Bioequivalence	Overlay is allowed

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
Volunteers		
MPTP-12012 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fasting Bioequivalence	The applicant evaluated irritation. However, the study duration is only for 9 hours.
MPTP-12046 - Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Shire) in Healthy Adult Volunteers	Cumulative Irritation and Sensitization (n=100)	The sponsor noted data integrity issue and deficiencies in procedure by Novum Pharmaceutical Research Service. Due to data integrity issue, not recommended for the review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206497

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/14/2022 09:35:44 AM
To: BRAD.DAVIS@VIATRIS.COM
CC:
BCC: Megan.Tychinski@fda.hhs.gov
Subject: ANDA 206497, Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr

Hello,

Attached is the official copy of your action letter for this ANDA. Please confirm receipt of this email with the RPM, Megan Tychinski (Megan.Tychinski@fda.hhs.gov) for your ANDA.

Thanks,

Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Please find the attached documents below:

A206497N000DPM-ApprovalLetter01.pdf

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL AP or TA (NEW STRENGTH)**

RPM and TL: Megan Tychinski / Joe Shin

ANDA #: 206497 Applicant: Mylan Technologies Inc.
Established Product Name: Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr

Basis of Submission (BOS)/RLD (Application#/Proprietary Name/Applicant): NDA 021514, Daytrana Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, Noven Pharmaceuticals, Inc.

If BOS discontinued: [insert hyperlink to FRN] ☐ Safety/effectiveness FRN pending

Select, as applicable:

☒ RX ☐ OTC

☐ History of tentative or split approval action

☐ Shared Bio Studies (list ANDA number(s)) ☐ Shared Labeling (list ANDA number(s) _____)

☐ Memo uploaded for PAL item or OGDP confirmation

Priority: ☒ First Generic Approval (i.e., no other generics approved) ☐ Drug Shortage ☐ PEPFAR ☐ CGT

☐ Other priority _____

Misc: ☐ REMS ☒ Combination product ☐ Suitability Petition ☐ 180-day language ☐ MOU ☐ PEPFAR

☒ ***RPM Has Verified the Following:*** **Date: 3/1/2022**

1. ANDA number, NDA/RLD, Drug product and strength(s) are correct on all discipline/subdiscipline reviews
2. All submissions have been reviewed: Relevant disciplines are adequate and finalized/archived in the appropriate system of record
3. Most recent BE guidance is included in the review or a memo has been uploaded
4. No RLD updates or changes to exclusivity/patents impact endorsed labeling
5. All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d). (Not applicable to supplements)
6. OSIS Clinical Endpoint and Bioequivalence Site Inspections acceptable or not applicable
7. No blocking legal or regulatory issue (refer to Policy Alert Tracker)
8. OGD Communications has been notified if Priority Approval (First generic, Drug Shortage, PEPFAR, CGT, other OGD Communications priorities)
9. OMIR is Approve with no new facility alerts and a DP and API manufacturer listed in Submission Facility Status View
10. No open issues or tasks in Platform
11. No pending consults
12. Filing review completed for NSA or reformulation
13. PNR review is current
14. Correct language, format and content in action letter (e.g., relevant contact from 356h form)
15. Endorsements are within 29 days

Discipline Completion Dates:

Bioequivalence **2/17/2022** Labeling **7/23/2021** Clinical **2/12/2018**	Integrated Quality Assessment: _____ If there is no IQA, provide the applicable date(s): • Chemistry **2/22/2022** • Microbiology • Biopharmaceutics/Dissolution **2/17/2022** DMF No(s). (b) (4) Date(s) Acceptable **5/17/2021**

Additional Notes (if applicable)

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 3/9/2022
Name: ARC

Patent/Exclusivity Certification:

☐ **No Relevant Patents** ☐ **PI** ☒ **PII** ☐ **PIII** ☒ **PIV** ☐ **section viii**

Reminders:

- Check the policy alert list for any pending exclusivity determinations
- Verify in the Orange Book there are no unexpired ODE's that cover the active moiety
- Confirm the ANDA is not blocked by other ANDA's eligibility for 180-day CGT exclusivity
- Confirm S/E determination completed for RLDs in the discontinued section of the OB

RLD = **Daytana** NDA# **21514** ☒ **RX or** ☐ **OTC**
Date Checked in Orange Book#: **3/9/2022**

Type of Letter:

☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL AP or TA (NEW STRENGTH)

Forfeiture Information

- Confirm whether the first applicant remains eligible for 180-day exclusivity (i.e., that a forfeiture event under section 505(j)(5)(D) has not occurred) and document the determination

Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐
If yes, the date forfeiture memo was completed
Date _____ ANDA # _____

Competitive Generic Therapy 75 Day Special Forfeiture Rule:
First Applicant: ANDA # _____
Date of Approval: _____
75 Day Date: _____

180 Day Exclusivity Information

Is applicant eligible for H-W 180 day exclusivity Yes ☐ No ☐
☐ Sole
☐ Shared
Is applicant eligible for CGT 180 day exclusivity Yes ☐ No ☐
☐ Sole
☐ Shared
Is applicant blocked by a triggered CGT 180 day exclusivity
Yes ☐ No ☐
If no, the date and time checked for notification of commercial marketing: Date _____ Time: _____

Comments:

BOS = Daytrana, NDA 21514. ANDA submitted on 12/13/2013 with a PII certification to patent '446, a PIV certification to patents '705 and '211 (both exp 9/30/2018), and an exclusivity statement that the NPP exl expired. ANDA ACK for filing on 12/13/2013 for the 10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9hrs and 30 mg/9hrs strengths (LO dated 8/27/2015).

3/4/2014 patent amendment: PIV cert to newly listed '802 patent (exp 10/7/2025). Patent listed after ANDA submitted but before it was ACK for filing (no stay).
7/29/2015 patent amendment: PIV cert to newly listed '370 patent (exp 10/7/2025). Patent listed after ANDA submitted but before it was ACK for filing (no stay).
9/11/2015 patent amendment: Notice to FDA that Mylan sent notice of PIV cert.

9/29/2015 patent amendment: Documentation of delivery & receipt of notice of PIV cert. Notice sent via (b) (4) to Noven Pharmaceuticals in Miami, FL and Hisamitsu Pharmaceuticals in Tosu-Shi, Japan (both delivered 9/14/2015).
11/6/2015 patent amendment: Copy of complaint filed on 10/27/2015 in USDC for the District of Delaware for infringement of the '705, '211, '802, and '370 patents. CA no. 15-00979.
11/9/2016 patent amendment: Copy of Stipulation and Order of Dismissal entered on 10/27/2016 in 15-00979 to dismiss, with prejudice, all claims and counterclaims.
9/1/2017 patent amendment: PIV cert to newly listed '981 patent (exp 10/7/2025).
10/4/2017 patent amendment: Documentation of delivery & receipt of notice of PIV cert for the '981 patent. Notice sent via (b) (4) to Noven in Miami, FL x2 (both delivered 9/5/2017).
11/3/2017 patent amendment: Notice to FDA of no suit on PIV cert to patent '981.

180-day was forfeiture in the context of (b) (4) when the last qualifying patent for 180-day expired on 9/30/2018. 180-day is no longer a barrier to final AP.

There are no new patents listed in OB. Applicant has provided PIV cert to all unexpired patents and litigation has been dismissed. ANDA is eligible for immediate final AP.

180 Day/CGT Exclusivity Status/Landscape: N/A. Last qualifying patent for 180-day expired 9/30/2018
If known, impact on pending exclusivity determinations: N/A
If Tentative Approval, if known, anticipated full approval date: N/A

2. Final Decision

Date: 3/14/2022
Name: CAP

☒ Verified the following:

1. Completion of the following endorsement tasks, if applicable:
    a. Division of Legal and Regulatory Support Endorsement
    b. Paragraph IV Evaluation
    c. REMS Endorsement
    d. Quality Endorsement
    e. Bioequivalence Endorsement
    f. Clinical-Bioequivalence Endorsement
    g. Labeling Endorsement
    h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates in DARRTS since the Labeling Endorsement
5. No new issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments received since Quality Endorsement
9. No new amendments received since the RPM Team Leader Endorsement

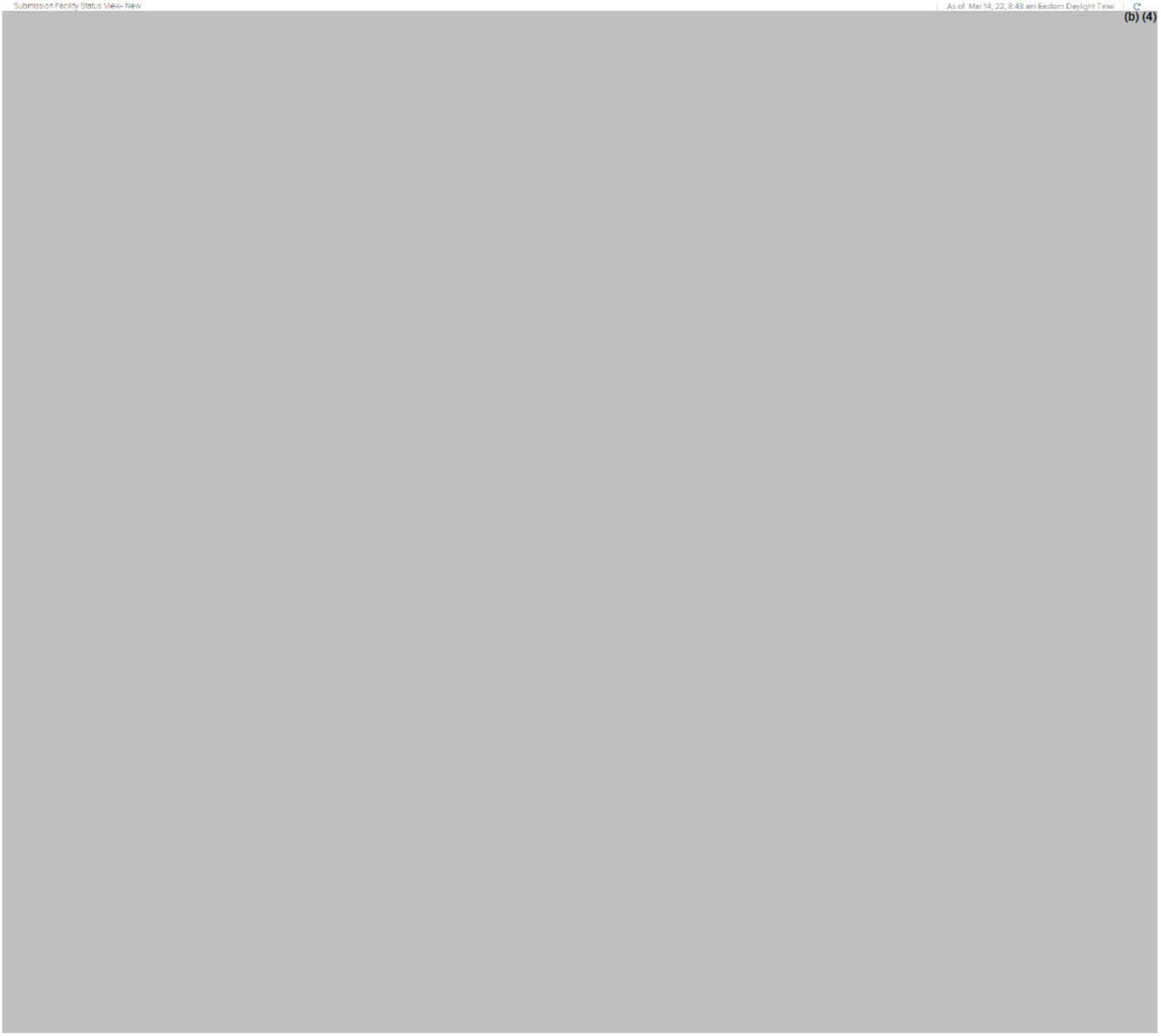
This **ANDA** is ready for **FULL APPROVAL**.

****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL****

Submission Facility Status View- New

As of: Mar 14, 22, 8:43 am Eastern Daylight Time

(b) (4)



(b) (4)

[redacted]

Endorsement Signatures (To be provided by endorsees in the event of Platform unavailability):

- Division of Legal and Regulatory Support Endorsement
  - Sign & Date_____
- Paragraph IV Evaluation
  - Sign & Date_____
- REMS Endorsement
  - Sign & Date_____
- Quality Endorsement
  - Sign & Date_____
- Bioequivalence Endorsement
  - Sign & Date_____
- Clinical-Bioequivalence Endorsement
  - Sign & Date_____
- Labeling Endorsement
  - Sign & Date_____
- RPM Team Leader Endorsement
  - Sign & Date_____
- ORO IO Endorsement
  - Sign & Date_____

REFERENCES / ASSOCIATED DOCUMENTS

Reference Name
4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Author	Role	Version	Change Date	Summary of Changes
Heather Strandberg	Author	1.0	2014-10-01	New Form
Kevin Denny	Reviser	2.0	2017-10-03	Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 Remove content adequately captured in the platform Update information captured in the Division of Legal and Regulatory Support Endorsement section Other minor administrative corrections to format and content
Kevin Denny	Reviser	3.0	2018-01-14	Update Final Decision section
Joe Shin	Reviser	4.0	2019-03-04	Changes made: 1) "No Relevant Patents" checkbox added to patent types; 2) Basis of Submission was updated to include (NDA#/Proprietary Name/Applicant); 3) Removed "(CR)" from the second checkbox in the RPM Evaluation section; 4) Added "Shared BE studies..." and "Shared Labeling..." bullets to the review date section; 5) Added a not applicable checkbox for the MMA question; 6) Sentence revised to include not applicable cases in the OSIS question
John Ibrahim/QM Team	Reviser/QM	5.0	2021-08-18	• Update page 1 (revisted ANDA information section, RPM checklist, and discipline completion dates) • QM Team updated Header, document #, & title to conform to OGD Controlled Documents Program naming conventions & formatting standards • QM Team updated Footer to conform to ISO 8601 – International Time & Date Standards

From: Thomas, Teena
To: Tychinski, Megan
Cc: Thomas, Teena
Subject: RE: ANDA 206497 - GDUFA 3/15/2022, DCR endorsement
Date: Wednesday, March 02, 2022 1:44:50 PM
Attachments: image001.png
image002.jpg
image003.jpg
image004.jpg
image005.jpg
image006.jpg

Hi Megan,

DCR TL informed me that: we do not think this change is going to impact our initial I/S/A study review conclusion.

Thank you,
Teena

From: Tychinski, Megan <Megan.Tychinski@fda.hhs.gov>
Sent: Wednesday, March 2, 2022 10:35 AM
To: Thomas, Teena <Teena.Thomas@fda.hhs.gov>
Subject: ANDA 206497 - GDUFA 3/15/2022, DCR endorsement

Hi Teena,

ANDA 206497 is routing for Full Approval endorsements, and I see that Lisa has already completed endorsement. I did want to confirm one thing with you before moving the ANDA forward. Last cycle, the applicant submitted their CR response on 2/25/2021, in which new batches were manufactured. OB completed an updated review of the new batches and asked the applicant to submit updated dissolution, which was submitted in the 12/16 2021 amendment. I wanted to confirm that these submissions have no impact on the Adequate DCR review from 2/12/2018, which primarily focuses on the Irritation/sensitization/adhesion study.

Thank you,

Megan

Megan Tychinski, PharmD, CAPM
Regulatory Project Manager
Office of Generic Drugs, FDA
10903 New Hampshire Ave
Building 75, Room 3708
Silver Spring, MD 20993
(p) 240-402-2717
Megan.Tychinski@fda.hhs.gov

2 page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/16/2022 05:07:37 PM
To: BRAD.DAVIS@VIATRIS.COM
CC: jennifer.nguyen@fda.hhs.gov
BCC: megan.tychinski@fda.hhs.gov
Subject: INFORMATION REQUEST ANDA 206497

Hello,

Please acknowledge receipt of the attached Quality IR and submit your response by February 18, 2022.

Kind regards,
Jennifer Nguyen

Please find the attached documents below:

A206497DP_IR.pdf

ANDA 206497

INFORMATION REQUEST

Mylan Technologies Inc.
3711 Collins Ferry Road
Morgantown, WV 26505
Attention: Bradley Davis

Dear Bradley Davis:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 13, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methylphenidate Transdermal System 10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9 hrs, and 30 mg/9 hrs.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug Product

(b) (4)

[redacted]

We request a prompt written response, no later than February 18, 2022 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment.

The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager, at jennifer.nguyen@fda.hhs.gov or (240) 402 - 8729.

Sincerely,

{See appended electronic signature page}

Jennifer Nguyen
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jennifer Nguyen

Digitally signed by Jennifer Nguyen
Date: 2/16/2022 05:05:44PM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/20/2021 10:20:19 AM
To: brad.davis@viatris.com
CC:
BCC: Megan.Tychinski@fda.hhs.gov
Subject: ANDA 206497, Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr

ANDA 206497
AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Mylan Technologies Inc.
3711 Collins Ferry Road
Morgantown, WV 26505
Attention: Bradley Davis
Head of Regulatory Science

Dear Bradley Davis:

Please see the attached letter in reference to your Abbreviated New Drug Application (ANDA) dated December 16, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr.

If you have any questions, call Regulatory Project Manager, Megan Tychinski, at (240) 402-2717.

Sincerely,

Division of Project Management
Office of Regulatory Operations
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

Please find the attached documents below:

A206497N000DPM-AcknowledgementLetter01.pdf

ANDA 206497

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Mylan Technologies Inc.
3711 Collins Ferry Road
Morgantown, WV 26505
Attention: Bradley Davis
Head of Regulatory Science

Dear Bradley Davis:

This is in reference to your amendment received on December 16, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements.* The GDUFA goal date for review of this priority minor amendment is March 15, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Megan Tychinski, Regulatory Project Manager, at (240) 402 - 2717.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Megan Tychinski

Digitally signed by Megan Tychinski
Date: 12/20/2021 10:13:05AM
GUID: 556dc3e3004eeaee540b388a26735dfb

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 09/29/2021 10:26:35 AM
To: BRAD.DAVIS@VIATRIS.COM
CC:
BCC: Megan.Tychinski@fda.hhs.gov
Subject: ANDA 206497, Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr

Hello,

Attached is the official copy of your action letter for this ANDA. Please confirm receipt of this email with the RPM, Megan Tychinski (Megan.Tychinski@fda.hhs.gov) for your ANDA.

Thanks,

Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Please find the attached documents below:

A206497N000DPM-CompleteResponse03.pdf

GDUFA II PRE FY2015 COMPLETE RESPONSE CHECKLIST**

RPM: Megan Tychinski **Action Type: Complete Response**

✓**RX or** ☐ **OTC** **ANDA #: 206497** **Applicant: Mylan Technologies Inc.** **Cohort Year: CY-2**
ANDA Drug Name and Strength: Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr and 3.3 mg/hr

Basis of Submission (RLD): NDA 021514, Daytrana Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, Noven Pharmaceuticals, Inc.

MAPP 5240.3 Priority ANDA: ✓ *(Is ANDA based on an approved Suitability Petition?* ☐ *Yes* ✓ *No)*
Does the ANDA contain REMS? ☐**Yes** ✓**No** *(If YES, CR Letter must go through the Safety Review Team; clearance may take 2-3 weeks)*

Regulatory Project Manager Evaluation:		**Date: 9/20/2021**	
Yes/N/A	**No**		
✓	☐	Have all submissions been reviewed and relevant disciplines finalized in CDER Informatics Platform? (date or N/A)	
		Date of Product Quality Review **8/30/2021 – Inadequate, Minor** Date of Bioequivalence Review **9/16/2021 – Inadequate, Minor** Date of Labeling Review **7/23/2021 - Adequate**	If applicable: Date of Last Complete Response **2/26/2018** Date of Microbiology Review **N/A** Date of Dissolution Review **1/11/2018 - Adequate** Date of Clinical Review **2/12/2018 - Adequate** Date of REMS Review **N/A**
✓	☐	Is DMF adequate and/or has the first cycle review been completed? **DMF** (b) (4) **Adequate, 5/17/2021**	
✓	☐	Are all consults complete? **Pharm Tox consult – review uploaded 6/28/2021**	
✓	☐	Are all issues resolved?	
✓	☐	Have all Policy issues (e.g., citizen petitions) been resolved? **Not Applicable** *If Policy issue, check with OGDP if necessary (e.g., to see whether CP blocks CR issuance).	
✓	☐	Is Overall Manufacturing Inspection Recommendation task acceptable/withhold? **Approve, 4/18/2021**	
✓	☐	Is OSIS complete (if applicable)? **Complete per BE review, 9/16/2021**	
		Notes (if applicable): **MMA okay; BE Guidance revised 11/2019; RLD Labeling revised 6/25/2021; Comparative (Threshold) Analyses – Adequate review, 6/1/2021**	
Draft Complete Response Letter			
✓	☐	Is CR letter drafted and uploaded to "Final Decision" task?	
Review Discipline/Division Endorsements			
✓	☐	If ANDA has a pending citizen petition, did RPM notify and obtain clearance from Office of Generic Drug Policy at OGDpolicy@fda.hhs.gov? Date **N/A**	
✓	☐	If ANDA contains REMS, did RPM notify and obtain clearance from REMS Coordinator? Date **N/A**	
Project Close-Out			
✓	☐	Is CR checklist uploaded into "Generate Action Package and assign Take Action tasks" task?	

***Entire Complete Response Checklist to be completed by the RPM*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 07/06/2021 10:24:45 AM
To: BRAD.DAVIS@VIATRIS.COM
CC:
BCC: Megan.Tychinski@fda.hhs.gov
Subject: ANDA 206497, Methylphenidate Transdermal System

ANDA 206497
AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Mylan Technologies Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Bradley Davis
Head of Regulatory Science, Dermals

Dear Sir:

Please see attachment regarding your 7/1/2021 amendment to ANDA 206497.

Sincerely,

Megan Tychinski
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

Please find the attached documents below:

A206497N000DPM-AcknowledgementLetter01.pdf

ANDA 206497

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Mylan Technologies Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Bradley Davis
Head of Regulatory Science, Dermals

Dear Sir:

This is in reference to your amendment received on July 1, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements.* The GDUFA goal date for review of this priority minor amendment is September 30, 2021.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Megan Tychinski, Regulatory Project Manager, at (240) 402 - 2717.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Megan Tychinski

Digitally signed by Megan Tychinski
Date: 7/06/2021 10:08:25AM
GUID: 556dc3e3004eeaee540b388a26735dfb

OPQ Consult Template

Topic (select from dropdown): Impurity

Primary Contact Name/Division/Office: Cedar Boakye | DIMRP/Branch 7

(Enter the name of the chemistry reviewer as it appears in Outlook)

1. **Application/Supplement Number:** A206497
   or DMF Number _____ **and Referencing ANDA Number** _____

   If the consult is for a DMF review, is it part of a DMF cluster review? (multiple DMFs for ANDAs referencing the same RLD) **Yes:** ☐ **No:** ☐

   RLD application number: NDA 21514 ,
   and product name: DAYTRANA®

2. **Target Action Date:** 08/24/2021

3. **Consult Due Date** 07/24/2021
   (Regular Consult: 3 months from consult request date / Fast Lane: 5 weeks from consult request date):

4. **Request Expedited Consult Review: Yes:** ☑ **No:** ☐
   If yes, the request must fit one of the following criteria:
   - ☑ **First Generic**
   - ☐ **Drug shortage**
   - ☐ **Patent Expiration within 6 months; Forfeiture Date** _____
   - ☐ **Expedited review granted**
   - ☐ **GDUFA Goal Date is within** ____ **months**

5. **Request Fast Lane Consult Review: Yes:** ☐ **No:** ☐
   (Fast Lane is only for specific questions related to genotoxicity or product use.)
   If yes, the request must fit one of the following requests:

   ☐ **AMES data review (complete package)**
   Do the AMES data and methods support the firm's conclusion that the impurity in question is not Genotoxic? See attached package in section 10

   ☐ **MDD calculation in support of M7 TTC**
   What is the maximum daily dose (MDD) for the listed RLD. (RLD name or #) _____
   Insert approved labeling below when needed.

   ☐ **Request for Duration of Use Calculation in support of M7 TTC**
   What is the maximum duration of treatment for the drug product considering all indications listed on the label? Please note that "off label" use does not apply.

M7: "In the case of intermittent dosing, the acceptable daily intake should be based on the total number of dosing days instead of the time interval over which the doses were administered and that number of dosing days should be related to the relevant duration category in Table 2. For example, a drug administered once per week for 2 years (i.e. 104 dosing days) would have an acceptable intake per dose of 20 ug."

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

Table 3: Acceptable Total Daily Intakes for Multiple Impurities

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Total Daily intake [µg/day]	120	60	30	5

☐ **Confirmation of term 'Advanced' cancer as the only indication**
The firm is requesting exclusion of PGI limit requirements claiming that the drug product is used for advanced cancer treatments ONLY. Please confirm that this is correct. Please note that "off label" use does not apply.

☐ **Clarification of product use** (population, duration, frequency)
The use instructions for the RLD are unclear (see RLD label in section 9. Please provide the following information about product use

6. **Specific request**: (chose one)
(For Fast Lane consults, see section 5 above and leave this section blank.)

☑ **a. Is the** ☑ **Maximum Daily Intake** ☐ **Specification Limit (chose one) of** [redacted] (b) (4) **for** _____ **acceptable in the product based on the MDD, route of administration and proposed product use?**

☐ **b. Is the size of the generic tablet/capsule safe for the intended use and population?**

☐ **c. Are the use instructions in section** _____ **of the product label for the generic product** ☐ **accurate** ☐ **appropriate (chose one)?**

☐ **d. Other consult request**
(Add a clear request for an opinion on the issue of concern)

7. **Reason for consult:** (This section should be a brief paragraph. Additional information can be provided under item 9. Describe the concerns about the level or presence of an ingredient or impurity/ product use/ label instructions/ specific differences from RLD that may have clinical effect/ tablet or capsule size/ other concerns.
Provide a brief history of comments to and from the applicant regarding the issue.)

(b) (4)

8. **Maximum Daily Intake/Exposure Calculation** (Insert the calculation of Maximum Daily Intake (MDI) of an inactive ingredient or Total Daily Intake (TDI) of an impurity based on the MDD.)

Calculation:

(b) (4)

Calculation guide
Inactive ingredient (mg/unit) x # units in MDD = MDI
Impurity limit (ppm or %) x MDD = TDI in mg or mcg
Solvent limit (ppm or %) x MDD = TDI in mg/day

MDD is usually in mcg, mg or g
(MDD x %)/100 or (MDD x ppm)/1,000,000 = TDI in mcg, mg or g
For liquids, convert w/v or v/v into weight/dose x number doses.
Transdermal Systems may be stated as weight/patch.

9. **Additional background information where needed** (Include relevant RLD information or other information that supports the consult request or explains the concern. For concerns about an impurity, describe the type of impurity, chemical structure and level reported in the RLD. For concerns about size, include a comparison of the RLD and generic.)

10. **Location and submission date of referenced information** (Provide the specific section(s) in eCTD submission or pages in paper submissions. For paper submissions, scanned copies of relevant pages should be included in section 13.)
    a. **Location:** 3.2.P.2. (sequence 0022)
    b. **Date:** 02/25/21

11. **Chemistry Reviewer Name** Cedar Boakye
    Date: 04/13/2021

12. **BC/QAL/TL concurrence with the consult:** ☑
    BC/QAL/TL Name Meenal Chavan

13. **Attachments:** (This section may be left blank if the location is in eCTD and clearly stated under item 11. For paper submission, include information other than the referenced documents cited in item 6 such as written summaries, data from other references, cross-references, reference to previous consults. These can be pasted at the end of the template.) **Attachment**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/26/2021 04:02:19 PM
To: BRAD.DAVIS@VIATRIS.COM
CC: jennifer.nguyen@fda.hhs.gov; megan.tychinski@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST ANDA 206497

Hello,

Please acknowledge receipt of the attached Quality Information Request and submit your response by April 2, 2021.

Kind regards,

Jennifer Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA

Please find the attached documents below:

A206497DP_IR.pdf

ANDA 206497

INFORMATION REQUEST

Mylan Technologies Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Bradley Davis

Dear Bradley Davis:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 13, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methylphenidate Transdermal System 10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9 hrs, and 30 mg/9 hrs.

We are reviewing the Quality section of your submission and have the following comments and information requests:

Drug Product

We request a prompt written response, no later than April 2, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an

amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/DRUG PRODUCT

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager, at jennifer.nguyen@fda.hhs.gov or (240) 402 - 8729.

Sincerely,

{See appended electronic signature page}

Jennifer Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jennifer Nguyen

Digitally signed by Jennifer Nguyen
Date: 3/26/2021 03:59:07PM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/02/2021 08:18:09 AM
To: BRAD.DAVIS@VIATRIS.COM
CC:
BCC: Megan.Tychinski@fda.hhs.gov
Subject: ANDA 206497, Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr

ANDA 206497

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Bradley Davis
Head of Regulatory Science, Dermals

Dear BRADLEY DAVIS,

Please see the attached letter in reference to your Abbreviated New Drug Application (ANDA) dated February 25, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

If you have any questions, call Regulatory Project Manager, Megan Tychinski, at (240) 402-2717.

Sincerely,

Division of Project Management
Office of Regulatory Operations
OFFICE OF GENERIC DRUGS

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

Please find the attached documents below:

A206497N000DPM-AcknowledgementLetter01.pdf

ANDA 206497

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Bradley Davis
Head of Regulatory Science, Dermals

Dear Sir:

This is in reference to your amendment received on February 25, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is August 24, 2021. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence was not submitted or not accepted, the GDUFA goal date for review of this priority major amendment is December 24, 2021.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Megan Tychinski, Regulatory Project Manager, at (240) 402 - 2717.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Megan Tychinski

Digitally signed by Megan Tychinski
Date: 3/02/2021 08:14:44AM
GUID: 556dc3e3004eeaee540b388a26735dfb

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/07/2020 09:00:06 AM
To: brad.davis@mylanlabs.com
CC:
BCC:
Subject: ANDA 206497 General Advice Letter

ANDA 206497

Dear Sir:

Please see the attached General Advice letter for ANDA 206497 and confirm receipt of this email to Frank Giannandrea at frank.giannandrea@fda.hhs.gov.

Sincerely,

Frank Giannandrea, Pharm.D.
Division of Project Management
Office of Regulatory Operations
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

Please find the attached documents below:

A206497N000DPM-GeneralAdviceLetter01.pdf

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

GENERAL ADVICE

Mylan Technologies, Inc.
110 Lake Street
St. Albans, VT 05478
Attention: Bradley Davis
Head of Regulatory Science, Dermals

Dear Sir,

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

This communication is to inform you that FDA has insufficient information to determine whether any differences in design for the user interface of your proposed product as compared to the reference listed drug (RLD) are acceptable and whether your proposed product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. One consideration is whether the proposed product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use.

Specifically, we request additional information regarding the proposed user interface for your product as compared to the user interface of the RLD. One way of providing information to assist us in evaluating the user interface of your proposed product as compared to the user interface of the RLD would be to submit to your ANDA the results of three comparative analyses (e.g., comparative labeling analysis, comparative task analysis, comparison of design of the delivery device), as well as your overall assessment of any identified differences for your proposed product when compared to the RLD. For background information on providing this type of information, see the draft guidance for industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), available at https://www.fda.gov/media/102349/download. Depending on the results of the threshold analyses discussed in this draft guidance, submission of additional data may be warranted, such as data from comparative use human factors studies, to assess the acceptability of differences identified in the user interface for your proposed product. As always, you can use an alternative approach to providing this information if it satisfies the requirements of the applicable statutes and regulations for approval.

Although FDA has issued a CR letter to your application and you have not yet submitted your response, this general advice letter is not an amended CR letter. However, your ANDA may not

be approved until we are able to conclude that your application meets all the requirements for approval, including addressing any potential issues related to your proposed user interface and labeling, to ensure that your proposed generic combination product can be expected to have the same clinical effect and safety profile as its RLD when administered to patients under the conditions specified in the labeling. You may choose to submit the comparative analyses and assessment in an amendment responding to this general advice letter or in your response to the CR letter. Please note that FDA review of amendments received in the period between FDA's issuance of a CR letter and the applicant's response to the CR letter are deferred until a response to the CR letter is received.

We also provide the following recommendations:

- Your comparative analyses and assessment should be placed in the eCTD section M5.3.5.4- Other Study reports and related information.
- If you believe that comparative analyses are not applicable to your specific ANDA, provide the appropriate justification within your CR resubmission as to why you believe that comparative analyses are not applicable to your product and, if appropriate, include an alternative approach that addresses the issues outlined in this letter.
- When you submit your response to the CR letter, prominently identify the submission with the following wording in bold capital letter at the top of the first page of the submission:

  RESUBMISSION DISCIPLINES(i.e., any other disciplines from the Complete Response Letter)/COMPARATIVE ANALYSES / CLINICAL
- In addition to the information requested above, we request one sample of the to-be-marketed proposed product and one sample of the RLD. The proposed product should be affixed with the to-be-marketed immediate container label. Please contact us prior to submitting samples. This request is separate from any request for samples that may come to you from the Office of Pharmaceutical Quality.
- Please contact FDA as described below for questions regarding specific submission needs, including test and reference samples. For controlled substances, FDA will accept a placebo sample.
- The requested samples should be submitted under a separate cover letter and mailed to the following address:

  Nitin K. Patel, Pharm.D.
  Senior Regulatory Project Manager
  Division of Clinical Review
  Office of Generic Drugs
  Center for Drug Evaluation and Research, FDA
  Bldg. 75, Room 2510
  10903 New Hampshire Ave,
  Silver Spring, MD 20993

If you have any questions with regard to this matter, please contact Nitin K. Patel, Division of Clinical Review at Nitin.Patel@fda.hhs.gov.

Sincerely,

Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/05/2020 10:09:16 AM
To: brad.davis@mylanlabs.com
CC:
BCC: Megan.Tychinski@fda.hhs.gov
Subject: ANDA 206497, Extension Request

ANDA 206497

COMPLETE RESPONSE RESUBMISSION
EXTENSION REQUEST – GRANTED

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504
Attention: Bradley Davis
Head of Regulatory Science, Dermals

Dear Sir:

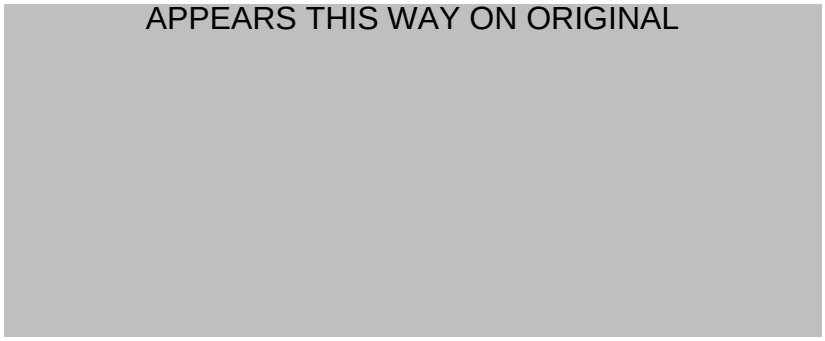
We acknowledge receipt on January 31, 2020 of your Administrative Amendment to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

Sincerely,

Megan Tychinski
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For

questions, please contact the Regulatory Project Manager assigned to your application.



Please find the attached documents below:

A206497N000DPM-DunnerGranted02.pdf

ANDA 206497

COMPLETE RESPONSE RESUBMISSION
EXTENSION REQUEST – GRANTED

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504
Attention: Bradley Davis
Head of Regulatory Science, Dermals

Dear Sir:

This notification is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

We refer you to our complete response (CR) letter dated February 26, 2018, which detailed the deficiencies identified during our review of your ANDA. After receiving a CR letter, an applicant must take one of the following actions: resubmit the ANDA addressing all the deficiencies in the letter; withdraw the ANDA; or request an opportunity for hearing, pursuant to 21 CFR 314.110(b)(1), 21 CFR 314.110(b)(2), and 21 CFR 314.110(b)(3), respectively. Additionally, the Agency may consider an applicant's failure to take an action described in 21 CFR 314.110(b) within one year after issuance of a CR letter to be a request by the applicant to withdraw the ANDA (21 CFR 314.110(c)(1)).

You submitted a letter dated January 31, 2020, requesting an extension of time to respond to our CR letter. In your correspondence, you requested that FDA grant an extension until February 26, 2021 to respond to our CR letter. Upon review of your letter and the basis for an extension contained therein, we are granting your request.

Please resubmit the ANDA addressing all deficiencies identified in our CR letter, in conformance with the extension date set forth in your letter dated January 31, 2020. Please note that FDA may consider an applicant's failure to resubmit the application within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application (21 CFR 314.110(c)(1)).

If you have further questions you may contact Megan Tychinski, Regulatory Project Manager, at (240) 402 - 2717.

Sincerely yours,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Megan Tychinski

Digitally signed by Megan Tychinski
Date: 2/05/2020 09:56:33AM
GUID: 556dc3e3004eeaee540b388a26735dfb

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/26/2019 02:08:36 PM
To: brad.davis@mylanlabs.com
CC:
BCC: Megan.Tychinski@fda.hhs.gov
Subject: ANDA 206497, Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr

ANDA 206497

COMPLETE RESPONSE RESUBMISSION
EXTENSION REQUEST – GRANTED

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504
Attention: Bradley Davis
Head of Regulatory Science

Dear Sir:

Please see attached for your courtesy copy of our response to your amendment submitted February 19, 2019.

Sincerely,

Megan Tychinski
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

Please find the attached documents below:

A206497N000DPM-DunnerGranted01.pdf

ANDA 206497

COMPLETE RESPONSE RESUBMISSION
EXTENSION REQUEST – GRANTED

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504
Attention: Bradley Davis
Head of Regulatory Science

Dear Sir:

This notification is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

We refer you to our complete response (CR) letter dated February 26, 2018, which detailed the deficiencies identified during our review of your ANDA. After receiving a CR letter, an applicant must take one of the following actions: resubmit the ANDA addressing all the deficiencies in the letter; withdraw the ANDA; or request an opportunity for hearing, pursuant to 21 CFR 314.110(b)(1), 21 CFR 314.110(b)(2), and 21 CFR 314.110(b)(3), respectively. Additionally, the Agency may consider an applicant's failure to take an action described in 21 CFR 314.110(b) within one year after issuance of a CR letter to be a request by the applicant to withdraw the ANDA (21 CFR 314.110(c)(1)).

You submitted a letter dated February 19, 2019, requesting an extension of time to respond to our CR letter. In your correspondence, you requested that FDA grant an extension until February 26, 2020 to respond to our CR letter. Upon review of your letter and the basis for an extension contained therein, we are granting your request.

Please resubmit the ANDA addressing all deficiencies identified in our CR letter, in conformance with the extension date set forth in your letter dated February 19, 2019. Please note that FDA may consider an applicant's failure to resubmit the application within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application (21 CFR 314.110(c)(1)).

If you have further questions you may contact Megan Tychinski, Regulatory Project Manager, at (240) 402 - 2717.

Sincerely yours,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Megan Tychinski

Digitally signed by Megan Tychinski
Date: 2/26/2019 02:00:54PM
GUID: 556dc3e3004eeaee540b388a26735dfb

GDUFA II PRE FY2015 COMPLETE RESPONSE CHECKLIST**

RPM: Megan Tychinski **Action Type: Complete Response**

✓ **RX or** ☐ **OTC** **ANDA #: 206497** **Applicant: Mylan Technologies, Inc.** **Cohort Year: CY2**

ANDA Drug Name and Strength: Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr

Basis of Submission (RLD): NDA 21514, Daytrana (methylphenidate transdermal system), 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, Noven Pharmaceuticals, Inc.

MAPP 5240.3 Priority ANDA: ✓ *(Is ANDA based on an approved Suitability Petition?* ☐ *Yes* ✓ *No)*

Does the ANDA contain REMS? ☐ **Yes** ✓ **No** *(If YES, CR Letter must go through the Safety Review Team; clearance may take 2-3 weeks)*

Regulatory Project Manager Evaluation:		**Date: 2/22/2018**
Yes/N/A	**No**	
✓	☐	Have all submissions been reviewed and relevant disciplines finalized in CDER Informatics Platform? (date or N/A)
		Date of Product Quality Review 2/10/2018 Date of Bioequivalence Review 4/19/2016 Date of Labeling Review 1/22/2018 If applicable: Date of Last Complete Response 7/27/2016 Date of Microbiology Review N/A Date of Dissolution Review 1/11/2018 Date of Clinical Review 2/12/2018 Date of REMS Review N/A
✓	☐	Is DMF adequate and/or has the first cycle review been completed (DMF (b) (4) **Adequate, 7/31/2017; Unsolicited Quality Amendment submitted 2/13/2018**
✓	☐	Are all consults complete?
✓	☐	Are all issues resolved?
✓	☐	Have all Policy issues (e.g., citizen petitions) been resolved? **Not Applicable** *If Policy issue, check with OGDP if necessary (e.g., to see whether CP blocks CR issuance).
✓	☐	Is Overall Manufacturing Inspection Recommendation task acceptable/withhold? **Approve, 9/27/2017**
✓	☐	Is OSIS complete (if applicable)? **Acceptable per DCR, 7/28/2016; Complete per BE, 4/19/2016**
		Notes (if applicable): **RLD labeling revised 11/6/2017; BE Guidance revised 10/2016** **See CR response to 6e upon return: if safety assessment submitted, Pharm/Tox review may be needed.**
Draft Complete Response Letter		
✓	☐	Is CR letter drafted and uploaded to "Final Decision" task?
Review Discipline/Division Endorsements		
✓	☐	If ANDA has a pending citizen petition, did RPM notify and obtain clearance from Office of Generic Drug Policy at OGDpolicy@fda.hhs.gov? Date N/A
✓	☐	If ANDA contains REMS, did RPM notify and obtain clearance from REMS Coordinator? Date N/A
Project Close-Out		
✓	☐	Is CR checklist uploaded into "Quality Check and Close Project" task?

***Entire Complete Response Checklist to be completed by the RPM*

From:	Berendt, Robert
To:	Flotildes, Charmaine; Prodduturi, Suneela; Tychinski, Megan
Subject:	RE: Comment on ANDA-206497-ORIG-1-AMEND-15 (ref# 16649306)
Date:	Friday, February 23, 2018 12:33:53 PM
Attachments:	image001.png image010.png

Hi Charmaine and Megan,

Yes, I confirm that AET = Analytical Evaluation Threshold in all cases where the acronym is used in the DP deficiency language.

Also, I noticed an apparent typo in the compiled deficiencies: 6d is missing the word "Clarify" at the beginning of the sentence. I.e.:

(b) (4)

Kind regards,
Bob

From: Flotildes, Charmaine
Sent: Friday, February 23, 2018 12:28 PM
To: Berendt, Robert <Robert.Berendt@fda.hhs.gov>; Prodduturi, Suneela <Suneela.Prodduturi@fda.hhs.gov>
Cc: Flotildes, Charmaine <Charmaine.Flotildes@fda.hhs.gov>
Subject: FW: Comment on ANDA-206497-ORIG-1-AMEND-15 (ref# 16649306)

Good afternoon,

Can you please address OGD's inquiry below? Thanks.

Respectfully,

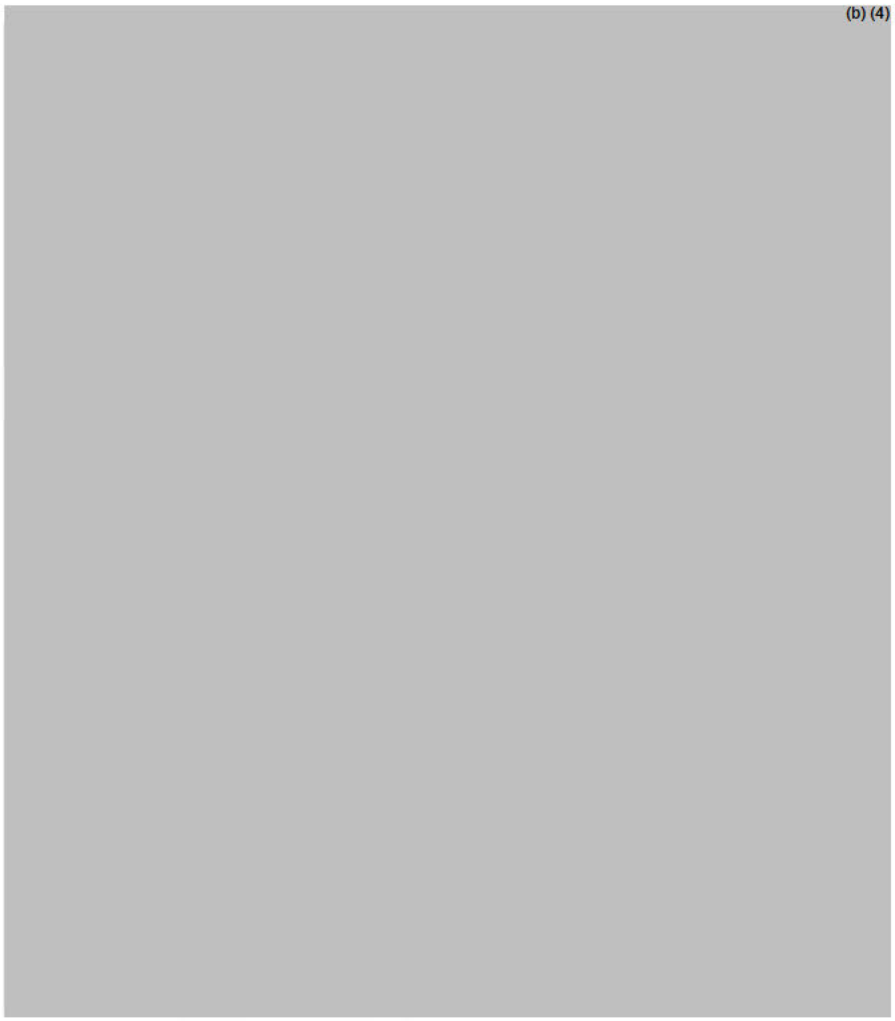
Charmaine, RBPM

From: Tychinski, Megan
Sent: Friday, February 23, 2018 12:23 PM
To: Flotildes, Charmaine <Charmaine.Flotildes@fda.hhs.gov>
Subject: RE: Comment on ANDA-206497-ORIG-1-AMEND-15 (ref# 16649306)

Hi Charmaine,

I'd like to confirm that 'AET' stands for Analytical Evaluation Threshold in all of the deficiencies for ANDA 206497. If so, I plan to move the full term up from Deficiency 6d to 5c (see below) and then use only the acronym for the remainder of the deficiency sections. Is this acceptable?

(b) (4)



Thanks!

Megan

From: Charmaine Flotildes [mailto:charmaine.flotildes@fda.hhs.gov]
Sent: Monday, February 12, 2018 7:27 AM
To: Tychinski, Megan <Megan.Tychinski@fda.hhs.gov>
Subject: Comment on ANDA-206497-ORIG-1-AMEND-15 (ref# 16649306)

(b) (4)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 09/21/2017 02:55:22 PM
To: brad.davis@mylanlabs.com
CC: rebecca.wong@fda.hhs.gov; megan.tychinski@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST: ANDA 206497

September 21, 2017

ANDA 206497
INFORMATION REQUEST
Original ANDA

MYLAN TECHNOLOGIES, INC.
781 CHESTNUT RIDGE ROAD
P.O. BOX 4310
MORGANTOWN, WV 26504
UNITED STATES

Attention: Bradley Davis

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted on December 13, 2013, and your amendment dated July 27, 2017, under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr.

Please see the attached file for deficiency comments.

Provide a complete response to these deficiencies by October 20, 2017. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-

mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
BIOEQUIVALENCE - DISSOLUTION
REFERENCE #17673671

If FDA does not receive a complete response by October 20, 2017, the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence.

If you have any questions, contact Rebecca Wong, Office of Bioequivalence Project Manager, at 301-348-1464 or rebecca.wong@fda.hhs.gov.

Sincerely,

Rebecca Wong, PharmD, BCPS
OFFICE OF GENERIC DRUGS
OFFICE OF BIOEQUIVALENCE
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

September 21, 2017

ANDA 206497
INFORMATION REQUEST
Original ANDA

MYLAN TECHNOLOGIES, INC.
781 CHESTNUT RIDGE ROAD
P.O. BOX 4310
MORGANTOWN, WV 26504
UNITED STATES

Attention: Bradley Davis

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted on December 13, 2013, and your amendment dated July 27, 2017, under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr.

Please see the attached file for deficiency comments.

Provide a complete response to these deficiencies by October 20, 2017. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
BIOEQUIVALENCE - DISSOLUTION
REFERENCE #17673671

If FDA does not receive a complete response by October 20, 2017, the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence.

If you have any questions, contact Rebecca Wong, Office of Bioequivalence Project Manager, at 301-348-1464 or rebecca.wong@fda.hhs.gov.

Sincerely,

Rebecca Wong, PharmD, BCPS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

OFFICE OF GENERIC DRUGS
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U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

DISSOLUTION DEFICIENCY

ANDA	206497
APPLICANT	MYLAN TECHNOLOGIES, INC.
DRUG PRODUCT	METHYLPHENIDATE TRANSDERMAL SYSTEM, 10 MG/9 HR, 15 MG/9 HR, 20 MG/9 HR AND 30 MG/9 HR
DATE	SEPTEMBER 21, 2017

Please refer to your ANDA 206497 submitted on December 13, 2013, and your amendment dated, July 27, 2017.

Your proposal to change the FDA-recommended drug release specification of (b) (4) in 4 hr to (b) (4) in 4 hr is not acceptable. Per the DB policy, the drug release specifications are established based on the drug release data obtained from fresh (not stored) lots. Accordingly, the FDA-recommended specification of (b) (4) at 4 hr was based on release rate for all four strengths of the fresh test product lot at 4 hr. The DB does not revise specifications based on stability data. Therefore, as communicated previously, please acknowledge your acceptance of the following FDA-recommended drug release method and specifications for your test product:

Medium	0.01 N HCl
Volume	900 mL
Apparatus	Apparatus VI (Cylinder)
Speed	50 rpm
Temperature	32°C ± 0.5°C
Specifications*	(b) (4) n 0.5 hr in 1.5 hr in 4 hr

*percent of labeled content

Alternatively, you may submit additional comparative drug release data on 12 dosage units each of all strengths of the test product from three fresh production lots, and unexpired reference lots, for the Agency to determine if any revision of drug release specification is warranted.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 08/04/2017 08:13:20 AM
To: brad.davis@mylanlabs.com
CC: USRegAffairs@mylan.com
BCC: Megan.Tychinski@fda.hhs.gov
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 206497

ANDA 206497

NOTIFICATION --
TARGET ACTION DATE

Mylan Technologies, Inc.
110 Lake St.
St. Albans, VT 05478
Attention: Bradley Davis
Head of Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) received December 13, 2013, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

We acknowledge your response to the Complete Response letter dated July 27, 2017.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our new internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by the action date. A complete set of IRs means that each pending discipline communicated

its comments to the applicant. In that case, the TAD will be met if the last discipline communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is February 27, 2018.

Please contact your Regulatory Project Manager, Megan Tychinski at (240) 402-2717 for an additional status update of your application.

Sincerely,

Megan Tychinski
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

OSIS CONSULT: Request for Clinical OSIS Inspection

DCR requests your evaluation of the clinical endpoint study sites submitted to the ANDA.
Please refer to below list of investigators/sites for the site selection for the OSI Inspection.

ANDA #	Applicant	Drug Product:	Priority Code:	Study Number	Study Title	Site Number	Number of Subjects Enrolled
206497	Mylan Technologies	Methylphenidate HCL Patch	Cohort-2014	MPTP-11007	Comparative Evaluation of the Cumulative Irritation of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) following a 48 to 72 hour Wear in Healthy Adult Volunteers	1	32
				MPTP-12046	Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Shire) in Healthy Adult Volunteers		100
						1	42
						2	none
						3	58

MPTP-12130	Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr;Mylan) to Daytrana® (10 mg/9 hr; Noven) in Healthy Adult Volunteers	1	100

Principal Investigator	Site Name	Street Number	City	State	Zip	Country
Mark J. Allison, MD, CPI	Celerion, Inc.	2420 West Baseline Road	Tempe	AZ	85283	USA
William F. Lamberton, M.D.	Novum Pharmaceutical Research Services	5900 Penn Avenue	Pittsburgh	PA	15206	USA
n/a						
Darin B. Brimhall, D.O., FACP, CPI	Novum Pharmaceutical Research Services	3760 Pecos McLeod	Las Vegas	NV	89121	USA

Alan K. Copa, Pharm.D. PRACS Institute 4801 Amber Valley parkway Fargo ND 58104, USA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

GENERAL ADVICE

Mylan Technologies, Inc.
110 Lake Street
St. Albans, VT 05478
Attention: Juliane M. Foley
Director, Regulatory Affairs

Dear Madam,

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

This communication is to inform you that FDA recently announced the availability of new and revised draft guidances that set forth product-specific bioequivalence (BE) recommendations, including product-specific BE recommendations that may be relevant to your application. These draft guidances are available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

Consistent with 21 CFR 320.24(a), product-specific BE recommendations reflected in these draft guidances represent FDA's current thinking on the most accurate, sensitive, and reproducible approach for conducting BE testing. If, upon review of product-specific BE recommendations, you choose to submit any additional data or information to your ANDA to support approval, please consider the following:

- This general advice letter is not a Complete Response (CR) letter. If your application is currently under review, an action letter will be issued once all reviews are finalized. Please note that FDA, at its discretion, may defer the review of any amendment submitted before the issuance of an action letter until the next review cycle.

- If FDA has issued a CR letter to your application and you have not yet submitted your complete response, this general advice letter is not an amended CR letter. You may choose to submit additional data or information in an amendment or in your response to the CR letter. Please note that FDA review of amendments received in the period between FDA's issuance of a CR letter and the applicant's response to the CR letter are deferred until a complete response to the CR letter is received.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDA and Master Files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions with regard to this matter, please contact Megan Tychinski, Regulatory Project Manager at (240) 402-2717.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEGAN A TYCHINSKI
11/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

MEETING REQUEST
WRITTEN RESPONSES

Mylan Technologies, Inc.
110 Lake St.
St. Albans, VT 05478
Attention: Juliane M. Foley
Director, Regulatory Affairs

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

We also refer to your August 10, 2016, correspondence requesting a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the complete response letter dated July 27, 2016.

Further reference is made to our Meeting Granted letter dated August 19, 2016, wherein we stated that written responses to your questions would be provided in lieu of a teleconference.

The enclosed document constitutes our written responses to the questions contained in your Post Complete Response Teleconference Meeting Request dated August 10, 2016.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017 ANDA and Master Files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, call Megan Tychinski, Regulatory Project Manager at (240) 402-2717.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Post Complete Response Teleconference Meeting
Meeting Category: End of Review

Application Number: 206497
Product Name: Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr
Applicant Name: Mylan Technologies, Inc.

A. BACKGROUND

Mylan Technologies, Inc. requested clarification concerning deficiencies listed on the complete response letter issued July 27, 2016.

B. QUESTIONS AND RESPONSES

Question 1

Mylan notes from FDA COMMENT 1 that the Agency "…applied the four criteria described in the FDA product-specific bioequivalence guidance to your data, of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the RLD, respectively…" Would the Agency please clarify the exact method employed to identify the reported 18 and 9 potential sensitization results?

FDA Response:

We analyzed sensitization data using methods recommended in the FDA's guidance for Methylphenidate[1]. A subject was considered to be potentially sensitized if all of the following criteria were met.

a. The subject had at least 1 evaluation occurring at more than 24 hours (eg, at 48 or 72 hours) after the removal of the Challenge Phase patch.

b. The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.

[1] Draft Guidance on Methylphenidate Film, Extended Release/Transdermal Recommended Jul 2010
http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm220196.pdf

c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.

d. If the subject completed a Re-Challenge Phase, the above 3 criteria were met during both the Challenge Phase and the Re-Challenge Phase.

For criterion c, we consider the scores obtained during the Challenge Phase to be "generally higher" than the Induction Phase if the maximum score in the Challenge and Re-Challenge (if applicable) Phase is higher than the maximum score in the Induction Phase.

Question 2

As noted in FDA COMMENT 2, the Agency states, "We note that you interpreted the term *generally higher* in one of the four sensitization criteria differently from FDA." Would the Agency please clarify the method employed to identify the 33 versus 27 potential sensitization results?

FDA Response:

We note that you interpreted the term "generally higher" in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we reevaluated your data using your interpretation.

Based on your definition of "generally higher," a subject was considered to be potentially sensitized if all of the following criteria were met.

a. The subject had at least 1 evaluation occurring at more than 24 hours (eg, at 48 or 72 hours) after the removal of the Challenge Phase patch.

b. The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.

c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.

d. If the subject completed a Re-Challenge Phase, the above 3 criteria were met during both the Challenge Phase and the Re-Challenge Phase.

For criterion c, we followed your interpretation and considered the scores obtained during the Challenge Phase to be "generally higher" than the Induction Phase if the mean score in the Challenge and Re-Challenge Phase (if applicable) is higher than the mean score in the Induction Phase. When you submit an amendment to your ANDA, we recommend you provide justification of your interpretation of the term "generally higher" in criterion c and also provide the methods you used to identify 36 (TEST) versus 32 (RLD) potential sensitization results.

Question 3

Please clarify how the investigator opinion should be considered for the determination of a potential sensitization reaction. Has the use of the independent investigator's clinical judgment in the determination of potential subject sensitization been replaced with the four criteria described in the FDA product-specific bioequivalence guidance? If so, we will need to understand the specific details for using a numerical algorithm in place of a clinical interpretation of sensitization.

FDA Response:

The product specific guidance for Methylphenidate states, "A narrative description of each reaction in the Challenge Phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization." The criteria for sensitization as provided in the product specific guidance are as follows.

a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.

b. The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.

c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.

d. If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.

Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization.

Along with these criteria, we consider the investigator's opinion as a factor when adequately supported by a sound scientific rationale.

In this case, absent adequate scientific justification of the investigator's opinion in determining sensitization, we put more weight on the four criteria stated in the product specific guidance for Methylphenidate. However, if you think that we should put more weight on the opinion of investigator to determine the sensitization, we recommend you provide your justification for doing so (e.g. scientific reason or basis) when you submit an amendment to this ANDA.

Megan Tychinski

Digitally signed by Megan Tychinski
Date: 9/09/2016 10:56:29AM
GUID: 556dc3e3004eeaee540b388a26735dfb

Post Complete Response Memo

ANDA number	206497
Drug Product	Methylphenidate Transdermal System
Strength(s)	10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
Applicant Name	Mylan Technologies, Inc.
Treatment Indication	treatment of Attention Deficit Hyperactivity Disorder
Reference Listed Drug (RLD)	Daytrana® Transdermal System, 3.3 mg/hr
NDA number for RLD	NDA 021514
RLD Applicant Name	Noven Pharmaceuticals, Inc.
Original ANDA Submission Date	12/13/2013
Materials Reviewed	FDA Clinical review by primary reviewer Sunny Tse, Ph.D. completed on 01/20/2016, post OSIS inspection addendum 07/25/2016 08/10/2016 (eCTD Sequence 0012) : Post Complete Response Meeting Request
Primary Reviewer	Sunny Tse, PhD Clinical Reviewer Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office Generic Drugs (OGD)
Secondary Reviewer	Ying Fan, PhD Acting Team Leader, ANDA Team DCR, OB, OGD
Tertiary Reviewer	Daiva Shetty, MD Acting Director DCR, OB, OGD
Date of Completion	09/08/2016

Background:
On 12/13/2013, the applicant Mylan submitted an original abbreviated new drug application (ANDA) for Methylphenidate Transdermal System seeking for the approval to the reference listed drug (RLD) Daytrana® Transdermal System.

On 07/27/2016, the Agency sent a complete response letter to the applicant, Mylan Technologies, Inc. which included deficiency comments from the clinical discipline. The deficiency comments were as follows:

The sensitization data in Study MPTP 12130 is not adequate to ensure that the sensitization potential of the proposed generic methylphenidate transdermal system (Test) is no worse than that of the reference listed drug product (RLD) as follows.

We do not agree with your numbers of subjects sensitized or potentially sensitized to each product. When we applied the four criteria described in the FDA product-specific bioequivalence guidance to your data,[1] of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the RLD, respectively, with 100% more test sites than reference sites showing potential sensitization.

We note that you interpreted the term generally higher in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we reevaluated your data using your interpretation. Using your interpretation of generally higher, 33 test versus 27 RLD skin sites showed potential sensitization. The proportions are 50% for test versus 40.9% for RLD, with 22% more test sites than RLD sites showing sensitization.

The point estimate for the proportion of skin sites showing potential sensitization was higher for the test product compared with the RLD regardless of which interpretation of generally higher we used.

We note that there are several formulation differences between your product and the RLD, which makes a difference in potential sensitization biologically plausible.

To address these deficiencies, we recommend one of the following.

1. *Provide adequate justification and evidence that potential sensitization of your proposed methylphenidate transdermal system is no worse than that of the reference listed drug.*

2. *Conduct new sensitization study with the to-be-marketed product. Please refer to the Product-Specific Recommendation for Methylphenidate Film, Extended Release/Transdermal recommended in July 2010 on FDA's guidance page: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm220196.pdf*

On 08/10/2016, the applicant submitted a post complete response teleconference meeting request, which included 3 questions for discussion pertaining to the clinical discipline's deficiency comments. On 08/19/2016, the Agency communicated to the applicant that the questions in their 08/10/2016 meeting request would be addressed in the form of a written response. The applicant's 3 questions from their 08/10/2016 post complete response teleconference meeting request and the clinical discipline's corresponding answers are as follows:

Question 1:

---

[1] Draft Guidance on Methylphenidate Film, Extended Release/Transdermal Recommended Jul 2010 http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm220196.pdf

Mylan notes from FDA COMMENT 1 that the Agency "…applied the four criteria described in the FDA product-specific bioequivalence guidance to your data, of 66 subjects who entered the challenge phase, 18 (27.3%) and 9 (13.6%) skin sites showed potential sensitization to the test product and the RLD, respectively…" Would the Agency please clarify the exact method employed to identify the reported 18 and 9 potential sensitization results?

FDA Response:

We analyzed sensitization data using methods recommended in the FDA's guidance for Methylphenidate[1]. A subject was considered to be potentially sensitized if all of the following criteria were met:

> *a. The subject had at least 1 evaluation occurring at more than 24 hours (eg, at 48 or 72 hours) after the removal of the Challenge Phase patch.*
>
> *b. The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.*
>
> *c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.*
>
> *d. If the subject completed a Re-Challenge Phase, the above 3 criteria were met during both the Challenge Phase and the Re-Challenge Phase.*

For Criterion c, we consider the scores obtained during the Challenge phase to be "generally higher" than the Induction phase if the maximum score in the Challenge and Re-Challenge (if applicable) phase is higher than the maximum score in the induction phase.

1 Draft Guidance on Methylphenidate Film, Extended Release/Transdermal Recommended Jul 2010
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm220196.pdf

Question 2:

As noted in FDA COMMENT 2, the Agency states, "We note that you interpreted the term *generally higher* in one of the four sensitization criteria differently from FDA." Would the Agency please clarify the method employed to identify the 33 versus 27 potential sensitization results?

FDA Response:

We note that you interpreted the term "generally higher" in one of the four sensitization criteria differently from FDA. Although we could not determine if your interpretation was pre-planned, we reevaluated your data using your interpretation.

Based on your definition of "generally higher," a subject was considered to be potentially sensitized if all of the following criteria were met:

a. The subject had at least 1 evaluation occurring at more than 24 hours (eg, at 48 or 72 hours) after the removal of the Challenge Phase patch.

b. The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.

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d. If the subject completed a Re-Challenge Phase, the above 3 criteria were met during both the Challenge Phase and the Re-Challenge Phase.

For Criterion c, we followed your interpretation and considered the scores obtained during the Challenge phase to be "generally higher" than the induction phase if the mean score in the Challenge and Re-Challenge phase (if applicable) is higher than the mean score in the Induction phase. When you submit an amendment to your ANDA, we recommend you provide justification of your interpretation of term "generally higher" in criterion c and also provide the methods you used to identify 36 (TEST) versus 32 (RLD) potential sensitization results.

Question 3:

Please clarify how the investigator opinion should be considered for the determination of a potential sensitization reaction. Has the use of the independent investigator's clinical judgment in the determination of potential subject sensitization been replaced with the four criteria described in the FDA product-specific bioequivalence guidance? If so, we will need to understand the specific details for using a numerical algorithm in place of a clinical interpretation of sensitization.

FDA Response:

The product specific guidance for Methylphenidate states: "A narrative description of each reaction in the Challenge Phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization." The criteria for sensitization as provided in the product specific guidance are as follows:

a. *The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.*
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c. *The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.*
d. *If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.*

Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization

Along with these criteria, we consider the investigator's opinion as a factor when adequately supported by a sound scientific rationale.

In this case, absent adequate scientific justification of the investigator's opinion in determining sensitization, we put more weight on the four criteria stated in the product specific guidance for Methylphenidate. However, if you think that we should put more weight on the opinion of investigator to determine the sensitization, we recommend you provide your justification for doing so (e.g. scientific reason or basis) when you submit an amendment to this ANDA.

Ying Fan

Digitally signed by Ying Fan
Date: 9/09/2016 09:46:45AM
GUID: 507d9e07000062a73c410afff19b793c

Daiva Shetty

Digitally signed by Daiva Shetty
Date: 9/09/2016 10:13:59AM
GUID: 5081924f00008b85e43df3f5824475e5

Sunny Tse

Digitally signed by Sunny Tse
Date: 9/09/2016 09:43:56AM
GUID: 508da6ff0002855c7da84880bd716ed2

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY

Mylan Technologies, Inc.
110 Lake St.
St. Albans, VT 05478
Attention: Juliane M. Foley
Director, Regulatory Affairs

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

We also refer to your August 10, 2016, correspondence requesting a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the complete response letter dated July 27, 2016.

We have determined that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a teleconference will not be scheduled. Our goal date for providing our written responses is September 9, 2016.

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If you have any questions, call Megan Tychinski, Regulatory Project Manager at (240) 402-2717.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY

Mylan Technologies, Inc.
110 Lake St.
St. Albans, VT 05478
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We also refer to your August 10, 2016, correspondence requesting a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the complete response letter dated July 27, 2016.

We have determined that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a teleconference will not be scheduled. Our goal date for providing our written responses is September 9, 2016.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017 ANDA and Master Files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, call Megan Tychinski, Regulatory Project Manager at (240) 402-2717.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Megan Tychinski

Digitally signed by Megan Tychinski
Date: 8/19/2016 12:54:52PM
GUID: 556dc3e3004eeaee540b388a26735dfb

BACKLOG & COHORT YEAR 1-2 COMPLETE RESPONSE CHECKLIST**

RPM: Megan Tychinski **Action Type: Complete Response**

☒ **RX or** ☐ **OTC** **ANDA #: 206497** **Applicant: Mylan Technologies, Inc.** **Cohort Year: CY2**
ANDA Drug Name and Strength: Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr
Basis of Submission (RLD): NDA 21514, Daytrana (methylphenidate transdermal system) 10mg/9 hours (1.1 mg/hr), 15mg/9 hours (1.6 mg/hr), 20mg/9 hours (2.2 mg/hr), and 30mg/9 hours (3.3 mg/hr) Noven Pharmaceuticals, Inc.
MAPP 5240.3 Priority ANDA: ☒
(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ☒ *No)*

Does the ANDA contain REMS? ☐ **Yes** ☒ **No** *(If YES, CR Letter must go through the Safety Review Team; clearance may take 2-3 weeks)*

Regulatory Project Manager Evaluation:		**Date: 7/20/2016**
Yes/N/A	**No**	
☒	☐	Have all submissions been reviewed and relevant disciplines finalized in CDER Informatics Platform? (date or N/A)
		Date of Product Quality Review 4/26/2016 Date of Bioequivalence Review 4/26/2016 Date of Labeling Review 2/28/2016 If applicable: Date of Last Complete Response N/A Date of Microbiology Review N/A Date of Dissolution Review 3/31/2016 Date of Clinical Review 7/25/2016 Date of REMS Review N/A
☒	☐	Is DMF adequate and/or has the first cycle review been completed (DMF (b) (4)
☒	☐	Are all consults complete?
☒	☐	Are all issues resolved?
☐	☒	Have all Policy issues (e.g., citizen petitions) been resolved? *If Policy issue, check with OGDP if necessary (e.g., to see whether CP blocks CR issuance).
☒	☐	Is Overall Manufacturing Inspection Recommendation task **acceptable**/withhold? OPF WH confirmation date: *N/A*
☒	☐	Is OSIS complete (if applicable)? Complete, 7/15/2016
Draft Complete Response Letter		
☒	☐	Is CR letter drafted and uploaded to "Final Decision" task?
Review Discipline/Division Endorsements		
☒	☐	If ANDA has a pending citizen petition, did RPM notify and obtain clearance from Office of Generic Drug Policy at OGDpolicy@fda.hhs.gov? Date 7/15/2016
☒	☐	If ANDA contains REMS, did RPM notify and obtain clearance from REMS Coordinator? Date N/A
Project Close-Out		
☒	☐	Is CR checklist uploaded into "Quality Check and Close Project" task?

***Entire Complete Response Checklist to be completed by the RPM*

From: Hiatt, Mary
To: Tychinski, Megan
Subject: RE: ANDA 206497, Policy Alert
Date: Fr day, July 15, 2016 1:30:25 PM
Attachments: image001.png
image002.png
image003.png

Hi Megan,

As we just discussed, we will not need a memo to file for a CR for this ANDA Please contact me if the ANDA appears to be heading towards approval – that action will need a memo from Policy before it can be taken

Thank you,

Mary Alice

From: Tychinski, Megan
Sent: Thursday, April 28, 2016 10:59 AM
To: Hiatt, Mary
Subject: RE: ANDA 206497, Policy Alert

Will do, thanks!

From: Hiatt, Mary
Sent: Thursday, April 28, 2016 10:57 AM
To: Tychinski, Megan
Subject: RE: ANDA 206497, Policy Alert

Good to know – looks like we may have to draft a more extensive memo, so I ll take the extra time! Let me know if anything else comes up or the CR will need to go out sooner

---

From: Tychinski, Megan
Sent: Thursday, April 28, 2016 10:55 AM
To: Hiatt, Mary
Subject: RE: ANDA 206497, Policy Alert

Hi Mary,

No rush As it turns out, there is a consult on this product and now my CR will likely be issued in July

Thank you!

Megan

From: Hiatt, Mary
Sent: Wednesday, April 27, 2016 8:44 PM
To: Tychinski, Megan
Subject: RE: ANDA 206497, Policy Alert

Hi Megan,

I need to look into this a little more and will get back to you I think it s affected but I want to confirm – this petition was recently assigned to me so I m not sure what our approach has been previously for this petition

Mary Alice

From: Tychinski, Megan
Sent: Wednesday, April 27, 2016 11:16 AM
To: Hiatt, Mary
Subject: ANDA 206497, Policy Alert

Hi Mary,

I am preparing to issue a Complete Response for ANDA 206497, Daytrana Patches I see the following listing for reservoir patches on the policy alert list and wanted to check with you on whether this ANDA is affected

(b) (4)

[redacted]

(b) (4)

Can this CR still be issued?

Thanks for your help!

Megan Tychinski, PharmD
Regulatory Project Manager
Office of Generic Drugs, FDA
10903 New Hampshire Ave
Building 75, Room 3718
Silver Spring, MD 20993
(p) 240-402-2717
Megan.Tychinski@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 04/29/2016 08:56:37 AM
To: joseph.sobecki@mylan.com
CC: juliane.foley@mylanlabs.com
BCC: Megan.Tychinski@fda.hhs.gov
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 206497

ANDA 206497

NOTIFICATION --
TARGET ACTION DATE

Mylan Technologies, Inc.
110 Lake Street
St. Albans, VT 05478
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 13, 2013, received December 13, 2013, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by the action date. A complete set of IRs means that each pending discipline communicated its comments to the applicant. In that case, the TAD will be met if the last discipline

communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is July 28, 2016.

Please contact your Regulatory Project Manager, Megan Tychinski at (240) 402-2717 for an additional status update of your application.

Sincerely,

Megan Tychinski
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Office of Research and Standards
Policy Guidance Document

Policy Guidance No:	Addendum to Panorama Project ID 173862
RLD No:	NDA 21514
ANDA No:	206497, (b) (4)
Title/Subject:	Assessment of Partial AUC Requirement for Methylphenidate Transdermal System
Submission Date:	October 27, 2015
Drug Product:	Methylphenidate Hydrochloride Transdermal System
Submitter:	Division of Bioequivalence (DB) II, OGD
Reviewers:	Xiaoyan Yang, Ph.D., Vittal Shivva, Ph.D., Nan Zheng, Ph.D., Lanyan (Lucy) Fang, Ph.D., Liang Zhao, Ph.D.
Review Date:	April 24, 2016

EXECUTIVE SUMMARY

This review document serves as an addendum to the consult response to Division of Bioequivalence II (DBII) dated on March 15, 2016, entitled as "assessment of partial AUC (AUC) requirement for the generic review of methylphenidate transdermal system". The reviewer added analysis results on a "reduced" dataset by excluding some subjects (or pAUC values) from the prior whole dataset per reviewer divisions' general practice. Specially, DBII excluded pAUC values from BE evaluation if less than 4 non-zero PK data points were available to calculate the pAUC, while the initial BE assessment did not exclude any subjects for BE evaluation. This addendum presents the results from the "reduced" BE datasets from ANDA206497, (b) (4) The conclusions based on the reduced datasets remain the same as in the original consult response.

RESULTS

Evaluation of PK Endpoints in ANDA submission

The Science Reviewer reviewed the individual PK data in BE studies submitted in ANDA206497, (b) (4) If at least 4 non-zero PK points are needed for a $pAUC_{2-5}$ to be included in the BE evaluation, only a small portion of the observations in each study (i.e. 16/49 in ANDA 206497 Pilot Study, 0 in ANDA 206497 Pivotal Study, (b) (4) would be available to be included for the BE evaluation. Therefore, in this addendum, we evaluate BE based on $pAUC_{2-5}$ values which were calculated using at least 3 non-zero PK data. The other pAUCs values used for BE evaluation were calculated from at least 4 non-zero PK data (same practice as in DBII).

The same method as described in the original consult response was used in this addendum to evaluate PK endpoints in each ANDA submission. The calculation of PK parameters was carried out in Phoenix using the default algorithms, including the interpolation of concentration

at 2 h time point in ANDA 206497 Study 12012. Unless otherwise specified, BE was evaluated in Phoenix using the Bioequivalence module.

ANDA 206497: Pilot Study 11030

Twelve (12) observations [redacted] (b) (6) in Period 1, [redacted] (b) (6) in Period 2, and [redacted] (b) (6) in Period 3) on partial AUC_{2-5} were excluded from BE evaluation. 7 of these observations are in the reference product treatment. The BE evaluation was summarized in **Table 1**. Only BE evaluation for $pAUC_{2-5}$ changed slightly but remained out of BE limits. Other values remain same.

Table 1. Bioequivalence evaluation of Study 11030, test formulation B vs. Daytrana. PK parameters that failed BE testing are highlighted in Red. CV% > 30% is highlighted in magenta.

Parameters	Geometric Mean Ratio (%)	90% Confidence interval		dF	CV%
		LCL	UCL		
$pAUC_{2-5}$	156.68	111.56	220.05	11.25	73.40
$pAUC_{2-9}$	126.35	103.36	154.44	21	40.20
$pAUC_{2-12}$	113.23	97.29	131.77	21	29.88
$pAUC_{5-9}$	117.37	98.26	140.21	21	35.30
$pAUC_{9-12}$	97.68	87.07	109.59	21	22.44
AUC_t	106.80	94.70	120.45	21	23.50
C_{max}	99.55	88.88	111.50	21	22.12

ANDA 206497: Pivotal Study 12012

Four (4) observations on AUC_{5-9} and AUC_{2-9} [redacted] (b) (6) in Periods 3, 1, 2 and 3, respectively) were excluded from BE analysis. All of these observations were from the reference product treatment. 1 observation on partial AUC_{9-12} and AUC_{2-12} [redacted] (b) (6) in Period 3) was excluded. This observation is from the reference product treatment. The BE evaluation was summarized in **Table 2** (Phoenix) and **Table 3** (SAS). All PK parameters passed BE testing. The reference product possesses low-to-moderate (20%-38%) with-subject variability.

Table 2. Bioequivalence evaluation of Study 12012. CV% > 30% is highlighted in magenta.

Treatments	Parameters	Ratio of geometric mean (%)	90% Confidence interval		dF	CV%
			LCL	UCL		
R vs R	C_{max}	105.31	95.94	115.60	34	24.04
	AUC_t	103.66	95.54	112.47	34	20.98
	$pAUC_{1-9}$	102.53	88.52	118.75	28.16	38.46
	$pAUC_{2-9}$	102.59	88.67	118.70	28.12	38.17
	$pAUC_{3-9}$	102.83	89.14	118.62	27.99	37.34
	$pAUC_{5-9}$	103.76	91.31	117.90	27.69	33.16
	$pAUC_{2-12}$	110.36	97.47	124.95	31.14	32.31
	$pAUC_{9-12}$	108.11	98.46	118.71	30.77	24.06
T vs R	C_{max}	92.86	84.53	102.01	32.42	24.22
	AUC_t	93.55	86.90	100.71	33.01	18.91
	$pAUC_{1-9}$	102.58	89.77	117.23	30.17	34.81
	$pAUC_{2-9}$	102.40	89.73	116.87	30.14	34.46

	$pAUC_{3-9}$	101.84	89.58	115.77	30.06	33.38
	$pAUC_{5-9}$	98.94	88.37	110.76	29.91	29.20
	$pAUC_{2-12}$	102.83	90.48	116.88	32.70	33.41
	$pAUC_{9-12}$	93.00	84.30	102.62	32.09	25.37

Table 3. Bioequivalence evaluation of Study 12012 based on the scaled average bioequivalence criteria for highly variable drugs. CV% > 30% is highlighted in magenta.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	sWR	Criteria Bound	Method Used	OUTCOME
C_{max}	0.93	84.52	102.01	0.24	-0.013	Unscaled	PASS
AUC_t	0.93	86.90	100.71	0.21	-0.011	Unscaled	PASS
AUC_{1-9}	1.01	89.77	117.23	0.34	-0.061	Scaled/PE	PASS
AUC_{2-9}	1.01	89.73	116.88	0.34	-0.061	Scaled/PE	PASS
AUC_{3-9}	1.00	90.09	117.48	0.11	-0.059	Scaled/PE	PASS
AUC_{5-9}	0.97	88.37	110.76	0.30	-0.042	Scaled/PE	PASS
AUC_{2-12}	0.99	89.99	112.46	0.31	-0.050	Scaled/PE	PASS
AUC_{9-12}	0.90	84.23	98.67	0.23	-0.006	Unscaled	PASS

DISCUSSION

This addendum presented the analysis results based on modified BE datasets from three MPH patch ANDAs per BE reviewers' general practice, i.e. BE reviews routinely remove pAUC values which are calculated from less than 4 non-zero PK data points, while the Science Reviewers included all observations for the BE evaluation in the previous report. After excluding $pAUC_{2-9}$ which was calculated from less than 4 non-zero PK data points, the results contained in this addendum are similar to that from the DBII reviewer.

In general, it is probably a good practice to remove pAUC values when some concentration values are missing during the time frame and can cause biased/unreliable pAUC estimates. However, for the MPH patch products, removing the observations with insufficiently detectable concentrations in the early pAUCs can affect the BE evaluation of affected partial AUCs. Observations with very few detectable PK measurements may appear to be aberrant observations as they differ significantly from the other observations while, these observations do reflect the product performance. Removing these seemingly "aberrant" observations usually reduce the estimate of sample variability. In ANDA 206497 Study 12012, all of the removed $pAUC_{2-9}$ values were from the reference treatments. The removal of these observations reduces the residual variability of T/R comparison from 43.15% to 34.81% and reduces the estimate of within-subject variability of the reference product (sWR) from 45.15% to 38.17%. Reduced residual variability changes the BE conclusion on $pAUC_{2-9}$ from failure to pass based on the average bioequivalence criterion. Removing $pAUC_{2-5}$ values with less than 3 detectable PK measurements also reduces the variability on this PK parameter. However, it is still considered as highly variable for BE evaluation.

Removing observations with few number of detectable PK measurement needs caution considering the small number of sampling points at early time points. For the MPH transdermal system that is designed to have a 2-h lag time, requesting at least 3 or 4 data points for the partial AUC calculation could mean that subjects with concentration value of zero at 2 h (which is designed) is excluded from analysis. In this case, BE evaluation maybe biased as this may actually reflect the difference in lag time among different patch products. Excluding those

pAUCs due to concentrations value of zero at 2 h may result in a biased modified dataset that preclude BE evaluation incorporating all aspects. As such, applying the general rule to excluding pAUCs with few detectable PK measurements needs further considerations and should be used in a case-by-case manner.

Nevertheless, the revised BE analysis of the (b) (4) ANDAs remained consistent with the conclusions presented in the original consult response. We recommend that partial $AUC_{2\text{-}9}$ should be included for BE evaluation of generic MPH transdermal system to ensure comparable drug exposures during clinically relevant time windows.

Office of Research and Standards
Policy Guidance Document

Policy Guidance No:	Panorama Project ID 173862
RLD No:	NDA 21514
ANDA No:	206497, (b) (4)
Title/Subject:	Assessment of Partial AUC Requirement for Methylphenidate Transdermal System
Submission Date:	October 27, 2015
Drug Product:	Methylphenidate Hydrochloride Extended Release Oral Suspension
Submitter:	Division of Bioequivalence (DB) II, OGD
Reviewers:	Xiaoyan Yang, Ph.D., Vittal Shivva, Ph.D., Nan Zheng, Ph.D., Lanyan (Lucy) Fang, Ph.D., Liang Zhao, Ph.D.
Review Date:	March 4, 2016

EXECUTIVE SUMMARY

This document assesses whether partial AUCs should be recommended for the bioequivalence (BE) evaluation of generic methylphenidate hydrochloride (MPH) transdermal system, which is designed to have a lag time of 2 h after patch application and a wear time of 9 h. Although Daytrana® is designed for monophasic drug release, clinically relevant partial AUCs are important to ensure therapeutic equivalence throughout the treatment period because MPH has strong pharmacokinetic/pharmacodynamics (PK/PD) relationship. For transdermal delivery system, potential generic products can use a formulation design that may lead to different release patterns from that of Daytrana®. There are test formulations which can pass the average BE tests on C_{max}, AUC_t and AUC_{inf} but have therapeutic equivalence risk during specific treatment windows, for example, between 2 and 9 h after patch application. Including partial AUC_{2-9} can help detect those clinically relevant PK differences associated with different formulation designs. Partial AUC_{2-9} has moderate variability, therefore, is not expected to increase sample size significantly. Additionally, we encourage the firms to use Reference Scaled Average BE (RSABE) approach to evaluate BE in terms of the AUC_{2-9} in case of high intra-subject variability. In conclusion, we recommend that partial AUC_{2-9} be included for BE evaluation of generic MPH transdermal system to ensure comparable drug exposures during clinically relevant time windows. Lag time should be reviewed to ensure that minimal MPH is released before 2 h, but statistical evaluations are not recommended considering the large variability associated with low MPH concentration values before 2 h and the AUC_{2-9} assessment.

BACKGROUND

In November 2015, the Division of Bioequivalence II submitted a consult request to the Office of Research and Standards (ORS) which include the following questions:

- Whether partial AUCs or other parameters (T_{max}, T_{lag}) should be included in the bioequivalence (BE) guidance for MPH patch products;

- Whether there is any issue, such as T_{lag}, etc. in ANDA 206497.

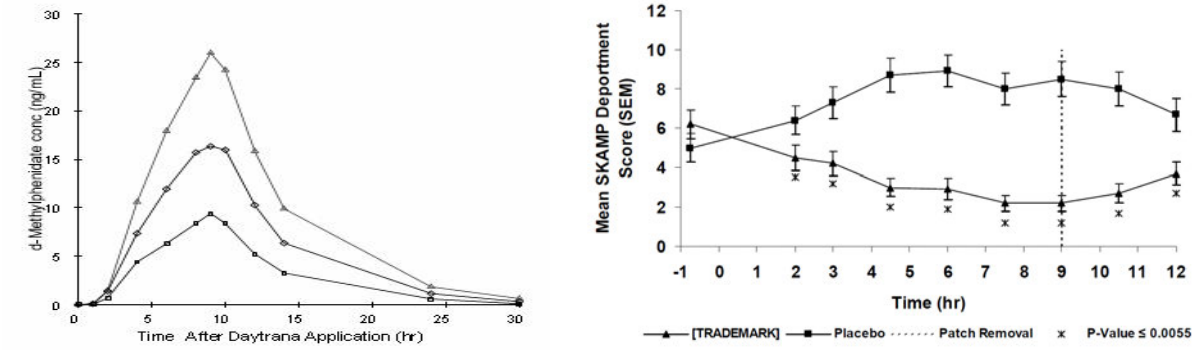
ANDA 206497 was submitted by Mylan Technologies, Inc. on December 13, 2013, comparing the test product, methylphenidate (MPH) transdermal system, 30 mg/9 h to the corresponding reference listed drug (RLD), Daytrana® (MPH transdermal system, NDA 021514), 30 mg/9 h. ANDA 206497 was the first generic that referenced NDA 021514 as per the filling review.

RLD Information

Daytrana® (NDA 021514, 10 mg/9 h, 15 mg/9 h, 20 mg/9 h, 30 mg/9 h) was approved on April 6, 2006 and marketed by Noven Pharmaceuticals (Noven). It is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) for children (ages 6-12) and adolescents (ages 13-17)[1].

Daytrana® contains the central nervous system stimulant MPH within its adhesive layer. According to current Daytrana® label, the patch should be applied to the hip once daily for a maximum of 9 h. Serum MPH levels increase over wear time, with the mean time of maximum concentration (T_{max}) reached between 8 and 10 h for a 9-h wear time (**Figure 1, left**). The elimination half-time of MPH is 3-4 h. In clinical trials, during the 9-h wear time, there was significant improvement compared to placebo treatment (**Figure 1, right**)[2]. The effects were apparent between 1 to 2 h and remained apparent up to 12.5 h after application. The lag time in the response is consistent with a slow rate of rise of MPH levels in plasma over the first 2 h.

Figure 1. Left: Mean Concentration-time Profiles for d-MPH in all Patients (N=34) following Administration of Single Applications (9-h Wear Time) of d,l-MPH Using Daytrana® 10 mg (□), 20 mg (◊) and 30 mg (Δ) per 9-h Patches. **Right:** Absolute Combined SKAMP Score after treatment with Daytrana® or Placebo in a randomized double-blind, placebo-controlled clinical study in children meeting Diagnostic and Statistica-l Manual criteria for ADHD to show a lag-time between 1 to 2 h and remained effects apparent up to 12.5 h.



MPH has a short half-life of 3-4 h; however, from Daytrana® label, the transdermal absorption of MPH may increase with repeat dosing: 1) 13% and 14 % increases in steady state AUC (AUC_{ss}) after 7 days relative to AUC_{inf} after single dose, 64% and 76% increases after 28 days in

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021514s011lbl.pdf

[2] NDA-21514, supporting document No.18, received on November 15, 2005.

pediatric and adolescent patients, respectively; 2) 69% and 100% increases in C_{max} within 4 weeks in children and adolescents, respectively. This is unexpected based on PK (short half-life leads to no drug accumulation) as there is no evidence that the clearance or rate of elimination would change between single and repeated dosing. There are two possible reasons underlying this observed accumulation: 1) The accumulation is mainly related to formulation factors, such as permeability enhancers contained in certain patch products. In this case, the bioequivalence established following a single dose BE study might not be able to be extrapolated to conditions following multiple dose administration. Therefore, multiple dose BE study(ies) should be considered for BE evaluation. 2) The increase in exposure is related to the active pharmaceutical ingredient (API). For example, rashes are generally observed for methylphenidate and amphetamine products and enhanced blood vessel permeability are anticipated associated with these products. In such case, single dose BE study should be adequate. In discussion with the colleagues with the Office of Clinical Pharmacology, it is agreed that there is no adequate data to support that the PK increase after repeated dosing is primarily driven by formulation factors and it is highly likely to be attributable to API. Thus, ORS considers that single dose BE study is adequate for BE evaluation.

(b) (4)

Noven is currently in the process of developing another formulation of Daytrana® under IND 54732.

ANDA History

As of March 8, 2016, FDA has received (b) (4) ANDAs (206497, (b) (4) that references Daytrana® as the RLD.

On December 13, 2013, Mylan Technologies, Inc. submitted ANDA 206497 with the results of PK endpoints BE studies. ANDA 206497 is the focus of analysis in this document.

(b) (4)

BE Recommendation for MPH Products

Stimulants such as MPH remain first-line treatment options for ADHD has unique pharmacology and extremely strong PK/PD relationships that has been rigorously assessed and established. The dose-exposure and exposure-response are highly correlated. Apparently moderate differences in

the PK profiles have clinical consequences for individuals. Partial AUCs with 3-5 h intervals for MPH products were recommended for BE evaluation of MPH extended-release (ER) formulations following a comprehensive and multiple discipline evaluation (tablet[3], capsule[4], and suspension[5]). Two generic MPH ER tablets, manufactured by (b) (4) and (b) (4) pass BE with C_{max} and AUC, but received post-marketing reports related to lack of efficacy after 6-7 h post dose administration. Consistently, PD simulations showed that approximately 21% reduction in PD were anticipated at 10 h post drug administration comparing to the reference product Concerta (NDA 21121). They are still approved and can be prescribed, but no longer recommended as automatically substitutable for Concerta[6]. The intervals of 3-5 h for partial AUCs are based on clinical relevance (e.g. a child has to have therapeutic response at numerous time points throughout the day).

As of December 2015, OGD posted BE guidance for multiphasic MPH modified-release oral products (tablet[3], capsule[4], and suspension[5]), recommending additional partial AUCs (AUC_{0-3}, AUC_{3-7}, and AUC_{7-12} for fasted study and AUC_{0-4}, AUC_{4-8}, and AUC_{8-12} for the fed study). Draft BE guidance for MPH modified-release transdermal product was published in July, 2010[7]. It recommends a single-dose, fasting, two-treatment, two-period crossover in vivo study for BE evaluation with conventional PK endpoints study (C_{max} and AUCs), and a randomized, evaluator-blinded, in vivo within-subject repeat test study for the evaluation of skin irritation, sensitization and adhesion. The necessity of partial AUCs is unclear.

Other Regulatory History

On August 27, 2012, Noven submitted a citizen petition (Docket No.: FDA-2012-P-0932-0001)[8] under Section 505(q) of Federal Food, Drug and Cosmetic Act and the Food and Drug Administration's implementing regulations set forth at 21 C.F.R. §10.30. Among other things requested, that firm request FDA to include T_{max} as a BE endpoint:

- Demonstrates BE using the conventional PK measures of AUC and C_{max}, as well as the time to reach T_{max}, and if the T_{max} is different, conducts a qualitative visual inspection of the concentration profile over time curve to ensure BE

In the FDA's response letter (Docket No.: FDA-2012-P-0932-0003) to this citizen petition, statistical acceptance criteria on T_{max} was not recommend because unlike the continuous variables C_{max} and AUC, T_{max} is a discrete variable to measure the rate of drug absorption from the test and reference products, and is not amenable to the same statistical evaluation used for C_{max} and AUC. In the letter, FDA also recommended a qualitative visual inspection of the concentration profile over time curve to ensure therapeutic bioequivalence, if the T_{max} for a proposed generic is different than the T_{max}, for the RLD.

[3] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm320007.pdf
[4] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm281454.pdf
[5] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm427808.pdf
[6] http://inside fda.gov:9003/downloads/library/onlineandprintjournals/ucm423964.pdf
[7] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf
[8] http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0932-0001

The agency also recommended the inclusion of partial AUCs such as AUC_{0-9}, AUC_{0-10} and AUC_{0-14} in BE evaluation of new formulation in a meeting discussion with Noven on December 16, 2011[9]. The sponsor expressed strong concerns for excessive sample size for partial AUCs and statistical issues with evaluating multiple partial AUCs. They claimed that pAUCs are unnecessary for Daytrana product as it is a monophasic release pattern. At the time of discussion, the agency did not have data to evaluate the within-subject variability of partial AUCs and, therefore, acknowledged the potential challenges and indicated that the sponsor can include pAUCs as supportive evidence for BE establishment. However, in this current analysis, data from replicated studies are available for our analysis and the results showed that including pAUCs for BE evaluation is not expected to require excessive sample size.

This document is to address DBE questions regarding partial AUCs requirements and additional BE measures for the BE evaluation of MPH transdermal system. Because food effects are not considered clinically significant for Daytrana®[1], and the patch has a lag time of 2 h and wear time of 9 h, we will evaluate the mapped partial AUCs (AUC_{2-5}, AUC_{5-9}, AUC_{2-9}, and AUC_{2-12}) based on current BE recommendations on MPH ER products under the fasting condition only.

METHODS

Review of PK/PD Models in Literatures

We reviewed the population PK/PD model provided by Kimko et al[10] to predict time-course of clinical efficacy in pediatrics, using time course of MPH concentration in adults.

Evaluation of PK/PD Endpoints in ANDA Submissions

We reviewed the vivo BE studies (Study 11030 and Study 12012) in ANDA 206497 to evaluate differences in the PD profiles and to evaluate BE using different PK parameters, between the test and reference products or between the two reference product replicates.

We calculated PK parameters (C_{max}, AUC_{0-t}, AUC_{2-5}, AUC_{5-9}, AUC_{9-12}, AUC_{2-9}, and AUC_{2-12}) from the mean PK profile or individual PK data. AUC_{2-5}, AUC_{5-9}, and AUC_{9-12} are selected because these partial AUCs have been proposed for BE evaluation of MPH modified-release products under the fasting condition, considering a delay of 2 h for detectable MPH. AUC_{2-9} and AUC_{2-12} are selected because MPH transdermal patch system has T_{max} around 9 h and response ending time around 12 h.

A PK/PD model in literature was used to predict the PD profiles based on the mean PK profile in ANDA 206497. The ratio values of PD endpoints at different time points were calculated. If a more than 20% difference in PD endpoint is predicted compared to RLD at 2-12 h post dose, the test product is considered to have potential safety or efficacy concerns.

[9] NDA-21514, Communication Author: Grewwal, Renmeet, December 16, 2011.
[10] Kimko et al., Population pharmacodynamic modeling of various extended-release formulations of methylphenidate in children with attention deficit hyperactivity disorder via meta-analysis. J Pharmacokinet Pharmacodyn. 2012, 39(2):161-76

To evaluate BE between the test (T) and reference (R) product using the Bioequivalence module in Pheonix, geometric mean of the reference treatments was calculated first, then compared against T in a 6-sequence, 3-period study design (Seq1: TR0; Seq2: T0R; Seq3: RT0; Seq4: 0TR; Seq5: R0T; Seq6: 0RT; 0 is not included in the BE evaluation). If there were 0 values or missing values in one of the R treatments, the geometric mean will be set as the same value as the other R treatment. We also used SAS to estimate BE between the test and reference product, applying the average BE criteria or the reference-scaled BE criteria for highly variable drugs. When SAS is used, the original 6-sequence assignment was regroup to a 3-sequence assignment. BE comparison of two reference treatments, Reference 1 (R_1) and Reference 1 (R_2) was conducted based on a 6-sequence, 3-period design (Seq1: TR_1R_2; Seq1: TR_2R_1; Seq3: R_1TR_2; Seq4: R_2TR_1; Seq5: R_1R_2T; Seq6: R_2R_1T; T is not included in the BE evaluation) using Pheonix.

We also calculated C_{max}, $AUC_{0\text{-}t}$, $AUC_{2\text{-}5}$, $AUC_{5\text{-}9}$, $AUC_{2\text{-}9}$, $AUC_{9\text{-}12}$, and $AUC_{2\text{-}12}$, and evaluated BE using different PK parameters for data submitted in [redacted] (b) (4)

Population PK Model

MPH plasma concentrations of the first reference treatment in ANDA 206497 Pivotal Study 12012 were collected for developing a population PK model using the nonlinear mixed-effect modeling approach (NONMEN®). Fist-order estimation algorithm in NONMEM was used in the final population PK model.

Typical response in an individual was predicted using the method mentioned as shown in Equation 1 below.

$$y_{ij} = f\left(D_i, t_{ij}, \boldsymbol{\theta}_\mathbf{i}\right) \cdot \exp\left(\varepsilon_{1,ij}\right) + \varepsilon_{2,ij} \quad (1)$$

where $y_{i\,j}$ represents the observed j_{th} concentration in the i_{th} individual, f is the functional form of the structural model that predicts the data, D_i is the dose administered to the i_{th} individual, t_{ij} represents the j_{th} time point in the i_{th} individual, $\boldsymbol{\theta}_\mathbf{i}$ is the vector of parameter values for the i_{th} individual, $\varepsilon_{1,i\,j}$ represents the exponential random error and $\varepsilon_{2,i\,j}$ represents the additive random error.

Typical model for between subjects variability used exponential model for all parameters (Equation 2) except for oral bioavailable fraction where an additive model was used. Final estimate of bioavailable fraction in an individual was constrained between 0 to 1 using explicit function as described in Equation 3.

$$\theta_{ip} = \beta_p \cdot exp\left(\eta_{ip}\right) \quad (2)$$

$$\theta_F = \beta_F + \eta_F \text{ and } F \text{ was constrained between 0, 1 using: } F = \frac{1}{1 + exp^{(-(\theta_F))}} \quad (3)$$

θ_{ip} represents the p^{th} parameter value in ith individual, β_p is the population value for the p^{th} parameter, η_{ip} is the random effect for p^{th} parameter in the i^{th} individual.

The population pharmacokinetic parameters of MPH were estimated using nonlinear mixed-effect modeling with first-order conditional estimation with interaction method.

Simulation in a Typical Study Subject

We simulated single-dose PK profiles in a typical study subject by changing absorption lag time (ALAG) from 0.5 to 5 h for the reference formulation. We also simulated PK profiles by changing ALAG and release rate while remaining absolute bioavailability (F) constant. The PK sampling times are: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, and 30 h post dose. With each simulated PK profile, we calculated C_{max}, $AUC_{2\text{-}5}$, $AUC_{2\text{-}9}$, $AUC_{9\text{-}12}$, $AUC_{2\text{-}12}$, and $AUC_{0\text{-}t}$ for a single dose. The PK endpoint with a ratio that is most different from 1 is considered as the most sensitive BE measure to the change in formulation-specific parameters.

Evaluation of Study Power Using Different PK Endpoints

We simulated 1000 single-dose, 2 sequence, 2-period, 2-treatment, crossover BE studies in 60 subjects and calculated the chance of passing the average BE criteria comparing a test formulation to the reference formulations. The PK sampling times are: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, and 30 h post dose. Each test formulation has the same population mean in all but one formulation-specific PK parameters and the same inter-subject variability as that of the reference formulation. The PK endpoint with the lowest passing rate is considered as the most sensitive BE measure to the change in formulation-specific parameters.

RESULTS

Review of PK/PD Models in Literatures

Mean PK data from various extended-release MPH formulations studied in adults and mean PD data from nine pediatric efficacy studies from the literature were summarized (**Table 1**). Meta-analysis was conducted to assess the relationship of total MPH concentration in blood and the clinical outcome (combined SKAMP score). The final PKPD model takes into account the placebo nature of the clinical outcome and uses a direct effect model to describe the change from baseline (CFB) SKAMP scores (**Table 2**):

1) $CFB = (SKAMP_{post\ baseline} - SKAMP_{baseline})$
2) $CFB = Time*Slope + PD + Intercept$
3) $PD = \delta + Emax*[MPH] /(EC50 + [MPH])$

where δ is a constant describing the observed differences in baseline values on assessment days with active or placebo treatments in the studies due to the different treatment methods during the days preceding the assessment days.

Table 1. Summary of Studies used for PKPD analysis.

Study ID	Source of data		Response Type	Available treatments/dose levels			
	Concentration	Response		Concerta	Metadate CD	dMPH	Ritalin LA
1	[11,12]	[13]	Raw score	18	20		
2	[11,12]	[13]	Raw score	36	40		
3	[12]	[13]	Raw score	54	60		
4	[14]	[15]	CFB			20	
5	[12, 14]	[16]	CFB	36, 54		20, 30	
6	[11]	[17]	Raw score	18, 36			20
7	[12, 14]	[18]	CFB	36, 54		20, 30	
8	[14]	[19]	Raw score			20	
9	[11]	ABC	Raw score	18			
10	[11]	ABC	Raw score	36			
11	[12]	ABC	Raw score	54			

* ABC: internal individual data; CFB: change from baseline; dMPH: racemic mixture equivalent is twice the nominal d-MPH dose

Table 2. Parameter estimates of the final SKAMP meta-analysis PKPD model.

Parameter (Unit)	Description	Value	RSE (%)
E_{max}	Maximum drug effect	27.8	15.8
$EC_{50,start}$ (ng/mL)	Concentration that responds to half E_{max}	7.55	25.2
Δ	Baseline correction	-2.88	28.8

Prospective clinical trial simulation based on this model can aid in predicting clinical efficacy with a known concentration-time profile in adults, assuming the same PK/PD relationship.

Evaluation of PK/PD Endpoints in ANDA Submission

[11] http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteefor PharmaceuticalScienceandClinicalPharmacology/UCM207955.pdf

[12] Gonzalez et al., Methylphenidate bioavailability from two extended-release formulations. Int J Clin Pharmacol Ther. 2002,40(4):175–184

[13] Swanson et al., COMACS Study Group. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). Pediatrics 2004, 113(3 Pt 1):e206– e216

[14] Tuerck et al., Dose-proportional pharmacokinetics of d-threo-methylphenidate after a repeated-action release dosage form. J Clin Pharmacol 2007, 47(1):64–69

[15] Brams et al., A randomized, double-blind, crossover study of once-daily dexmethylphenidate in children with attention-deficit hyperactivity disorder: rapid onset of effect. CNS Drugs 2008, 22(8):693–704

[16] Muniz et al., Efficacy and safety of extended-release dexmethylphenidate compared with d, l-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. J Child Adolesc Psychopharmacol 2008, 18(3):248–256

[17] Lopez et al., Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. Paediatr Drugs. 2003, 5(8):545–555

[18] Silva et al., Treatment of children with attention-deficit/hyperactivity disorder: results of a randomized, multicenter, double-blind, crossover study of extended-release dexmethylphenidate and d, l-Methylphenidate and Placebo in a laboratory classroom setting. Psychopharmacol Bull. 2008, 41(1):19–33

[19] Silva et al., Efficacy and duration of effect of extendedrelease dexmethylphenidate versus placebo in schoolchildren with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2006, 16(3):239–251

1. ANDA 206497

The sponsor submitted one pilot Study 11030 and two pivotal Studies 11125 and 12012 to evaluate BE between its generic MPH transdermal system, 30 mg/9h to Daytrana® following a single transdermal system application of 9 h duration. Because C_{max} and AUC_{inf} in Study 11125 failed the BE testing, this study is not included in the current analysis.

Pilot Study 11030 was a single-dose, randomized, 6-sequence, 3-period, 3-treatment crossover pilot study to investigate BE between 2 test formulations and the RLD in healthy adult subjects under fasting conditions. The dose level is 30 mg/9 h applied to intact skin of hip. Blood samples were drawn at 0 h (pre-dose) and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, and 24 h after dosing. Patients were randomly distributed into six sequences (Seq1: T_1T_2R, left hip; Seq1: T_1T_2R, right hip; Seq3: T_2RT_1, left hip; Seq4: T_2RT_1, right hip; Seq5: RT_2T_1, left hip; Seq6: RT_2T_1, right hip). Test formulation B (T_2) passes BE testing on C_{max}, AUC_t, and AUC_{inf}, and is included for further analysis. The mean concentration versus time profile of MPH is illustrated graphically in **Figure 2**. The PK/PD model is utilized to predict clinical efficacy using the mean PK profiles in the study population (**Figure 2)**. The concentrations from 2 to 6 h has significant difference and simulated effects also show >20% difference from 2 to 4 h and around 15% difference from 5 to 6 h. The differences of PD effect between test and reference products are about 69% at 3 h and 25% at 4 h. BE evaluation results using different PK parameters are summarized in **Table 3**. This analysis demonstrated that test product that are bioequivalent to RLD based on just C_{max} and AUC cannot ensure comparable exposures over clinically relevant time windows (2-9 h).

Figure 2. The average PK profiles (left) and simulated PD profiles (right) of Test Formulation B and the reference product in ANDA 206497, Pilot Study 11030.

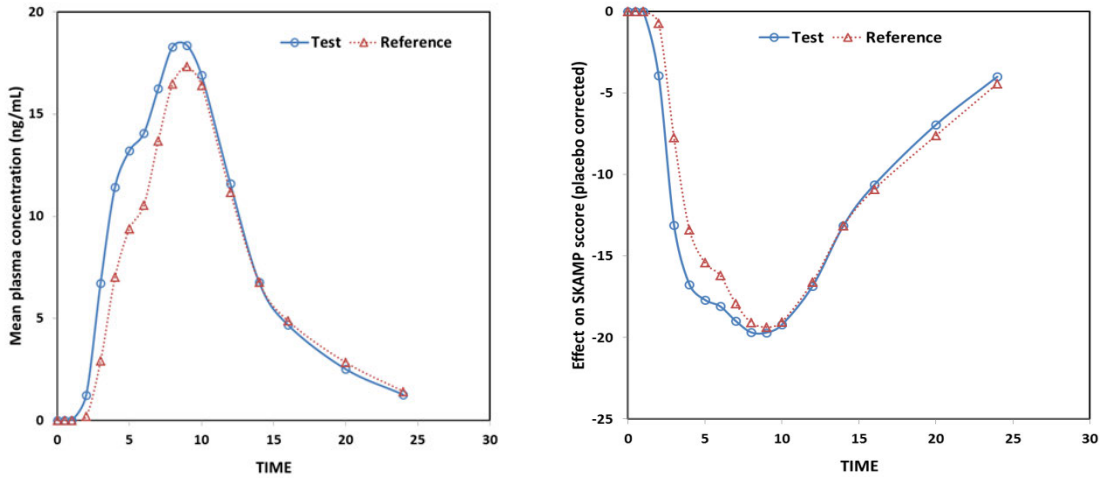


Table 3. Bioequivalence evaluation of Study 11030, Test Formulation B vs. Daytrana. PK parameters that failed BE testing are highlighted in Red. CV% > 30% is highlighted in magenta.

Parameters	Geometric Mean Ratio (%)	90% Confidence interval		dF	CV%
		LCL	UCL		
$pAUC_{2-5}$	162.21	112.06	234.80	18.01	73.56
$pAUC_{2-9}$	126.35	103.36	154.44	21	40.20
$pAUC_{2-12}$	113.23	97.29	131.77	21	29.88

$pAUC_{5-9}$	117.37	98.26	140.21	21	35.30
$pAUC_{9-12}$	97.68	87.07	109.59	21	22.44
AUC_t	106.80	94.70	120.45	21	23.50
C_{max}	99.55	88.88	111.50	21	22.12

Pivotal Study 12012 was a single-dose, randomized, 6-sequence, 3-period, 2-treatment, partial replicated crossover pivotal study to investigate BE between one test formulation to the RLD in healthy adult subjects under fasting conditions. Patients are randomly distributed into six sequences (Seq1: TRR, left hip; Seq1: TRR, right hip; Seq3: RTR, left hip; Seq4: RTR, right hip; Seq5: RRT, left hip; Seq6: RRT, right hip). The dose level is 30 mg/9 h applied to intact skin of hip. Blood samples were drawn at 0 h (pre-dose) and 1, 3, 5, 7, 8, 8.5, 9, 9.5, 10, 11, 12, 14, 16, 20, 24, and 30 h after dosing. The mean concentration versus time profile of MPH and the predicted PD profiles were illustrated graphically in **Figure 3**. The PK and PD differences between test and reference are less than 20% except the concentration (30%) and effect (24%) at time 3 h which is considered clinically insignificant (please refer to the Discussion section of this document). BE conclusions were summarized in **Table 4** (Phoenix) and **Table 5** (SAS).

Figure 3. The average PK profiles and simulated PD profiles of test formulation and reference product in ANDA 206497 Pivotal Study 12012.

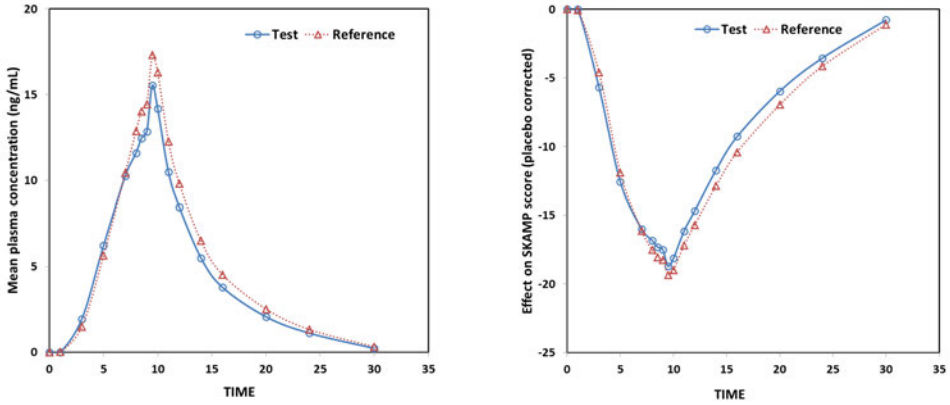


Table 4. Bioequivalence evaluation of Study 12012. PK parameters that failed BE testing are highlighted in Red. CV% > 30% is highlighted in magenta.

Treatments	Parameters	Ratio of geometric mean (%)	90% Confidence interval		dF	CV%
			LCL	UCL		
R vs R	C_{max}	105.31	95.94	115.60	34	24.04
	AUC_t	103.66	95.53	112.47	34	20.98
	$pAUC_{2-5}$	105.69	79.74	140.07	28.92	81.40
	$pAUC_{2-9}$	115.19	97.21	136.50	31.33	45.15
	$pAUC_{2-12}$	104.41	91.03	119.76	34	35.99
	$pAUC_{5-9}$	115.80	99.25	135.11	31.24	40.68
	$pAUC_{9-12}$	103.11	92.61	114.79	34	27.83
T vs R	C_{max}	91.33	83.67	99.69	34	22.55
	AUC_t	92.42	86.12	99.18	34	18.10
	$pAUC_{2-5}$	116.17	88.35	152.74	31.56	78.75
	$pAUC_{2-9}$	111.43	94.72	131.09	34	43.15
	$pAUC_{2-12}$	100.99	89.22	114.31	34	32.33
	$pAUC_{5-9}$	107.41	92.59	124.60	34	39.16
	$pAUC_{9-12}$	91.64	83.50	100.56	34	23.98

Table 5. Bioequivalence evaluation based on the scaled average bioequivalence criteria for highly variable drugs.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	sWR	Criteria Bound	Method Used	OUTCOME
C_{max}	0.93	84.52	102.01	0.24	-0.013	Unscaled	PASS
AUC_t	0.93	86.91	100.73	0.21	-0.011	Unscaled	PASS
AUC_{2-5}	1.20	90.29	156.46	0.65	-0.096	Scaled/PE	PASS
AUC_{2-9}	1.10	96.05	133.62	0.42	-0.065	Scaled/PE	PASS
AUC_{2-12}	1.03	90.49	116.92	0.34	-0.060	Scaled/PE	PASS
AUC_{5-9}	0.93	84.30	102.63	0.27	-0.024	Unscaled	PASS
AUC_{9-12}	1.06	93.63	127.15	0.39	-0.067	Scaled/PE	PASS

(b) (4)

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(b) (4)

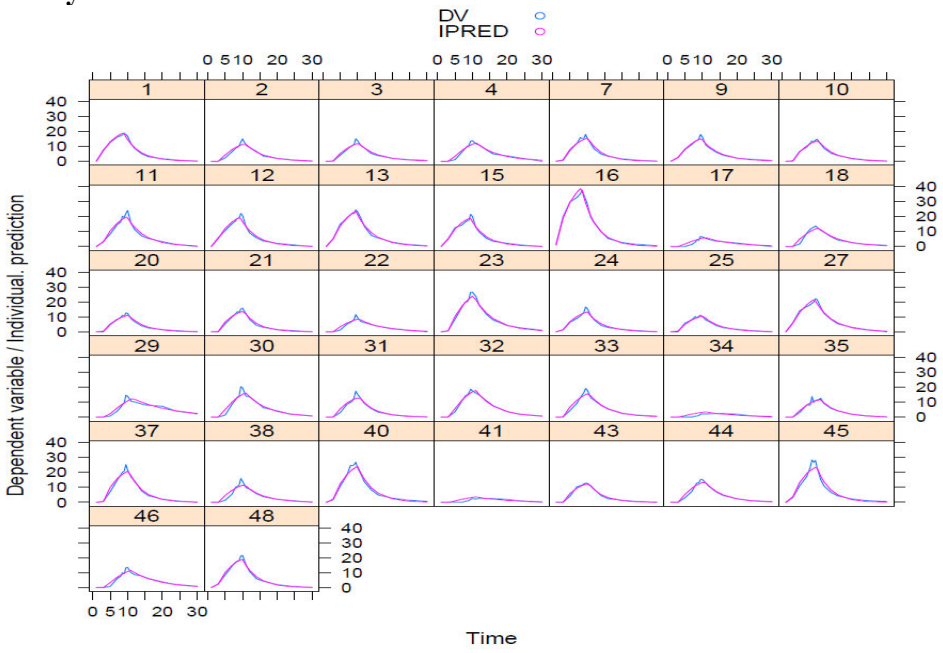
Population PK model.

A one-compartment model with zero-order absorption and first-order elimination adequately described MPH pharmacokinetics (**Figure 6** and **Table 7**). Population mean estimate of clearance (CL) was 202 L/day and apparent volume of distribution (V) was 1030 L. Estimation of absorption lag time (ALAG) and duration of zero-order input were 2.08 h and 7.39 h, respectively. Mean estimate of bioavailability (F) was fixed to 0.36 (36%). The between-subject variability estimates for V, ALAG, and F were 29.9%, 44.0% and 61.2%.

Table 7. The final PK model (without covariates). One compartment PK model with zero order absorption and first-order elimination; N.A.: not available.

Parameter	Population Mean (%RSE)	Inter-subject Variability (%RSE)	Note
CL (L/h)	202 (6)	N.A.	First-order clearance
V (L)	1030 (9)	29.9 (40)	Apparent volume of distribution
D (h)	7.39 (2)	N.A.	Duration of zero-order input
ALAG (h)	2.08 (13)	44.0 (79)	Lag time for zero-order
F	0.36 (fixed)	61.2 (30)	Fractional dose input
Residual error (proportional) [%]	13.8 (16)	N.A.	.
Residual error (additive) (ng/mL)	0.0676 (34)	N.A.	.

Figure 6. Plot of observed (——) and population predicted (——) concentration versus time for pivotal study of ANDA 206497.



Simulation in a Typical Study Subject.

To assess the sensitivity of partial AUC as BE metrics, several concentration-time profiles were simulated using lag time in the range of 0.5 to 5 h with and/or without changing release rate, separately. Since the patch formulation is expected to be monophasic, zero-order absorption and first-order elimination with fixed bioavailability, lag time is the main parameter that will influence the profiles of MPH in future applications; however the release rate from the formulation might be constant or changing with time. Effect of lag time on the PK profiles with release rate constant in a typical study and the ratio of PK measures to that of the reference formulation were shown in **Figure 7** at left or right column, respectively. **Figure 8** demonstrated the effect of ALAG on the PK profiles with release rate changing in a typical study subject (left) and the ratio of PK measures to that of the reference formulation (right). **Figure 7** shows that pAUCs more sensitive than conventional C_{max} and AUC in detecting the T_{lag} changes. It shows that including pAUCs in BE evaluation can ensure comparable T_{lag} of test products.

Figure 7. Effect of lag time on the PK profiles with release rate constant in a typical study (left) and the ratio of PK measures to that of the reference formulation (right).

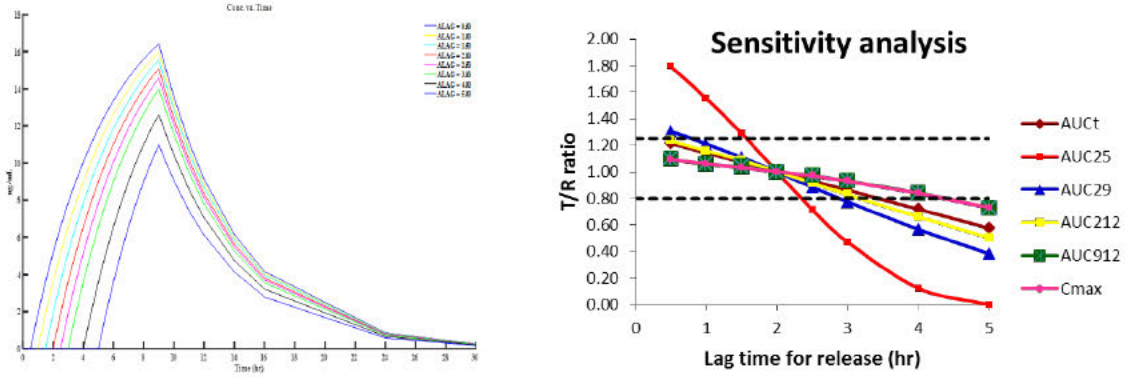
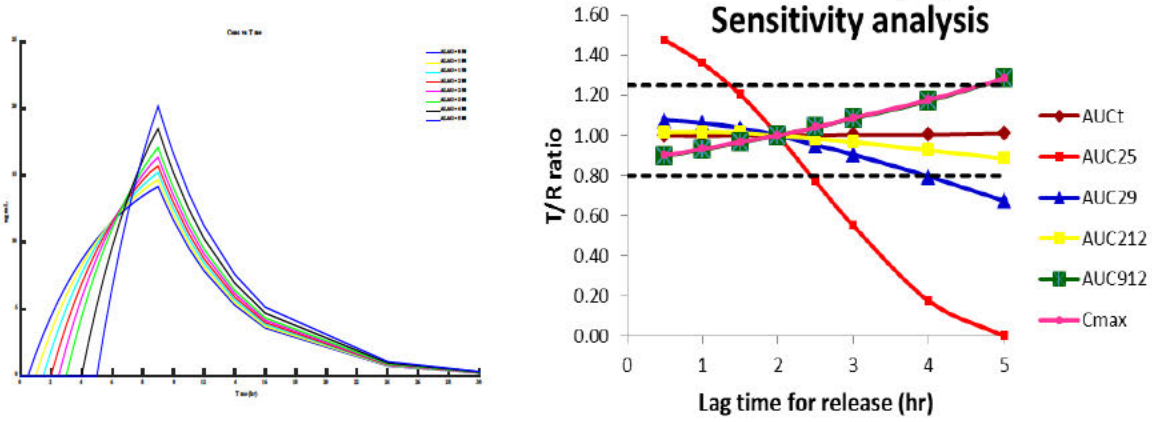


Figure 8. Effect of ALAG on the PK profiles with release rate changing in a typical study (left) and the ratio of PK measures to that of the reference formulation (right).

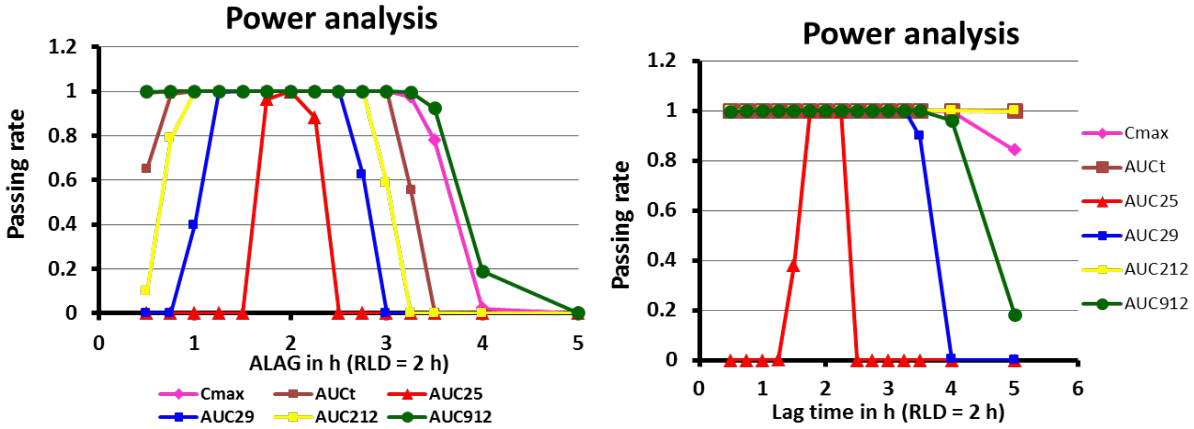


Evaluation of Study Power Using Different PK Endpoints.

The passing rate of 1000 simulated 2-way crossover BE studies is presented in **Figure 9**. pAUCs are more sensitive to formulations than AUC_t. Partial $AUC_{2\text{-}5}$ is very sensitive to lag time

changing and requires large sample size to pass BE criteria. The passing rate with partial AUC_{2-9} is high (>80%) when ALAG changes between 1.25 and 2.5 h.

Figure 9. Passing rate of 1000 simulated, 2-way crossover BE studies in which the test product has a different of ALAG with release rate constant (left) or changing (right).



DISCUSSION

Evaluation of ANDA submission.

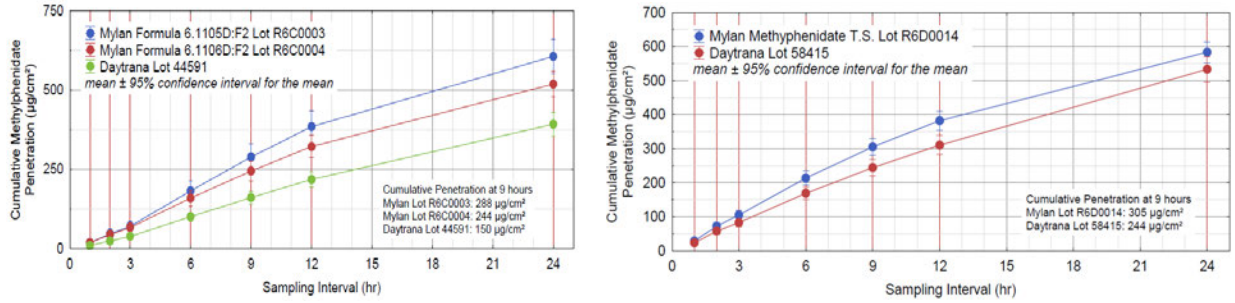
In Pilot Study 11030 of ANDA 206497, the mean plasma profiles are similar between Test Formulation B and Daytrana® in terms of C_{max} and AUCs. The concentrations from 2 to 6 h has significant difference and the simulated PD effects also show >20% difference from 2 to 4 h and around 15% difference from 5 to 6 h compared to RLD (**Figure 2**). The differences of PD effect between test and reference products are about 69% at 3 h and 25% at 4 h (**Figure 2**). While test formulation B passed the average BE tests on C_{max}, AUC_t and AUC_{inf}, it failed in the partial AUC test (**Table 3**) including AUC_{2-5}, AUC_{2-9}, AUC_{2-12}, and AUC_{5-9}. The failure of these partial AUCs (suggesting incomparable drug exposures during these time windows) and the observed difference in PD effect are consistent with each other and indicate adding pAUCs in these clinically relevant time windows can ensure therapeutic equivalence.

In Pivotal Study 12012 of ANDA 206497, the test formulation was modified from Test Formulation B in Pilot Study 11030. The mean plasma profiles are similar between test and reference products. Differences in PK and PD are less than 20% at all of the sampling time points except for 3 h. A 30% and 24% difference was observed in PK and PD, respectively, at 3 h after patch application (**Figure 3**). Because the product is expected to have a lag time of 2 h, MPH concentration is observed to be highly variable due to the low levels soon after the end of the lag time (i.e., 3 h). Hence the predicted 24% difference in PD effect only at 3 h post dose is considered clinically insignificant. Based on BE evaluation between the two reference treatments, partial AUCs (except AUC_{2-5}) have moderate variability (27%-45%) which should not significantly increase regulatory burden (**Table 4**). While test formulation passed the average BE tests on C_{max}, AUC_t and AUC_{inf}, it also marginally passed partial AUCs except partial AUC_{2-5} (**Table 4**). When these partial AUCs of test and reference were further compared for BE

evaluation, they pass BE testing using the average or reference scaled BE testing criteria. This is reflected in the predicted small difference on PD effect shown in **Figure 3**.

In ANDA 206497, in vivo skin permeation studies were conducted to compare the drug delivery performance of test and reference products which were used in Pilot Study 11030 and Pivotal Study 12012 (**Figure 10**). The thickness of the skin contact adhesive layer of Test Formulation A (Lot R6C003) is higher than that of Test Formulation B (Lot R6C004) in the pilot study. The area of two test formulations in the pilot study was 90% of that of the reference product (34 cm^2 vs. 37.5 cm^2). The results of the in vitro skin permeation study demonstrated that the Test Formulation B in the pilot study had a higher delivery rate, per unit area, than the reference (**Figure 10, left**). The results also demonstrated that adjusting the thickness of the skin contact adhesive layer resulted in changes to the in vivo skin permeation rate. The Test Formulation B in the pivotal study was resized into 28 cm^2 vs. 37.5 cm^2 of the reference in pivotal study. The test had a higher accumulation of in vitro skin permeation than that RLD, which was consistent with the in vivo PK data (**Figure 10, right**).

Figure 10. Cumulative in vitro skin permeation study for the formulations in pilot study (left) and in pivotal study (right) in ANDA 206497[22].



In summary, partial $AUC_{2\text{-}9}$ can detect formulation differences. When ANDAs have comparable PK, they can pass partial $AUC_{2\text{-}9}$ with a reasonable sample size or reference-scaled average BE. There appears to have IVIVC between in vitro skin permeation and in vivo cumulative AUCs, but the methodology is not well established for regulatory review at this time.

Simulation in a Typical Study Subject

Our simulation shows that when the input rate (release rate) is unaffected by changing lag time, partial $AUC_{2\text{-}5}$ is the most sensitive metric parameter followed by partial $AUC_{2\text{-}9}$ for detecting differences between drug products (**Figure 7**). Both partial $AUC_{2\text{-}12}$ and partial $AUC_{9\text{-}12}$ are sensitive enough to detect differences for large changes in lag time and more sensitive than C_{max} and AUC_t. When the release rate is changed based on difference in lag time (i.e. so that the overall drug release is maintained constant), partial $AUC_{2\text{-}5}$ demonstrated higher sensitivity than C_{max} and AUC_t at every tested ALAG values (**Figure 8**). The partial $AUC_{2\text{-}9}$ demonstrated higher sensitivity than C_{max} and is slightly higher sensitivity than AUC_t. Partial $AUC_{2\text{-}5}$ has high within-subject variability (81.40%), leading to significant regulatory burden. Partial $AUC_{2\text{-}9}$ has

[22] ANDA-206497, supporting document No. 1, December 13, 2013.

moderate to high variability but should not bring significant regulatory burden for BE evaluation if the firms choose to evaluate the BE using RSABE approach.

Evaluation of Study Power Using Different PK Endpoints.

When release rate is unaffected with change in lag time, partial AUC_{2-5} is hard to pass even with a small change in lag time (±0.5 h from 2 h), leading to a high regulatory burden (**Figure 9**). Partial AUC_{2-9} has much higher passing rate and can pass with a lag time between 1.5 to 2.5 h. When release rate can change according to lag time, partial AUC_{2-5} is still hard to pass while partial AUC_{2-9} has great passing rate and can pass if ALAG <3 h (**Figure 10**). This formulation differences (lag time change within 0.5 h of 2 h) is small and tolerable based on observed variations in Daytrana® treatments. The high chance of passing BE within this range of change indicates that $pAUC_{2-9}$ is not too sensitive to small formulation changes.

Evaluation of Formulation Complexity

Extended/controlled release transdermal delivery system includes reservoir systems and matrix type. Based on the PK data of 37 transdermal patch ANDA applications (approved/ pending/ complete response/ refuse to receive), the PK profile can follow monophasic or multiphasic patterns. In some ANDA applications, they may have comparable PK and pass the average BE tests on C_{max} and AUC_t, but will fail in some meaningful partial AUC test. (b) (4) Hence, we conclude that the transdermal patch is a complex system; potential generic products can use any formulation design and may have different release pattern. There are test formulations which can pass the average BE tests on C_{max}, AUC_t and AUC_{inf} but fail in partial AUC test and have therapeutic equivalence risk. Including partial AUC can help detect those formulations especially for those with strong PK/PD relationship and used for pediatrics.

Figure 11. The average PK profiles of test formulation and reference transdermal patch products in (b) (4)

(b) (4)

(b) (4)

[24] ANDA-206497, supporting document No. 1, November 26, 2013.

CONCLUSION

1. Although Daytrana® is designed for monophasic drug release, MPH has very strong PK/PD relationship and clinically relevant partial AUCs were needed to ensure therapeutic equivalence throughout the duration of treatment.
2. The transdermal patch is a complex system. For transdermal delivery system, potential generic products can use any formulation design and may have different release pattern. There are test formulations which can pass the average BE tests on C_{max}, AUC_t and AUC_{inf} but have potential therapeutic inequivalence risk.
3. Partial AUC_{2-9} is needed to ensure comparable drug exposures during 2-9 h, and, therefore, to detect difference in formulations which could not be captured by C_{max}, AUC_t, and AUC_{inf}.
4. Partial AUC_{2-9} is not expected to increase sample size significantly. Also, the firms can choose to conduct replicated BE studies using RSABE approach to evaluate BE for pAUCs.
5. There appears to have IVIVC between in vitro skin permeation and in vivo cumulative AUCs, but the methodology is not well established for regulatory review at this time.
6. It is helpful to visually check lag time between the test and reference product, however, statistical evaluation would not be necessary.

RESPONSE TO OB QUESTIONS

1. Whether partial AUCs or other parameters (T_{max}, T_{lag}) should be included in current guidance

Even though the transdermal patch is not a multiphasic drug release delivery system, considering that MPH demonstrated strong PK/PD link (i.e., the shape of PK profile has impact on the PD response) and the patch is labeled to have 9-h wear time after patch application, this reviewer recommends that partial AUC during 2 to 9h (AUC_{2-9}) be included in BE evaluation. Additionally, this partial AUC is not over sensitive to formulation differences and has reasonable within-subject variability that is not associated with significantly large sample size. Additionally, the firms can choose to evaluated BE using RSABE approach.

2. Whether there is any issue, such as T_{lag}, etc. in ANDA 206497

Daytrana® label has a specific wording on the lag time and need to be applied 2 h before the effect is needed. A qualitative visual inspection of PK profile is recommended to ensure comparable T_{lag}. Adequate PK samples are needed before 2 h to ensure that minimal MPH are released before 2 h and similar to Daytrana®, but statistical evaluations are not recommended considering the great variability associated with low MPH concentration values before 2 h and the AUC_{2-9} assessment.

In the pivotal study in ANDA 206497, the average PK profiles of the test and reference products are superimposable. By visual inspection, there appears to be no significant differences in T_{lag}, T_{max}, C_{max}, and the initial rate of increase in plasma level, between the test and reference products.

MEMORANDUM

Date: February 24, 2016

From: Division of Clinical Review, OGD

Subject:

Pharmacology/Toxicology Consult - ANDA-206497; Methylphenidate Transdermal System 10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr. Review safety concerns for the amount of hydrophobic colloidal silica.

PharmTox consult request to DCR from Division of Bioequivalence II (DB) dated 11/17/2015, has been completed for ANDA 206497 (Methylphenidate Transdermal System). DCR consulted OND and this consult was reviewed by Division of Psychiatry Products (DPP).

DCR subsequently reviewed the OND consult response. The review recommendation is acceptable from an OND perspective and DCR concurs with their recommendation.

The OND consult review is accessible under Pharm/Tox Primary Review, dated 24-Feb-2016, version 1.0 and is titled: OND DPP PharmTox Consult review ANDA 206497 Hydrophobic Colloidal Silica.pdf .

Casey Hadsall
Project Manager, Pharmacology/Toxicology
Division of Clinical Review
FDA | CDER | OGD
Office: (240) 402-6760 | casey.hadsall@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/12/2016 07:14:15 AM
To: joseph.sobecki@mylan.com
CC:
BCC: TEENA.THOMAS@FDA.HHS.GOV,megan.tychinski@fda.hhs.gov
Subject: [EASILY CORRECTABLE DEFICIENCY] Original ANDA 220004

ANDA 206497

[EASILY CORRECTABLE DEFICIENCY]
Original ANDA
Reference number: 220004

Mylan Technologies Inc.
110 Lake St.
St. Albans, VT 05478

Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
Joseph.sobecki@mylan.com

Dear Mr. Joseph J. Sobecki:

Please refer to your Abbreviated New Drug Application (ANDA) dated and submitted on December 13, 2013 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Patch: 10 mg/9 hr,15 mg/9hr,20 mg/9hr, 30 mg/hr.

Clinical
For the skin irritation, sensitization, and adhesion study (Study # MPTP-12130), we requested the following information on 01/20/2016:
Explain how you determined sensitization potential for the following subjects: Subjects (b) (6) (test, reference), (b) (6) (test), (b) (6) (test), (b) (6) test), (b) (6) (test, reference), (b) (6) (test), (b) (6) (reference), (b) (6) (test, reference), (b) (6) reference), (b) (6) reference), (b) (6) (reference) (b) (6) (reference), (b) (6) (reference), and (b) (6) (reference). Please explain them in details in the

following table format:
Subject IdentifierTreatment
(test/reference)Study Phase
(induction, challenge, rechallenge)Days elapsed for given study phaseDays elapsed since 1st patch applicationVisit NumberSum of Dermal Response and Other Effects, raw dataSum of Dermal Response and Other Effects, LOCFPotentially Sensitized? (yes/no)Reason

On 02/02/2016, you submitted your response explaining the definition that you used for sensitization potential and included a table (Table 1) explaining the reason for each subject we requested. However, it is not clear to us about the subject treatment data presented and the corresponding reason you presented in the table for each subject. Here are two examples:

For Subject (b) (6) test product treatment arm challenge phase:
1.You stated that “Product F (test) challenge scores are not greater than those seen in the induction phase which is an incomplete characteristic of an allergic response.” In the “Sum of Dermal Response and Other Effects, LOCF score” column, there are four scores of 2 in the challenge phase, and five scores of 1 in the induction phase. Please explain why you think the challenge phase scores are not greater than the induction phase scores.
2.In the “Potentially Sensitized? (yes/no)” column, Subject (b) (6) test product treatment arm is marked as “Yes”. Please explain why this subject in the test product treatment arm is considered to be sensitized even though an incomplete characteristic of an allergic response was identified.
3.You also stated that “Product H (reference) is characteristic of an allergic response.” Please elaborate on your definition of an allergic response and explain why Product H (reference) is characteristic of an allergic response.
4.In addition, you stated “Subject meets protocol requirements for Re-challenge.” Please explain why this subject meets protocol requirements for re-challenge. If the subject meets protocol requirements for re-challenge, explain why re-challenge was not conducted.

For Subject (b) (6) test product treatment arm re-challenge phase:
1.You stated that “Per protocol subject does not meet the criteria as being sensitized for either treatment as the challenge and re-challenge reactions are not higher than seen in the induction/irritation phase of sufficient magnitude to indicate sensitization”. In the “Sum of dermal response & other Effects LOCF” column, there are six scores of 1 and three scores of 2 in the induction phase, three scores of 2 and one score of 1 in the challenge phase,

and two scores of 2 and two scores of 4 in the re-challenge phase. Please explain why the challenge and re-challenge reactions are not higher than seen in the induction phase of sufficient magnitude to indicate sensitization.

Please note these are representative examples. We have similar requests for clarification of all “Reason(Sensitization Analysis – Narrative)” entries in the table.

Please elaborate/clarify each entry in the “Reason (Sensitization Analysis – Narrative)” column in the table.
Provide a complete response to these deficiencies by February 18, 2016. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

If FDA does not receive a complete response to these deficiencies by February 18, 2016, the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA’s website. If you have any questions, contact Teena Thomas at 301 796 0549.

Sincerely,

Teena Thomas
Project Manager
Division of Clinical Review
[OFFICE OF GENERIC DRUGS]
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

[EASILY CORRECTABLE DEFICIENCY]
Original ANDA
Reference number: 220004

Mylan Technologies Inc.
110 Lake St.
St. Albans, VT 05478

Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
Joseph.sobecki@mylan.com

Dear Mr. Joseph J. Sobecki:

Please refer to your Abbreviated New Drug Application (ANDA) dated and submitted on December 13, 2013 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Patch: 10 mg/9 hr,15 mg/9hr,20 mg/9hr, 30 mg/hr.

Clinical

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Explain how you determined sensitization potential for the following subjects: Subjects (b) (6) (test, reference), (b) (6) (test), (b) (6) (test), (b) (6) (test), (b) (6) (test, reference), (b) (6) (test), (b) (6) (reference), (b) (6) test, reference), (b) (6) reference), (b) (6) (reference), (b) (6) (reference), (b) (6) (reference), (b) (6) (reference), and (b) (6) (reference). Please explain them in details in the following e format:

Subject Identifier	*Treatment (test/reference)*	*Study Phase (induction, challenge, rechallenge)*	*Days elapsed for given study phase*	*Days elapsed since 1st patch application*	*Visit Number*	*Sum of Dermal Response and Other Effects, raw data*	*Sum of Dermal Response and Other Effects, LOCF*	*Potentially Sensitized? (yes/no)*	*Reason*

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1. You stated that "Product F (test) challenge scores are not greater than those seen in the induction phase which is an incomplete characteristic of an allergic response." In the "Sum of Dermal Response and Other Effects, LOCF score" column, there are four scores of 2 in the challenge phase, and five scores of 1 in the induction phase. Please explain why you think the challenge phase scores are not greater than the induction phase scores.

2. In the "Potentially Sensitized? (yes/no)" column, Subject (b) (6) test product treatment arm is marked as "Yes". Please explain why this subject in the test product treatment arm is considered to be sensitized even though an incomplete characteristic of an allergic response was identified.
3. You also stated that "Product H (reference) is characteristic of an allergic response." Please elaborate on your definition of an allergic response and explain why Product H (reference) is characteristic of an allergic response.
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For Subject (b) (6) test product treatment arm re-challenge phase:

1. You stated that "Per protocol subject does not meet the criteria as being sensitized for either treatment as the challenge and re-challenge reactions are not higher than seen in the induction/irritation phase of sufficient magnitude to indicate sensitization". In the "Sum of dermal response & other Effects LOCF" column, there are six scores of 1 and three scores of 2 in the induction phase, three scores of 2 and one score of 1 in the challenge phase, and two scores of 2 and two scores of 4 in the re-challenge phase. Please explain why the challenge and re-challenge reactions are not higher than seen in the induction phase of sufficient magnitude to indicate sensitization.

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Sincerely,

Teena Thomas
Project Manager
Division of Clinical Review
[OFFICE OF GENERIC DRUGS]
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Clinical

For the skin irritation, sensitization, and adhesion study (Study # MPTP-12130), we requested the following information on 01/20/2016:

Explain how you determined sensitization potential for the following subjects: Subjects [redacted](test, reference), [redacted](test), [redacted](test), [redacted](test), [redacted](test, reference), [redacted](test), [redacted](reference), [redacted](test, reference), [redacted](reference), [redacted](reference), [redacted](reference) [redacted] reference), [redacted](reference), and [redacted] (reference). Please explain them in details in the following table format:

Subject Identifier	*Treatment (test/reference)*	*Study Phase (induction, challenge, rechallenge)*	*Days elapsed for given study phase*	*Days elapsed since 1st patch application*	*Visit Number*	*Sum of Dermal Response and Other Effects, raw data*	*Sum of Dermal Response and Other Effects, LOCF*	*Potentially Sensitized? (yes/no)*	*Reason*

On 02/02/2016, you submitted your response explaining the definition that you used for sensitization potential and included a table (Table 1) explaining the reason for each subject we requested. However, it is not clear to us about the subject treatment data presented and the corresponding reason you presented in the table for each subject. Here are two examples:

For Subject [redacted]test product treatment arm challenge phase:

1. You ated that "Product F (test) challenge scores are not greater than those seen in the induction phase which is an incomplete characteristic of an allergic response." In the "Sum of Dermal Response and Other Effects, LOCF score" column, there are four scores of 2 in the challenge phase, and five scores of 1 in the induction phase. Please explain why you think the challenge phase scores are not greater than the induction phase scores.
2. In the "Potentially Sensitized? (yes/no)" column, Subject [redacted]test product treatment arm is marked as "Yes". Please explain why this subject in the te roduct treatment arm is considered to be sensitized even though an incomplete characteristic of an allergic response was identified.
3. You also stated that "Product H (reference) is characteristic of an allergic response." Please elaborate on your definition of an allergic response and explain why Product H (reference) is characteristic of an allergic response.
4. In addition, you stated "Subject meets protocol requirements for Re-challenge." Please explain why this subject meets protocol requirements for re-challenge. If the subject meets protocol requirements for re-challenge, explain why re-challenge was not conducted.

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challenge reactions are not higher than seen in the induction phase of sufficient magnitude to indicate sensitization.

Please note these are representative examples. We have similar requests for clarification of all "Reason(Sensitization Analysis – Narrative)" entries in the table.

Please elaborate/clarify each entry in the "Reason (Sensitization Analysis – Narrative)" column in the table.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 01/20/2016 12:49:58 PM
To: joseph.sobecki@mylan.com
CC: Teena.Thomas@fda.hhs.gov; Megan.Tychinski@fda.hhs.gov
BCC: Margarita.Tossa@fda.hhs.gov
Subject: EASILY CORRECTABLE DEFICIENCY Original ANDA

ANDA 206497
EASILY CORRECTABLE DEFICIENCY
Original ANDA
REFERENCE # 212424

MYLAN TECHNOLOGIES INC
110 LAKE ST
ST ALBANS, VT 05478
UNITED STATES

Attention: Joseph J. Sobecki

Dear Sir/Madam,

Please provide a complete response to the deficiencies (see attached document) by February 3, 2016. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
CLINICAL
REFERENCE # 212424

If you do not submit a complete response by February 3, 2016, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies under GDUFA, available

on FDA’s website.

If you have any questions, contact Teena Thomas, Discipline Project Manager at teena.thomas@fda.hhs.gov or (301)796-0549

Sincerely,

OFFICE OF GENERIC DRUGS
OFFICE OF BIOEQUIVALENCE
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497
EASILY CORRECTABLE DEFICIENCY
Original ANDA
REFERENCE # 212424

MYLAN TECHNOLOGIES INC
110 LAKE ST
ST ALBANS, VT 05478
UNITED STATES

Attention: Joseph J. Sobecki

Dear Sir/Madam,

Please refer to your Abbreviated New Drug Application (ANDA) dated and submitted on December 13, 2013 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Patch 10Mg/9Hr, 15 Mg/9Hr, 20 Mg/9Hr& 30Mg/9Hr.

Clinical

We have the following comment for ANDA 206497:

For the skin irritation, sensitization and adhesion study (Study # MPTP-12130) you submitted on 12/13/2013, we request the following additional information:

- Explain how you determined sensitization potential for the following subjects: Subjects (b) (6)(test, reference), (b) (6)(test), (b) (6)(test), (b) (6)(test), (b) (6)(test, reference), (b) (6)(test), (b) (6)(reference), (b) (6) (test, refere , (b) (6)(reference), (b) (6)(reference), (b) (6)(reference), (b) (6)(reference), (b) (6) (reference), and (b) (6)(reference). Please explain them in details in the following table format:

Subject Identifier	Treatment (test/reference)	Study Phase (induction, challenge, rechallenge)	Days elapsed for given study phase	Days elapsed since 1st patch application	Visit Number	Sum of Dermal Response and Other Effects, raw data	Sum of Dermal Response and Other Effects, LOCF	Potentially Sensitized? (yes/no)	Reason

Please provide a complete response to the deficiencies by February 3, 2016. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
CLINICAL
REFERENCE # 212424

If FDA does not receive a complete response to these deficiencies by February 3, 2016, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies under GDUFA, available on FDA's website.

If you have any questions, contact Teena Thomas, Discipline Project Manager at teena.thomas@fda.hhs.gov or (301)796-0549

Sincerely,

OFFICE OF GENERIC DRUGS
OFFICE OF BIOEQUIVALENCE
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Clinical

We have the following comment for ANDA 206497:

For the skin irritation, sensitization and adhesion study (Study # MPTP-12130) you submitted on 12/13/2013, we request the following additional information:

- Explain how you determined sensitization potential for the following subjects: Subjects (b) (6) (test, reference), (b) (6) test), (b) (6) (test), (b) (6) (test), (b) (6) (test, reference), (b) (6) (test) (b) (6) (reference), (b) (6) (test, reference), (b) (6) (reference), (b) (6) (reference), (b) (6) (reference), (b) (6) (reference), (b) (6) (reference), and (b) (6) (reference). Please explain them in details in the following table format:

Subject Identifier	Treatment (test/reference)	Study Phase (induction, challenge, rechallenge)	Days elapsed for given study phase	Days elapsed since 1st patch application	Visit Number	Sum of Dermal Response and Other Effects, raw data	Sum of Dermal Response and Other Effects, LOCF	Potentially Sensitized? (yes/no)	Reason

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/29/2015 10:29:29 AM
To: joseph.sobecki@mylan.com
CC:
BCC: Megan.Tychinski@fda.hhs.gov
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 206497

ANDA 206497

NOTIFICATION --
TARGET ACTION DATE

Mylan Technologies, Inc.
110 Lake Street
St. Albans, VT 05478
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 13, 2013, received December 13, 2013, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr and 30 mg/9 hr.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by the action date. A complete set of IRs means that each pending discipline communicated its comments to the applicant. In that case, the TAD will be met if the last discipline

communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is May 2, 2016.

Please contact your Regulatory Project Manager, Megan Tychinski at (240) 402-2717 for an additional status update of your application.

Sincerely,

Megan Tychinski
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Recommendation to FDA statistician from DCR (12/21/2015)
Methylphenidate Transdermal System, 10mg/9hrs, 15mg/9hrs, 20mg/9hrs, & 30mg/9hrs

On 12/15/2015, DCR recommended no subject adjustments. Following communication with the FDA statistical reviewer, DCR agrees with the FDA statistical reviewer to exclude subject (b) (6) from the irritation and sensitization analyses. DCR has no further recommended changes to the irritation PP population and sensitization PP population. DCR agrees with the applicant's adhesion PP population.

ANDA #	Study #	PP subject adjustment requested (yes/no)	Subject number	Reason for inclusion/exclusion	Comments
206497	MPTP-12130	yes; remove from irritation PP population and sensitization PP population	(b) (6)	Subject (b) (6) Visit 10 irritation data was missing, so the subject test and reference patches were absent for 2 days in induction.	This combined irritation, sensitization, and adhesion study is requested for statistics review.

DCR recommends not to perform detailed reviews on the following studies:

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
MPTP-11030 - Single-Dose Pilot Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fed BE	(b) (4)
MPTP-11007 - Comparative Evaluation of the Cumulative Irritation of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) following a 48 to 72 hour Wear in Healthy Adult Volunteers	Cumulative Irritation Study (n=32)	(b) (4)
MPTP-11125 - Single-Dose	Fasting	Overlay is allowed

STUDY NUMBER AND TITLE	STUDY SUB TYPE	Reason for not reviewing study
Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Bioequivalence	
MPTP-12012 - Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana® (30 mg/9 hr; Shire) in Healthy Adult Volunteers	Fasting Bioequivalence	The applicant evaluated irritation. However, the study duration is only for 9 hours.
MPTP-12046 - Comparative Evaluation of the Adhesion, Cumulative Irritation Potential and Contact Sensitization of a Methylphenidate Transdermal System (10 mg/9 hr; Mylan) to Daytrana® (10 mg/9 hr; Shire) in Healthy Adult Volunteers	Cumulative Irritation and Sensitization (n=100)	The sponsor noted data integrity issue and deficiencies in procedure by Novum Pharmaceutical Research Service. Due to data integrity issue, not recommended for the review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION**	
TO *(Division/Office)*: OND: Division of Psychiatry Products (DPP)			FROM: OGD: Division of Clinical Review (DCR): Tiffany Hoang, PharmD	
DATE 11/25/2015	IND NO.	ANDA NO. 206497	TYPE OF DOCUMENT Original	DATE OF DOCUMENT December 13, 2013
NAME OF DRUG Methylphenidate Transdermal System 10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr	PRIORITY CONSIDERATION 60 days GDUFA		CLASSIFICATION OF DRUG Sympathomimetics	DESIRED COMPLETION DATE January 25, 2016
NAME OF FIRM: Mylan Technologies, Inc.				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☒ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	×OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL	☐ PRECLINICAL

Introduction:
In the original submission dated December 13, 2013, Mylan Technologies, Inc. submitted the results of the PK endpoint bioequivalence (BE) study comparing test product, Methylphenidate Transdermal System, 30 mg/9 hr and to the corresponding reference product, Noven Pharmaceuticals' Daytrana® (methylphenidate transdermal film), 30 mg/9 hr.

In addition to the PK endpoint BE study, the firm conducted irritation and sensitization study (30 mg/9 hr strength worn for a 2 or 3-day wear cycle for 9 applications) and irritation, sensitization and adhesion study (21 day continuous application of 10 mg/9 hr strength) per BE guidance[1].

The original submission, dated December 13, 2013, was "refuse to receive" due to insufficient information[2]. However, Division of Filing Review (DFR) has concluded that the original refuse to receive action was erroneously issued, and Mylan Technologies, Inc.'s submission, ANDA206497, has been identified as the first generic as per the filing review[3].

The test product contains hydrophobic colloidal silica as the inactive ingredient which is not listed in the CDER's Inactive Ingredient Guidance (IIG) for FDA-Approved Drug Products (See the table below).

Issue:
The OGD/Division of Clinical Review (DCR) requests a clinical consult to determine whether the amount of hydrophobic colloidal silica used in the formulation of Mylan's Methylphenidate Transdermal System should be of a safety concern. The amount of hydrophobic colloidal silica used in the skin contact adhesive of the firm's formulation is summarized in the following table:

Ingredient	30 mg/ 9 hours ($28.8\ cm^2$)	% w/w	Amount based on MDD	Maximum amount/day based on MDD of approved drug product
Hydrophobic Colloidal Silica NF	(b) (4)			(b) (4)

Firm's Justifications:

The following attached document[4] includes the firm's justification for the amount of hydrophobic colloidal silica in the test product.

---

[1] Bioequivalence Recommendations for Specific Drug Products for Methylphenidate Transdermal Film (*Recommended Jul 2010*) posted at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf

[2] DARRTS, ANDA206497, REV-CLBIOEQ-02(Filing Review) dated on 2/14/2014

[3] GDRP, ANDA206497, Filing Primary Review, A206497N000DFR_Memo.pdf dated on 8/27/2015. DARRTS, ANDA206497, REV-BIOEQ-07(Filing Review) dated on 1/19/2014. (b) (4)

[4] DARRTS, ANDA206497, SDN1, Module 3.2.P.1 a safety assessment, dated 12/13/2013

(b) (4)

Section I: Background

Formulation Data for the Test product

Ingredient	Amount (mg)				Amount (%)/Patch			
	10 mg/9 hrs (1.1 mg/hr) 9.6 cm²	15 mg/9 hrs (1.6 mg/hr) 14.4 cm²	20 mg/9 hrs (2.2 mg/hr) 19.2 cm²	30 mg/9 hrs (3.3 mg/hr) 28.8 cm²	10 mg/9 hrs (1.1 mg/hr) 9.6 cm²	15 mg/9 hrs (1.6 mg/hr) 14.4 cm²	20 mg/9 hrs (2.2 mg/hr) 19.2 cm²	30 mg/9 hrs (3.3 mg/hr) 28.8 cm²
Active Ingredient								
Methylphenidate	(b) (4)							
Inactive Ingredients – Adhesive Matrix								
Hydrophobic Colloidal Silica, NF (b) (4)								
(b) (4) Mineral Oil, NF (b) (4)								
Polyisobutylene Adhesive (b) (4) (b) (4)								
Total Matrix Weight								
Inactive Ingredients – Backing Film, Release Liner and Printing Ink								
Ethylene-Vinyl Acetate (b) (4) Polyester Film (b) (4)								
(b) (4) Fluoropolymer-Coated (b) (4) Release Liner (b) (4)								
White Ink (b) (4)								
Total Drug Product Weight (excluding Release Liner)								

(b) (4)

(b) (4)

Transdermal System

The test product contains methylphenidate in the solid matrix reservoir, while the reference product contains the methylphenidate in the adhesive. The amount of methylphenidate per patch in the test product is lower than that in the reference product. The size of the patchs for the test product is smaller than that for the reference product (see table below).

	10 mg/ 9 hr		15 mg/ 9 hr		20 mg/ 9 hr		30 mg/ 9 hr	
	API mg	cm^2	API mg	cm^2	API mg	cm^2	API mg	cm^2
Test	(b) (4)	9.6	(b) (4)	14.4	(b) (4)	19.2	(b) (4)	28.8
Reference		12.5		18.75		25		37.5

Residual assay results indicated the average theoretical dose delivered was (b) (4) for Mylan's Methylphenidate transdermal system, 30 mg/9 hr and was (b) (4) for Daytrana® Patch 30 mg/9 hr following a single 9 hour application.

(b) (4)

Section II: Conclusion

Considering that hydrophobic colloidal silica, used in the formulation of Mylan's Methylphenidate Transdermal System, is not listed in the CDER's Inactive Ingredient Guide (IIG) for FDA-Approved Drug Products, the OGD/DCR asks if the presence of such amount of hydrophobic colloidal silica should be of a safety concern.

The Bioequivalence review for ANDA206497 Methylphenidate Transdermal System will be finalized later.

Thank you for your consideration. Please address comments/questions to tiffany.hoang@fda.hhs.gov

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: Lesley-Anne Furlong, M.D, Acting Director Division of Clinical Review Office of Bioequivalence Office of Generic Drugs	FROM: Ethan M. Stier, Ph.D., R.Ph. Director Division of Bioequivalence II, Office of Bioequivalence Office of Generic Drugs

DATE November 17, 2015	IND NO.	ANDA NO. 206497	TYPE OF DOCUMENT Bioequivalence Review	DATE OF DOCUMENT December 13, 2013

NAME OF DRUG Methylphenidate Transdermal System 10mg/9hr, 15mg/9hr, 20mg/9hr and 30mg/9hr	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Sympathomimetics	DESIRED COMPLETION DATE January 17, 2016 TAD: May 02, 2016

NAME OF FIRM: Mylan Technologies, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☒ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL	☐ PRECLINICAL

Introduction:
In the original submission dated December 13, 2013, Mylan Technologies, Inc. submitted the results of the PK endpoint bioequivalence (BE) study comparing test product, Methylphenidate Transdermal System, 30 mg/9 hr and to the corresponding reference product, Noven Pharmaceuticals' Daytrana® (methylphenidate transdermal film), 30 mg/9 hr.

In addition to the PK endpoint BE study, the firm conducted irritation and sensitization study (30 mg/9 hr strength worn for a 2 or 3-day wear cycle for 9 applications) and irritation, sensitization and adhesion study (21 day continuous application of 10 mg/9 hr strength) per BE guidance[1].

The original submission, dated December 13, 2013, was "refuse to receive" due to insufficient information[2]. However, Division of Filing Review (DFR) has concluded that the original refuse to receive action was erroneously issued, and Mylan Technologies, Inc.'s submission, ANDA206497, has been identified as the first generic as per the filing review[3].

The test product contains hydrophobic colloidal silica as the inactive ingredient which is not listed in the CDER's Inactive Ingredient Guidance (IIG) for FDA-Approved Drug Products (See the table below).

Issue:
The Division of Bioequivalence (DB) requests a clinical consult to determine whether the amount of hydrophobic colloidal silica used in the formulation of Mylan's Methylphenidate Transdermal System should be of a safety concern. The amount of hydrophobic colloidal silica used in the skin contact adhesive of the firm's formulation is summarized in the following table:

Ingredient	30 mg/ 9 hours ($28.8\ cm^2$)	% w/w	Amount based on MDD	Maximum amount/day based on MDD of approved drug product
Hydrophobic Colloidal Silica NF (b) (4)	(b) (4)			

Firm's Justifications:

The following attached document[4] includes the firm's justification for the amount of hydrophobic colloidal silica in the test product.

---

[1] Bioequivalence Recommendations for Specific Drug Products for Methylphenidate Transdermal Film (*Recommended Jul 2010*) posted at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf

[2] DARRTS, ANDA206497, REV-CLBIOEQ-02(Filing Review) dated on 2/14/2014

[3] GDRP, ANDA206497, Filing Primary Review, A206497N000DFR_Memo.pdf dated on 8/27/2015. DARRTS, ANDA206497, REV-BIOEQ-07(Filing Review) dated on 1/19/2014. (b) (4)

[4] DARRTS, ANDA206497, SDN1, Module 3.2.P.1 a safety assessment, dated 12/13/2013

(b) (4)

Section I: Background

Formulation Data for the Test product

Ingredient	Amount (mg)				Amount (%)/Patch			
	10 mg/9 hrs (1.1 mg/hr) 9.6 cm²	15 mg/9 hrs (1.6 mg/hr) 14.4 cm²	20 mg/9 hrs (2.2 mg/hr) 19.2 cm²	30 mg/9 hrs (3.3 mg/hr) 28.8 cm²	10 mg/9 hrs (1.1 mg/hr) 9.6 cm²	15 mg/9 hrs (1.6 mg/hr) 14.4 cm²	20 mg/9 hrs (2.2 mg/hr) 19.2 cm²	30 mg/9 hrs (3.3 mg/hr) 28.8 cm²
Active Ingredient								
Methylphenidate	(b) (4)							
Inactive Ingredients – Adhesive Matrix								
Hydrophobic Colloidal Silica, NF (b) (4)								
(b) (4) Mineral Oil, NF (b) (4)								
Polyisobutylene Adhesive (b) (4) (b) (4)								
Total Matrix Weight								
Inactive Ingredients – Backing Film, Release Liner and Printing Ink								
Ethylene-Vinyl Acetate (b) (4) Polyester Film (b) (4)								
(b) (4) Fluoropolymer-Coated Release Liner (b) (4)								
White Ink (b) (4)								
Total Drug Product Weight (excluding Release Liner)								

(b) (4)

(b) (4)

Transdermal System

The test product contains methylphenidate in the solid matrix reservoir, while the reference product contains the methylphenidate in the adhesive. The amount of methylphenidate per patch in the test product is lower than that in the reference product. The size of the patchs for the test product is smaller than that for the reference product (see table below).

	10 mg/ 9 hr		15 mg/ 9 hr		20 mg/ 9 hr		30 mg/ 9 hr	
	API mg	cm^2	API mg	cm^2	API mg	cm^2	API mg	cm^2
Test	(b) (4)	9.6	(b) (4)	14.4	(b) (4)	19.2	31.10	28.8
Reference	27.5	12.5	41.25	18.75	55.0	25	82.5	37.5

Residual assay results indicated the average theoretical dose delivered was (b) (4) for Mylan's Methylphenidate transdermal system, 30 mg/9 hr and was (b) (4) for Daytrana® Patch 30 mg/9 hr following a single 9 hour application.

(b) (4)

Section II: Conclusion

Considering that hydrophobic colloidal silica, used in the formulation of Mylan's Methylphenidate Transdermal System, is not listed in the CDER's Inactive Ingredient Guide (IIG) for FDA-Approved Drug Products, the DB II asks if the presence of such amount of hydrophobic colloidal silica should be of a safety concern.

The Bioequivalence review for ANDA206497 Methylphenidate Transdermal System will be finalized later.

Thank you for your consideration. Please address comments/questions to ethan.stier@fda.hhs.gov.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 206497

INFROMATION REQUEST

Mylan Technologies Inc.
110 Lake Street
St. Albans, VT 05478
Attention: Joseph J. Sobecki.

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 13, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Methylphenidate Transdermal System, 10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9 hrs and 30 mg/9 hrs.

We are reviewing the Quality section of your submission and have the following comments and information requests.

Sample and Information Request:

1. Provide updated stability data for all submission batches.

2. To aid in review of the ANDA 206497, provide the following transdermal drug delivery system (TDDS) samples:

   - 5 samples of the smallest size TDDS from the most recently manufactured batch (< 12 months preferred).
   - 5 samples of the smallest size TDDS nearing the end of shelf-life (b) (4)
   - 5 samples of the largest size TDDS from the most recently manufactured batch (< 12 months preferred).
   - 5 samples of the largest size TDDS nearing the end of shelf-life (b) (4)
   - 5 samples of all remaining submission batches not represented by the above samples requested.
   - 5 samples for the largest and smallest size of the RLD

Include with the samples a table containing the batch/lot numbers, date of manufacture and the mean value (± standard deviation) for release liner peel, probe tack, shear and adhesion to steel tests associated with the sample lots provided above. Include values from the date of release and all applicable stability time points. The transdermal systems may be sent to the attention of:

Xiaoming Xu,
Food and Drug Administration
Division of Product Quality Research
10903 New Hampshire Ave
WO64, RM1028
Silver Spring, MD 20993
Tel: (301) 796-5035
DEA license: RX0466311 (Exp. 05/31/16)

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Quality
REFERENCE # 185507

If you have any questions, please contact Tania Mazza, Regulatory Business Project Manager, at 240-402-9013.

Sincerely,

Tania Mazza
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Tania B. Mazza -S

Digitally signed by Tania B Mazza S
DN: c US o U S Government ou HHS ou FDA ou People cn Tania B Mazza S 0 9 2342 19200300 100 1 1 2001169109
Date: 2015 11 10 11 41:56 05'00'

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/10/2015 11:44:51 AM
To: joseph.sobecki@mylan.com
CC:
BCC:
Subject: INFORMATION REQUEST

ANDA 206497

Hi Attached please find Information Request letter for ANDA 206497. Please confirm receipt of this email.

Thanks,

Tania Mazza

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/05/2015 08:44:05 AM
To: joseph.sobecki@mylan.com
CC: Megan.Tychinski@fda.hhs.gov
BCC:
Subject: EASILY CORRECTABLE DEFICIENCY Original ANDA 206497

Nov 5, 2015

ANDA 206497

EASILY CORRECTABLE DEFICIENCY
Original ANDA

Mylan Pharmaceuticals
110 Lake Street
St. Albans, VT 05478

Attention: Joseph J. Sobecki, Vice President, Regulatory Affairs, Mylan Pharmaceuticals

Dear Mr. Sobecki:

Please refer to your supplemental Abbreviated New Drug Application (ANDA) dated 06/19/2014 submitted on 06/19/2014 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Transdermal System, 10mg/9 hrs, 15 mg/9 hrs, 20 MG/9 hrs, and 30 MG/9 hrs.

The following Easily Correctable Deficiency has been identified:

For Pilot Bioequivalence Study 11030, no analysis data (if different from the raw data) or summary data (with PP population, PP exclusion reason, demographic information, etc.) for adhesion were located in the submission.

Please provide the above information in two SAS data sets in the .xpt format. In addition, please provide the define file and all computer programs that were used to generate the analysis datasets and analysis results for Study 11030 and Study 12130.

Please provide a complete response to these deficiencies by Nov 19th, 2015. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
DIVISION OF STATISTICAL REVIEW
REFERENCE # 183302

If FDA does not receive a complete response to these deficiencies by Nov 19th, 2015, the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Vivianna Cowl, Project Manager at 301-796-0761.

Sincerely,

Vivianna Cowl
Office of Biostatistics
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/04/2015 01:16:37 PM
To: joseph.sobecki@mylan.com
CC:
BCC: teena.thomas@fda.hhs.gov; megan.tychinski@fda.hhs.gov
Subject: [EASILY CORRECTABLE DEFICIENCY]Original ANDA, Reference number: 183306

ANDA 206497

[EASILY CORRECTABLE DEFICIENCY]
Original ANDA
Reference number: 183306

Mylan Technologies Inc.
110 Lake St
St. Albans, VT 05478

Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
joseph.sobecki@mylan.com

Dear Mr. Sobecki:

Please refer to your Abbreviated New Drug Application (ANDA) dated and submitted on December 13, 2013 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Patch 10Mg/9Hr, 15 Mg/9Hr, 20 Mg/9Hr& 30Mg/9Hr.

Clinical:

We have the following comment for ANDA 206497:

For your study # 11030, submitted under ANDA 206497 on 12/13/2013, we request the

following additional information:
•Provide the formulation components and composition for each lot number of your test product.
a.Treatment A (Methylphenidate Transdermal System 30 mg/9 hours), Lot number: R6C003
b.Treatment B (Methylphenidate Transdermal System 30 mg/9 hours), Lot number: R6C0004
•Provide to-be marketed formulation lot number

Provide a complete response to these deficiencies by November18, 2015. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

If FDA does not receive a complete response to these deficiencies by November 18, 2015, the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Teena Thomas, Discipline Project Manager at 301 796 0549.

Sincerely,

Teena Thomas
[OFFICE OF GENERIC DRUGS]
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

[EASILY CORRECTABLE DEFICIENCY]
Original ANDA
Reference number: 183306

Mylan Technologies Inc.
110 Lake St
St. Albans, VT 05478

Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
joseph.sobecki@mylan.com

Dear Mr. Sobecki:

Please refer to your Abbreviated New Drug Application (ANDA) dated and submitted on December 13, 2013 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Patch 10Mg/9Hr, 15 Mg/9Hr, 20 Mg/9Hr& 30Mg/9Hr.

Clinical

We have the following comment for ANDA 206497:

For your study # 11030, submitted under ANDA 206497 on 12/13/2013, we request the following additional information:

- Provide the formulation components and composition for each lot number of your test product.

    a. Treatment A (Methylphenidate Transdermal System 30 mg/9 hours), Lot number: R6C003

    b. Treatment B (Methylphenidate Transdermal System 30 mg/9 hours), Lot number: R6C0004

- Provide to-be marketed formulation lot number

Provide a complete response to these deficiencies by November18, 2015. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
Division of Clinical Review
REFERENCE # 183306

If FDA does not receive a complete response to these deficiencies by November 18, 2015, the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Teena Thomas, Discipline Project Manager at 301 796 0549.

Sincerely,

Teena Thomas
[OFFICE OF GENERIC DRUGS]
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Clinical

We have the following comment for ANDA 206497:

For your study # 11030, submitted under ANDA 206497 on 12/13/2013, we request the following additional information:

- Provide the formulation components and composition for each lot number of your test product.
    a. Treatment A (Methylphenidate Transdermal System 30 mg/9 hours), Lot number: R6C003
    b. Treatment B (Methylphenidate Transdermal System 30 mg/9 hours), Lot number: R6C0004
- Provide to-be marketed formulation lot number

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 08/27/2015 01:19:48 PM
To: joseph.sobecki@mylan.com
CC: ANDAFiling@fda.hhs.gov
BCC: ilinca.duveau@fda.hhs.gov; julia.lee@fda.hhs.gov; ted.palat@fda.hhs.gov
Subject: ANDA 206497 CORRESPONDENCE

ANDA 206497

Dear Joseph J. Sobecki:

Please see the attached correspondence, which will also be sent by USPS.

Best Regards,

Division of Filing Review
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

ACKNOWLEDGEMENT
ANDA RECEIPT

Mylan Technologies Inc.
110 Lake Street
St. Albans, VT 05478
Attention: Joseph J. Sobecki

Dear Joseph J. Sobecki:

We acknowledge receipt of your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act).

NAME OF DRUG: Methylphenidate Transdermal System, 10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9 hrs and 30 mg/9 hrs

DATE OF APPLICATION: December 13, 2013

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: December 13, 2013

Reference is made to your original ANDA dated December 13, 2013, and our refuse-to-receive correspondence dated May 15, 2014.

After further reconsideration, FDA has rescinded its refuse-to-receive (RTR) decision communicated in its May 15, 2014 letter.

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice.

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that the notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and on the first page of the submission should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the first page “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(5)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application. If you have further questions you may contact Martin Shimer, Deputy Director, Division of Legal and Regulatory Support at 240-402-8783.

Please note that after FDA refused to receive your application on May 15, 2014, you were eligible to receive a refund of 75% of your application filing fee. As a result of the decision to rescind the RTR, you must ensure that your GDUFA obligations are satisfied in full. If the refund has been processed by the Office of Financial Management, the Division of User Fee Management and Budget Formulation (DUFMBF) will contact you regarding the outstanding application filing fee. If you already paid the application filing fee for the submission of a comprehensive response to the RTR letter, DUFMBF will also contact you regarding a refund resulting from the payment of this second fee. Failure to satisfy your user fee obligations will be treated as a claim of the U.S. Government subject to Subchapter II of Chapter 37 of Title 31 of the United States Code.

This application is subject to the provisions of the Generic Drug User Fee Amendments of 2012 (GDUFA). Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Dat Doan, Project Manager Team Leader, at Dat.Doan@FDA.HHS.GOV[1] or 240-402-8926.

Sincerely,

Julia S. Lee -S

Digitally signed by Julia S. Lee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia S. Lee -S, 0.9.2342.19200300.100.1.1=2000511130
Date: 2015.08.27 08:22:12 -04'00'

for Johnny Young, M.A.
Director (Acting)
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Secure email between CDER and applicants may be useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

MEMORANDUM TO FILE

FROM: Johnny Young

SUBJECT: Decision to rescind the Refuse-to-Receive (RTR) determination for Abbreviated New Drug Application (ANDA) 206497 (Mylan Technologies Inc. (Mylan))

DATE: August 26, 2015

CC: Johnny Young
Shannon Hill
Julia Lee

The purpose of this memo is to clarify the rationale for Division of Filing Review's (DFR) decision to rescind its RTR determination for ANDA 206497 (Methylphenidate Transdermal System).

Background and Rationale

On December 13, 2013, Mylan Technologies Inc. (Mylan) submitted ANDA 206497 for Methylphenidate Transdermal System, 10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9 hrs, and 30 mg/9 hours. On May 15, 2014, DFR issued an RTR letter to Mylan for ANDA 206497 on the following basis:

> [Y]our data from a skin/irritation/sensitization/adhesion study (MPTP-12130) and the adhesion study (MPTP-11030) are not acceptable for receiving your ANDA. The submission is incomplete…[1]

The deficiency identified in the RTR letter reflected the Division of Clinical Review's (DCR) conclusion, following its review of the skin/irritation/sensitization/adhesion study (MPTP-12130) and the adhesion study (MPTP-11030) submitted as part of ANDA 206497, that the ANDA was inadequate to permit a substantive review.[2]

On June 19, 2014, Mylan submitted a reconsideration request for the May 15, 2014, RTR determination on the basis that the ANDA was substantially complete at the time of original submission. Mylan states that "[m]uch of the information requested was already present in some form in our original ANDA submission [and] holds that a technical review of data within the ANDA is not appropriate grounds for refusing to receive an ANDA."[3] As part of its reconsideration request, Mylan also provided certain additional information regarding its two studies, which information had been requested by DFR in the original RTR letter. On September

[1] Letter to J. Sobecki (Mylan) fr. W. Rickman (OGD/DLPS) re ANDA 206497 (May 15, 2014) (RTR Letter).
[2] Division of Clinical Review Checklist for Generic ANDA for Application Completeness re ANDA 206497 (February 14, 2014).
[3] Letter to K. Uhl (OGD) fr. J. Sobecki (Mylan) *Complete Response to Refuse to Receive Letter (Clinical Bioequivalence Information Provided)* re ANDA 206497 (June 19, 2014), at 1.

19, 2014, as part of its follow-up filing review, DCR determined that Mylan's responses that were submitted on June 19, 2014 were adequate for purposes of receiving the ANDA.[4]

Rationale

Upon further review, DFR has concluded that the original refuse-to-receive action was erroneously issued because DCR's characterization of the issues with Mylan's ANDA as major deficiences was based on an evaluation of the sufficiency of the information in the ANDA for *review* purposes, not the sufficiency of such information for *filing* purposes.

Given that Mylan included data and informaton related to its two studies as part of the original ANDA submission, the proper course of action would have been to characterize the incomplete information idenitifed by DCR in its filing review as minor deficiencies and permit the applicant an opportunity to remedy the omission.

If the issues related to Mylan's skin/irritation/sensitization/adhesion study (MPTP-12130) and the adhesion study (MPTP-11030) had been identified as minor deficiencies instead of as major deficiencies, Mylan would have been permitted to remedy such minor deficiencies within a period of time consistent with DFR practice at that time (*i.e.*, 10 business days) and the ANDA would have been considered received as of the date on which the ANDA was first submitted to FDA (*i.e.*, December 13, 2013), instead of the date on which such requested additional information was provided by Mylan (*i.e.*, June 19, 2014).[5]Therefore, DFR has rescinded the May 15, 2014, RTR determination. The receipt date for this ANDA is restored to the original December 13, 2013, date.

[4] Division of Clinical Review Checklist for Generic ANDA for Application Completeness re ANDA 206497 (September 19, 2014).

[5] Although Mylan would normally have 10 business days to remedy minor deficiencies (and Mylan's response to the RTR letter was submitted outside this 10 business-day timeframe), Mylan was not informed of this timeframe due to the mischaracterization of the deficiencies as major. Thus, as a matter of equity, we consider Mylan's June 19, 2014, response to be timely submitted for purposes of addressing the minor deficiencies.

ANDA FILING CHECKLIST

(CTD or eCTD FORMAT)

FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 206497 Resubmission to RTR
APPLICANT: Mylan Technologies, Inc.
RELATED APPLICATION(S):

DRUG NAME: **Methylphenidate**
DOSAGE FORM: Patch, 10 mg/9 hrs(1.1 mg/hr), 15 mg/9 hrs(1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr)

LETTER DATE: 12/13/2013
RECEIVED DATE: 6/19/2014

☒ P-IV
☐ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST: MaPP 5240.1 or MaPP 5240.3 or GDUFA (Approved/Denied)
☐ PEPFAR
☐ PET

Electronic or Paper Submission: Gateway Type II DMF# (b) (4)

BASIS OF SUBMISSION:
NDA/ANDA: NDA 21514
FIRM: NOVEN PHARMACEUTICALS INC
RLD: DAYTRANA

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: **DC4 Team 42** ☒ **Activity**	DBE Team: **DBE Team 3, Moheb Makary** ☒ **Activity**
RPM: **Andrew Kim** ☒ **FYI**	DBE PM: Scott Vehovic ☒ **FYI**
CHEM PQRPM: **Jennifer Nguyen** ☒ **FYI**	Division of Clinical Review: ☐ **Activity**
CHEM Team Leader: Huijeong Jung ☐ **No Assignment Needed in DARRTS**	DMF Review Team Leader: **Dave Skanchy** ☒ **FYI**
Dissolution Review: ~DissoTeam~ ☐ **FYI**	
Labeling Reviewer: **Alison Park** ☒ **Activity**	Micro Review: ☐ **Activity**
SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):	

Regulatory Reviewer: Tim Jetton /Ilinca Duveau Date: **8/6/2015**	Recommendation: ☒ **FILE** ☐ **REFUSE to RECEIVE**

Comments: EC-1
Therapeutic Code: 2020600 (Drugs for Minimal Brain Dysfunction (ADHD, etc))
On Cards: Yes
Archival copy: Gateway
Sections: I

- **For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
- **For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
- **For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**

1. Edit Application Property Type in DARRTS where applicable for

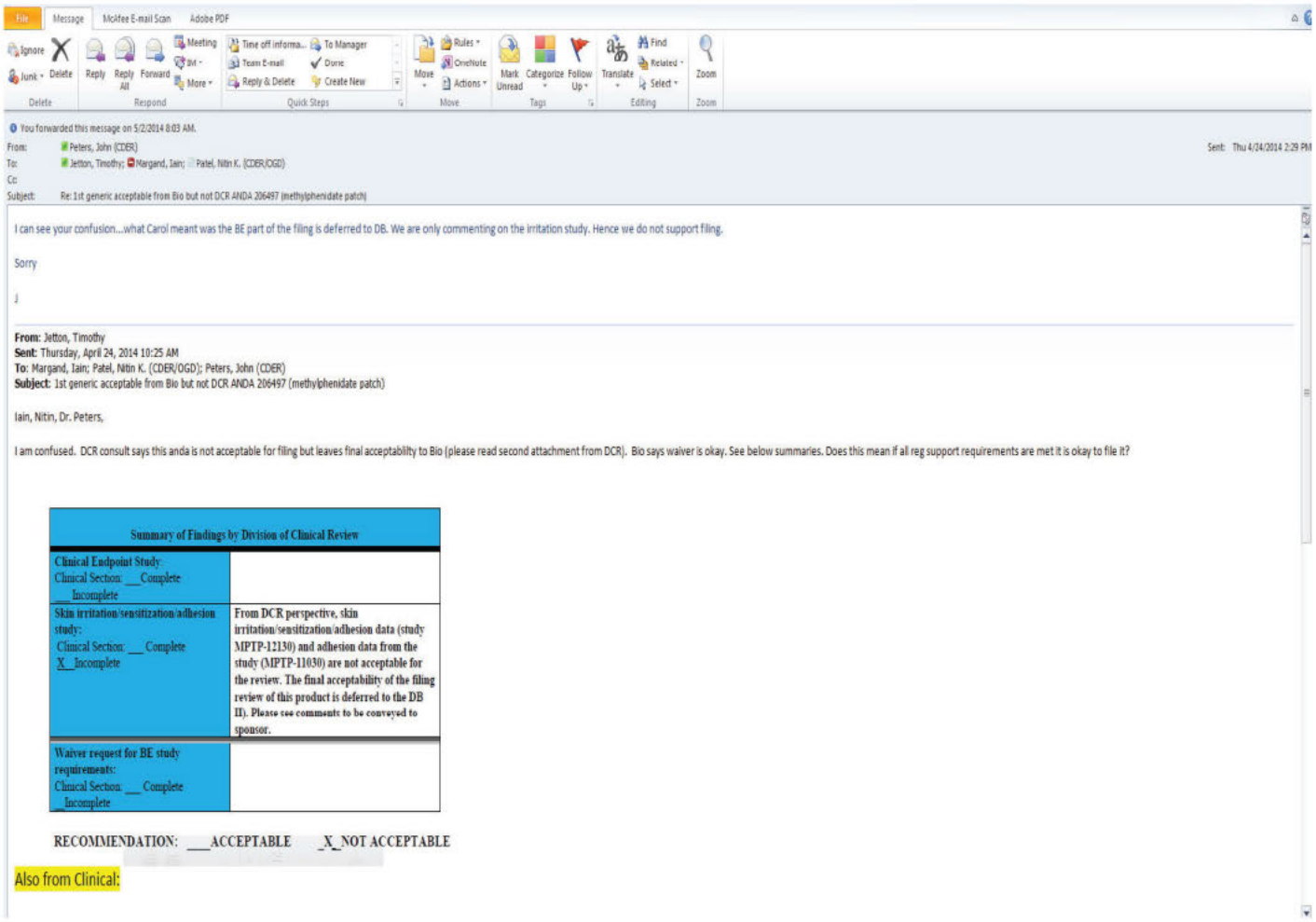
a. First Generic Received
☐ Yes ☒ No
b. Market Availability
☒ Rx ☐ OTC
c. Pepfar
☐ Yes ☒ No
d. Product Type
☐ Small Molecule Drug
e. USP Drug Product (at time of filing review)
☐ Yes ☒ No

2. Edit Submission Patent Records in DAARTS
☐ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
☐ Yes
4. EER (internal notation: RSB to submit at time of filing)
☐ Yes
5. GDUFA Obligation Met (Filing Fee, Type II DMF Fee, and Facility Fee)
☐ Yes - (internal notation-if not met contact: cder-om-collection@fda hhs.gov)
6. DMF Complete Assessment
☐ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

This ANDA is rescinded. Applicant's justifications are found on the FRS checklist. Please see Memo to file for further information.

1. RTR due to DCR see email below



You forwarded this message on 5/2/2014 8:03 AM.

From: Peters, John (CDER) Sent: Thu 4/24/2014 2:29 PM
To: Jetton, Timothy; Margand, Iain; Patel, Nitin K. (CDER/OGD)
Cc:
Subject: Re: 1st generic acceptable from Bio but not DCR ANDA 206497 (methylphenidate patch)

I can see your confusion...what Carol meant was the BE part of the filing is deferred to DB. We are only commenting on the irritation study. Hence we do not support filing.

Sorry

J

From: Jetton, Timothy
Sent: Thursday, April 24, 2014 10:25 AM
To: Margand, Iain; Patel, Nitin K. (CDER/OGD); Peters, John (CDER)
Subject: 1st generic acceptable from Bio but not DCR ANDA 206497 (methylphenidate patch)

Iain, Nitin, Dr. Peters,

I am confused. DCR consult says this anda is not acceptable for filing but leaves final acceptablilty to Bio (please read second attachment from DCR). Bio says waiver is okay. See below summaries. Does this mean if all reg support requirements are met it is okay to file it?

Summary of Findings by Division of Clinical Review	
Clinical Endpoint Study: Clinical Section: ___Complete ___Incomplete	
Skin irritation/sensitization/adhesion study: Clinical Section: ___ Complete X__Incomplete	From DCR perspective, skin irritation/sensitization/adhesion data (study MPTP-12130) and adhesion data from the study (MPTP-11030) are not acceptable for the review. The final acceptability of the filing review of this product is deferred to the DB II). Please see comments to be conveyed to sponsor.
Waiver request for BE study requirements: Clinical Section: ___ Complete __Incomplete	

RECOMMENDATION: ___ACCEPTABLE _X_NOT ACCEPTABLE

Also from Clinical:

ANDA FILING CHECKLIST
CLINICAL AND STATISTICS

ANDA:	**206497 – Resub-3**
APPLICANT:	**Mylan Technologies, Inc.**
DRUG NAME:	**Methylphenidate**
DOSAGE FORM:	**Transdermal Patch, 10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9 hrs and 30 mg/9 hrs**
NDA/ANDA:	NDA 21514
RLD:	**Daytrana**
RLD DOSAGE FORM:	**Transdermal System**
RLD FIRM:	Noven Pharmaceuticals, Inc.
APPROVAL DATE:	04/06/2006
PRIMARY REVIEWER:	Ilinca Duveau, Pharm.D.
SECONDARY REVIEWER:	Julia Lee, Pharm.D.

Primary Reviewer's Signature of Completion	**Summary:**
Expired certificate X Ilinca Duveau Filing Reviewer Signed by: Ilinca Duveau -S	☒ **COMPLETE** ☐ **INCOMPLETE**

☐ CLINICAL ENDPOINT STUDY (#)

For patches,
☒ IRRITATION/SENSITIZATION STUDY (#MPTP-12130)
☒ ADHESION STUDY (#MPTP-12130, MPTP-11030)

COMMENTS TO THE APPLICANT:

ONLY RTR deficiencies were assessed for completion. All other deficiencies found will not be addressed at the filing stage.

Study # 11125: Pivotal study (BE with PK endpoints) 36 subjects– see the BE checklist

CLINICAL STUDY REPORT
Methylphenidate Transdermal System (30 mg/9 hr) Mylan MPTP-11125 (Celerion AA97278)

1 TITLE PAGE

STUDY TITLE:	**Single-Dose Bioequivalence Study of Methylphenidate Transdermal System (30 mg/9 hr; Mylan) to Daytrana™ (30 mg/9 hr; Shire) in Healthy Adult Volunteers**

Objectives:
The primary objective of this study was to investigate the bioequivalence of Mylan's Methylphenidate Transdermal System, 30 mg/9 hr to Shire's Daytrana™, releasing 30 mg/9 hr, following a single-dose application of 9 hours. Secondary objectives were to assess adhesion and the acute dermal irritation after a single transdermal system application.

Study # 11030: Pilot Study – Single-dose Pilot Bioequivalence Study – 24 subjects

Objectives:	The primary objective of this study is to investigate the bioequivalence of Mylan's Methylphenidate Transdermal System, 30 mg/9 hr to Shire's Daytrana®, releasing 30 mg/9 hr, following a single-dose application of 9 hours. Secondary objectives are to assess adhesion and the acute dermal irritation after single patch applications.

Study #12130: Pivotal Study

Objectives:	The objective of this study is to evaluate the adhesion, cumulative dermal irritation and contact sensitization of a single formulation of Mylan's Methylphenidate Transdermal System; 10 mg/9 hours manufactured by Mylan Technologies Inc compared to Noven's Daytrana®10 mg (releasing 10 mg/9 hours) worn for a 2-3-day wear cycle for 9 applications at the same skin application site on the hip. In addition, the adhesive quality of Mylan's Methylphenidate Transdermal System will be compared to Noven's Daytrana® in all enrolled subjects during the first patch application. As a secondary objective, patches will be examined by the clinic staff to see if the labeling on the transdermal system is readable at the end of the 9-hour adhesion assessment on Study Day 1.

DCR consult performed on studies #12130 (irritation/sensitization/adhesion) and 11030 (listed as adhesion form a PK study).

Study #11030 is a Single-Dose Bioequivalence Study on 30 mg/9 hr, evaluating adhesion and acute dermal irritation. In the application (module 5.3.1.2) is listed as a pilot study, and per the Draft Guidance on Methylphenidate the skin irritation, sensitization and adhesion study should be performed on the 10 mg/9hr strength (not the 30 mg/9hr)

RTR deficiencies:

For the Study MPTP – 12130:

1. Adverse events in a SAS dataset – **provided**
2. Concomitant medications in a SAS dataset – **provided**
3. The frequency table for proportion of subjects with a meaningful degree of detachment – **applicant provided the data in the requested format within the cover letter**
4. The frequency table for mean days until removed or moved due to a significant irritation during induction period - **provided in the cover letter**
5. The frequency table for combined irritation scores (irritation and other effect scores) during re-challenge period – **provided in the cover letter**
6. Adhesion evaluation result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the reference product is less than or equal to 0 as recommended in the draft guidance for this product – **provided in the cover letter for 90% not 95%**

Arithmetic Mean (%CV)	Arithmetic Mean (%CV)
Treatment A Mylan	Treatment B Daytrana®
0.082 (264%)	0.336 (123%)

Least-Squares Mean			
Treatment A Mylan	Treatment B Daytrana®	μ_1-1.25μ_2[1]	90% Confidence Interval[2]
0.082	0.336	-0.338	-0.414 – -0.262

Per DCR this is acceptable.

7. The description and composition of Study MPTP-12130 test product Lot R6D0023. It is unclear whether the formulation provided in section 3.2.P.1 is for this lot or not – **explanation provided in the cover letter and also in the original submission in the Pharmaceutical Development Section.**
8. A list of subjects included in the evaluable population per treatment for adhesion analysis in a SAS.xpt file – **provided**
9. A list of subjects excluded from the evaluable population per treatment (if any) and reason for exclusion for adhesion analysis in a SAS.xpt file - **provided**

The following sections were listed in the RTR letter as part of the MPTP-12130 Study. However, they were duplicates of what was already asked in deficiencies #1, #2, and #3:

10. Adverse events in a SAS.xpt file
11. Concomitant medications in a SAS.xpt file
12. Adhesion scores in a SAS.xpt file – provided in the original submission

The following deficiencies listed in the RTR letter seem to be pertaining to study MPTP-11030 (pilot study)

13. Adhesion evaluation result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the RLD (30 mg/9 hr) minus 1.25 times the mean adhesion score for the reference product is less than or equal to 0 as recommended in the draft guidance for this product - **provided**
14. Table with proportion of subjects with meaningful degree of detachment - **provided**
15. The description and composition of Study MPTP-11030 test product Treatments A (Lot R6C0003) and B (Lot R6C0004). It is unclear whether the formulation provided in section 3.2.P.1 "Description and Composition" is for this lot or not – **explanation provided**

Per DCR filing review on September 1, 2014 the application was found to be complete and acceptable for filing. The following additional information is requested for the review of the study MPTP-11030 by DCR in the September, 2014 review.

1. A list of subjects included in the evaluable population per treatment for adhesion analysis in a SAS.xpt file
2. A list of subjects excluded from the evaluable population per treatment (if any) and reason for eclusion for adhesion analysis in a SAS.xpt file

These two deficiencies were listed as #8 and #9 in the RTR letter under study MPTP-1230, and the data has been provided. Therefore, the applicant cannot be held accountable for not submitting it for MPTP-11-30.

ALL STUDIES (#MPTP-11030, MPTP-12130)	COMMENT(S)
Draft/final guidance (include posted date) **YES**	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf Recommended July 2010
Protocol (original and amendments) **YES**	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\mptp-12130--protocol-or-amendment.pdf Original: September 21, 2012 (pp.4-59) **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\mptp-11030-protocol-or-amendment-meal-plan.pdf Amendment(version 2): February 14, 2011 (pp.3-50) Original needs to be provided
Study Report YES	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf (pp.1-70) Provide Report Date **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\study-report-body\mptp-11030--study-report-body.pdf (pp.2-61)
Clinical Site(s) and Study Investigator(s) list YES (if no U.S. sites used, ask for justification whether the sponsor's study population is representative of the disease state in the U.S. population) **Study Investigator(s) CVs YES**	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\study-report-body\mptp-11030--study-report-body.pdf **Investigator(s) CV:** **MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\mptp-12130--list-description-investigator-site.pdf **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\mptp-11030-list-description-investigator-site.pdf
Reasons for discontinuation from the study if discontinued NO (XPT)	**MPTP-12130:** Provide in XPT format **Pilot Study = MPTP-11030:** Not Applicable - no patients discontinued
Adverse Events YES (XPT)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\12130-ae.xpt **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-

	rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-ae.xpt
Concomitant Medications YES (XPT)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\12130-cm.xpt **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-cm.xpt
Individual subject's scores/data per visit YES (XPT)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130adheraw.xpt **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-adhe-r.xpt
Pre-screening of patients YES (screen inclusion and exclusion criteria in dataset, medical history in dataset, usually sample CRF)	**MPTP-12130:** \\cdsesub1\evsprod\ANDA206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130 **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\ANDA206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030
IRB Approval **Approval letters for protocol YES** **Approved consent/assent forms YES** (IRB letter/memo with stamped date of approval and/or IRB letterhead with date showing approval)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\mptp-12130--iec-irb-consent-form-list.pdf To be provided with a stamped date **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\mptp-11030-iec-irb-consent-form-list.pdf
Consent Forms YES (Dated)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\mptp-12130--iec-irb-consent-form-list.pdf **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\mptp-11030-iec-irb-consent-form-list.pdf
Protocol Deviations NO (XPT)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\mptp-12130--protocol-deviations.pdf Provide in XPT format **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\mptp-11030-protocol-deviations.pdf Provide in XPT format
All Case Report Forms YES (at minimum, should have for all patients who were dropped from the analysis population, demonstrated protocol deviations, demonstrated	**MPTP-12130:** \\cdsesub1\evsprod\ANDA206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\pracs

protocol violations, experienced serious adverse events, and a random sample of 10% of all enrolled patients)	**Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\ANDA206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\celerion
Clinical Raw Data/Medical Records YES	**MPTP-12130:** \\cdsesub1\evsprod\ANDA206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\pracs **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\ANDA206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\celerion
Financial Disclosure YES	\\cdsesub1\evsprod\anda206497\0000\m1\us\financial-certification-disclosure.pdf
Formulation YES	\\cdsesub1\evsprod\anda206497\0000\m3\32-body-data\32p-drug-prod\mptp-td-p-mti\32p1-desc-comp\description-and-composition.pdf
Placebo Formulation YES	No placebo formulation, compared to the RLD
All inactive ingredients below IID limits YES	\\cdsesub1\evsprod\anda206497\0000\m3\32-body-data\32p-drug-prod\mptp-td-p-mti\32p1-desc-comp\description-and-composition.pdf
Evidence provided by the sponsor to demonstrate that the difference in such inactive ingredients do not affect the safety and efficacy of the proposed drug product. (e.g., pharm/tox data, copy of references) **N/A**	Not addressed in the RTR letter
BioStudy Lot numbers and Date of Manufacture YES	\\cdsesub1\evsprod\anda206497\0000\m2\27-clin-sum\bioequivalence-summary-table-5.pdf
Exp. Date of RLD YES	\\cdsesub1\evsprod\anda206497\0000\m2\27-clin-sum\bioequivalence-summary-table-5.pdf
Bio-waiver requests for other strengths **Supporting Data YES**	\\cdsesub1\evsprod\anda206497\0000\m1\us\request-waiver-in-vivo-ba-study.pdf
RLD have REMS? NO If so, provided REMS? **Select**	Not applicable

CLINICAL ENDPOINT STUDY (#)	
Sponsor's study design consistent with the FDA guidance Select (e.g., treatment indication, patient population, dose, frequency, primary endpoint, application site	Not Applicable
Primary Endpoint **Defined** (within BE limits) **Select** **Superiority over placebo Select**	Not Applicable
Secondary Endpoint **Defined** (within BE limits) **Select** **Superiority over placebo Select**	Not Applicable

IRRITATION/SENSITIZATION STUDY (#MPTP-12130, MPTP-11030)	
Applicant's study	**MPTP-12130:**

design consistent with the FDA Guidance for Irritation/Sensitization YES (e.g., patch size, location, strength, application frequency, application duration, simultaneous or parallel, overlay or tape used)	\\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf **Pilot Study = MPTP-11030:** The study design is not consistent with the Draft Guidance on Methylphenidate (10mg/9h)
Tables provided for Irritation/Sensitization NO (e.g., mean, frequency, mean days of patch removal)	**MPTP-12130:** To be provided by applicant **Pilot Study = MPTP-11030:** To be provided by applicant
Applicant indicates no worse skin irritation and sensitization properties of the test product compared to that of the RLD YES (within non-inferiority limit, T-[1.25X R]<0)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf (pp.76) **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\study-report-body\mptp-11030--study-report-body.pdf (null hypothesis was rejected)
ADHESION STUDY (#MPTP-12130, MPTP-11030)	
Applicant's study design consistent with the FDA Guidance for Adhesion YES (e.g., patch size, location, strength, application frequency, application duration, simultaneous or parallel, overlay or tape used)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf **Pilot Study = MPTP-11030:** The study design is not consistent with the Draft Guidance on Methylphenidate (10mg/9h)
Tables provided for Adhesion NO (e.g., mean, frequency, proportion of subjects with adhesion score of 3 or more per treatment)	**MPTP-12130:** To be provided by applicant **Pilot Study = MPTP-11030:** To be provided by applicant
Applicant indicates no worse skin adhesion properties of the test product compared to that of the RLD YES (within non-inferiority limit, T-[1.25X R]<0)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0002\m1\us\cover-letter-0002.pdf **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\study-report-body\mptp-11030--study-report-body.pdf (null hypothesis was rejected)

STATISTICS

ALL STUDIES (#MPTP-12130, MPTP-11030)	COMMENT(S)
FDA Guidance available YES (Identify the guidance date)	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf Recommended July 2010
Study Protocol YES	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\mptp-12130--protocol-or-amendment.pdf Original: September 21, 2012 (pp.4-59) **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\mptp-11030-protocol-or-amendment-meal-plan.pdf Amendment(version 2): February 14, 2011 (pp.3-50) Original needs to be provided
Study Report YES	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf (pp.1-70) Provide Report Date **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\study-report-body\mptp-11030--study-report-body.pdf (pp.2-61)
Statistical Analysis Plan YES	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\study-report-body\mptp-12130--study-report-body.pdf **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\study-report-body\mptp-11030--study-report-body.pdf \\cdsesub1\evsprod\anda206497\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\study-report-body\mptp-11030-study-report-body--pk-report.pdf Separate report should be provided for both studies under the Statistical Methods Interim Analysis Plan folder
Data definition file YES (describes the variables in each data set)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\12130define.pdf

	\\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-12130\12130-ae-cm-def.pdf **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-ae-cm-def.pdf
Randomization Schedule NO (XPT)	**MPTP-12130:** Provide in XPT format **Pilot Study = MPTP-11030:** Provide in XPT format
Demographic Data NO (XPT)	**MPTP-12130:** Provide in XPT format **Pilot Study = MPTP-11030:** Provide in XPT format
Summary Data YES (XPT- usually it is the ADSL.xpt dataset with efficacy measures or the combined dataset of ADSL.xpt and efficacy dataset) (if nasal spray, a data table containing summary data from both period I & II – Placebo-run-in period & treatment period)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130summary.xpt **Pilot Study = MPTP-11030:** Provide in Summary Data in xpt format
Raw Data (NO-LOCF) YES (XPT)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130adheraw.xpt \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130irriraw.xpt **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-ae-cm-def.pdf
LOCF Data (not applicable for nasal spray) **YES** (XPT)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130adheloc.xpt \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130irriloc.xpt **Pilot Study = MPTP-11030:** To be provided

Identification of mITT Population Select **Reasons for Exclusion Select** (XPT) If transdermal, **Identification of Adhesion Population YES** **Reasons for Exclusion YES**	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130summary.xpt **Pilot Study = MPTP-11030:** To be provided
Identification of the PP Population Select **Reasons for Exclusion Select** (XPT) *If transdermal,* **Identification of Irritation Population YES** **Reasons for Exclusion YES** *When applicable* **Identification of Sensitization Population Select** **Reasons for Exclusion Select**	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130summary.xpt **Pilot Study = MPTP-11030:** To be provided
Date of Data Unblinded N/A	**MPTP-12130:** Not applicable **Pilot Study = MPTP-11030:** Not Applicable
Provides all SAS programs and list of all programs NO (Used to generate the analysis datasets and efficacy results)	**MPTP-12130:** To be provided **Pilot Study = MPTP-11030:** To be provided
NON-TRANSDERMAL STUDY (#)	
Subject's measurements/visits/dates Select (XPT)	
Data to evaluate treatment compliance Select (XPT)	
NASAL SPRAY STUDY (#)	
Individual subject's measurements per analysis relative Day (i.e., Day-7,...,Day-1,Day1..., Day 14) **Select** (XPT)	
Data to evaluate treatment & rating compliance for period I (Placebo-Run-In period) Select (XPT)	
Data to evaluate treatment & rating compliance for period II (Treatment Period) Select (XPT)	
ADHESION STUDY (#MPTP-12130, MPTP-11030)	
Adhesion measurements per patch (i.e., time points, scores, visit #, dates) **Select** (XPT)	**MPTP-12130:** \\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130adheraw.xpt **Pilot Study = MPTP-11030:** \\cdsesub1\evsprod\anda206497\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mptp-11030\11030-adhe-r.xpt
IRRITATION AND SENSITIZATION STUDY (#MPTP-11230, MPTP-11030)	
Subject's irritation measurements (i.e., time	**MPTP-12130:**

points, scores, visit #, dates) **Select** (XPT)	\\cdsesub1\evsprod\anda206497\0000\m5\datasets\mptp-12130\analysis\legacy\datasets\12130irriraw.xpt **Pilot Study = MPTP-11030:** not applicable
When applicable **Subject's sensitization measurements** (i.e., time points, scores, visit #, dates) **Select** (XPT)	Not aplicable

Irritation and Sensitization Study

Did the sponsor use the OGD recommended method to demonstrate irritation NI (non-inferiority)?

☒ YES ☐ NO

If NO, did the sponsor provide sufficient justification and documentation?

☐ YES ☐ NO

Adhesion Study

Did the sponsor use the OGD recommended method to demonstrate adhesion NI?

☒ YES ☐ NO

If NO, did the sponsor provide sufficient justification and documentation?

☐ YES ☐ NO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : August 15, 2014

TO : Director
Division of Clinical

FROM : Director, Division of Filing Review
Office of Generic Drugs

SUBJECT: **Response to RTR -** Examination of the bioequivalence study submitted with an ANDA for Methylphenidate Patch, 10 mg/9 hrs(1.1 mg/hr), 15 mg/9 hrs(1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr) to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Mylan Technologies, Inc. has submitted ANDA 206497 for Methylphenidate Patch, 10 mg/9 hrs(1.1 mg/hr), 15 mg/9 hrs(1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr). The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. In order to accept an ANDA, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Mylan Technologies, Inc. on June 19, 2014 for its Methylphenidate Patch product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

Division of Filing Review respectively requests that you finalize a response to this filing review consult by no later than 30-days from the date the consult was checked into DARRTS. If the 30th day falls on a Saturday, Sunday, or Federal holiday, the 30th day will be the next day that is not a Saturday, Sunday or Federal holiday. Thank you in advance for your consideration and input.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN E POLIFKO
08/15/2014

JOHNNY L YOUNG
09/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20903

ANDA 206497

USER FEES NOT RECEIVED - NOTIFICATION

Mylan Technologies, Inc.
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
781 Chestnut Ridge Road, P.O. Box 4310
Morgantown, WV 26504
E-mail: joseph.sobecki@mylan.com

June 27, 2014

Dear Joseph J. Sobecki:

Please refer to your abbreviated new drug application (ANDA) submitted for the following:

Name of Drug Product:	Methylphenidate Transdermal Patch, 10mg/9hrs, 15mg/9hrs, 20mg/9hrs & 30mg/9hrs
Date of Submission:	June 19, 2014
Submission Receipt Date:	June 19, 2014

Our records indicate that user fee obligations associated with your application remain outstanding. Pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA) § 744B, as added by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), an application is considered incomplete and cannot be received until all fees owed have been paid. We cannot begin a review of the adequacy of your application pursuant to § 505(j) until the Food and Drug Administration (FDA or the Agency) receives payment of the following outstanding fee obligations:

➢ANDA filing fee

I

The ANDA filing fee, incurred pursuant to § 744B(a)(3)(A), was due on June 19, 2014, the submission receipt date of the ANDA. Our records indicate that you submitted a payment in the amount of $0.00; the ANDA fee due was $63,860.00. As a result, your account reflects an outstanding balance of $63,860.00.

According to the Generic Drug User Fee Amendments of 2012 (GDUFA), the ANDA filing fee is required to be fully paid within 20 days from the submission receipt date. If this date falls on a weekend or holiday, the fee will be due on the next business day. Because the ANDA filing fee obligation has not been met in full by the above due date, you now have until July 9, 2014, to satisfy the obligation. Failure to satisfy the outstanding obligation by that date will result in the Agency refusing to receive your submission within the meaning of § 505(j)(5)(A). See § 744B(g)(3). In order to avoid this statutory penalty, please ensure the Agency receives the outstanding filing fee, in the amount of $63,860.00, no later than July 9, 2014.

II

Generic drug submissions may be delayed if the agency discovers that a sponsor is affiliated, as defined by FDASIA, with an entity that is on the publicly available arrears list for failure to satisfy a user fee obligation. Please consult your records, as well as the arrears list, and determine if you have an affiliate that is on the arrears list. The arrears list is available here: www.fda.gov/gdufa.

It is your responsibility to ensure that your user fee obligations are met for each fee type; please consult your records to ensure that all obligations are satisfied. The Agency will not receive your application until all user fee obligations are satisfied. Please submit the relevant cover sheets and fees as soon as possible.

In addition to the above mentioned penalties for non-payment, failure to meet your user fee obligations can be treated as a claim by the United States Government subject to subchapter II of chapter 37 of title 31, United States Code.

This correspondence embodies the Agency's most updated information; this information may be subject to change. You will be notified if additional obligations are identified or incurred. If you submitted all relevant fees before receiving this correspondence, please disregard this letter or contact our office immediately. If you have further questions, contact CDER's Office of Management, Office of User Fee Collections & Budget Formulation, by email at askgdufa@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Donal Parks, Director
Office of User Fee Collections & Budget Formulation
Office of Management
Center for Drug Evaluation and Research
US Food and Drug Administration

How to satisfy your fee obligations:

To make a payment towards your outstanding user fee obligations, you must complete a generic drug user fee cover sheet, available on the FDA Web site http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm322629.htm, and generate a user fee identification (ID) number.

Payment must be made in U.S. currency drawn on a U.S. bank by electronic check (ACH), check, bank draft, U.S. postal money order, or wire transfer.

FDA has partnered with the U.S. Department of the Treasury to utilize Pay.gov, a Web-based payment application, for online electronic payment. The Pay.gov feature is available on the FDA web site after completing the generics user fee cover sheet, and generating the user fee ID number.

Please include the user fee ID number on your check, bank draft, or postal money order, and make payable to the order of the Food and Drug Administration. Your payment can be mailed to: Food and Drug Administration, P.O. Box 979108, St. Louis, MO 63197-9000.

If checks are to be sent by a courier that requests a street address, the courier can deliver the checks to: U.S. Bank, Attention: Government Lockbox 979108, 1005 Convention Plaza, St. Louis, MO 63101. (Note: This U.S. Bank address is for courier delivery only.) Please make sure that the FDA post office box number (P.O. Box 979108) is written on the check, bank draft, or postal money order.

If paying by wire transfer, please reference your unique user fee ID number when completing your transfer. The originating financial institution may charge a wire transfer fee between $15.00 and $35.00. Please ask your financial institution about the fee and include it with your payment to ensure that your fee is fully paid. The account information is as follows: New York Federal Reserve Bank, U.S. Dept. of Treasury, TREAS NYC, 33 Liberty St., New York, NY 10045, Acct. No.: 75060099, Routing No.: 021030004, SWIFT: FRNYUS33, Beneficiary: FDA, 1350 Piccard Dr., Rockville, MD, 20850. The tax identification number of the Food and Drug Administration is 53-0196965.

Please note that review of your submission cannot begin until the bank receives your payment and the FDA is notified by a receipt from the bank stating that your payment has been received. For purposes of determining compliance with statutory deadlines, receipt occurs on the date the Office of Financial Management receives your payment.

When submitting documents unrelated to the payment of user fees, please cite the ANDA number listed above at the top of the first page of all submissions to this application. Send all ANDA-related review submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

Please send all DMF-related submission to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTOR F NG on behalf of DONAL R PARKS
06/27/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206497

Mylan Technologies, Inc.
Attention: Joseph J. Sobecki
110 Lake Street
St. Albans, VT 05478

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 13, 2013, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methylphenidate Transdermal Patch, 10mg/9hrs, 15mg/9hrs, 20mg/9hrs & 30mg/9hrs.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

From Department of Clinical Review perspective, your data from a skin irritation/sensitization/adhesion study (MPTP-12130) and the adhesion study (MPTP-11030) are not acceptable for receiving your ANDA. The submission is incomplete. Data requested below are the combined requests of the DCR and the statistical reviewers.

The following additional information is requested for the review:

For the Study MPTP-12130:

1. Adverse events in a SAS dataset (.xpt file)

2. Concomitant medications in a SAS dataset (.xpt file)

3. The frequency table for proportion of subjects with a meaningful degree of detachment. See below for an example.

		Adhesion score				
Product	N	100 (100% adhesion), N (%)	95 N (%)	85 N (%)	75 N (%)	<75, N (%)
A						
B						

4. The frequency table for mean days until removed or moved due to a significant irritation during induction period. See below for an example.

Irritation data			
Product	Combined irritation score (dermal response + other effects) > 3	Patches removed due to unacceptable degree of irritation	Mean days until patch was removed due to unacceptable degree or irritation
A			
B			

5. The frequency table for combined irritation scores (irritation and other effect scores) during re-challenge Period

6. Adhesion evaluation result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the reference product is less than or equal to 0 as recommended in the draft guidance for this product

7. The description and composition of Study MPTP-12130 test product Lot R6D0023. It is unclear whether the formulation provided in section "3.2.P.1 Description and Composition" is for this lot or not.

8. A list of subjects included in the evaluable population per treatment for adhesion analysis in a SAS .xpt file

9. A list of subjects excluded from the evaluable population per treatment (if any) and reason for exclusion for adhesion analysis in a SAS .xpt file

10. Adverse events in a SAS .xpt file

11. Concomitant medications in a SAS .xpt file

12. Adhesion scores in a SAS xpt file

13. Adhesion evaluation result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the RLD (30 mg/9 hours) is less than or equal to 0 as recommended in the draft guidance for this product

14. Table with proportion of subjects with meaningful degree of detachment (see comment #3 above for an example)

15. The description and composition of Study MPTP-11030 test product Treatments A (Lot R6C0003) and B (Lot R6C0004). It is unclear whether the formulation provided in section "3.2.P.1 Description and Composition" is for this lot or not.

Thus, your application will not be received within the meaning of Section 505(j) of the Act.

Since FDA has refused to receive this ANDA for reasons other than failure to pay Generic Drug User Fees, in accordance with Section 744B(a)(3)(D) of the Act, you are eligible to receive a refund of 75 percent of the filing fee for this application. To initiate the refund, e-mail CDERcollections@fda.hhs.gov with your Tax ID number (required for all domestic companies) or DUNS Number (required for all foreign companies), and the address where the refund is to be sent. This information is **required**, and FDA cannot process a refund without it.

You may either amend your application by providing a complete response to the Refuse to Receive letter or withdraw your application under 21 CFR 314.99. Submission of a complete response to the Refuse to Receive letter will be subject to the

same filing fee as a new original ANDA, pursuant to Section 744B(a)(3)(E) of the Act. If you elect to submit a complete response and wish to discuss payment options, or have additional user fee payment inquiries, e-mail CDERcollections@fda.hhs.gov for additional assistance.

If you have any questions please call:

Timothy Jetton
Project Manager
(240) 276-8668

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHANNON L HILL
05/15/2014
Signing for Wm Peter Rickman

ANDA FILING CHECKLIST

(CTD or eCTD FORMAT)

FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 206497
APPLICANT: Mylan Technologies, Inc.
RELATED APPLICATION(S):

DRUG NAME: **Methylphenidate**
DOSAGE FORM: Patch, 10 mg/9 hrs(1.1 mg/hr), 15 mg/9 hrs(1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr)

LETTER DATE: 12/13/2013
RECEIVED DATE: 12/13/2013

☒ P-IV
☐ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST: MaPP 5240.1 or MaPP 5240.3 or GDUFA (Approved/Denied)
☐ PEPFAR
☐ PET

Electronic or Paper Submission: Gateway Type II DMF# (b) (4)

BASIS OF SUBMISSION:
NDA/ANDA: NDA 21514
FIRM: NOVEN PHARMACEUTICALS INC
RLD: DAYTRANA

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: **DC4 Team 42** ☒ **Activity**	DBE Team: **DBE Team 3, Moheb Makary** ☒ **Activity**
RPM: **Andrew Kim** ☒ **FYI**	DBE PM: Scott Vehovic ☒ **FYI**
CHEM PQRPM: **Jennifer Nguyen** ☒ **FYI**	Division of Clinical Review: ☐ **Activity**
CHEM Team Leader: Huijeong Jung ☐ **No Assignment Needed in DARRTS**	DMF Review Team Leader: **Dave Skanchy** ☒ **FYI**
Dissolution Review: ~DissoTeam~ ☐ **FYI**	
Labeling Reviewer: **Alison Park** ☒ **Activity**	Micro Review: ☐ **Activity**
SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):	

Regulatory Reviewer: Tim Jetton Date: **4/24/14**	Recommendation: ☐ **FILE** ☒ **REFUSE to RECEIVE**

Comments: EC-1
Therapeutic Code: 2020600 (Drugs for Minimal Brain Dysfunction (ADHD, etc))
On Cards: Yes
Archival copy: Gateway
Sections: I

- **For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
- **For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
- **For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**

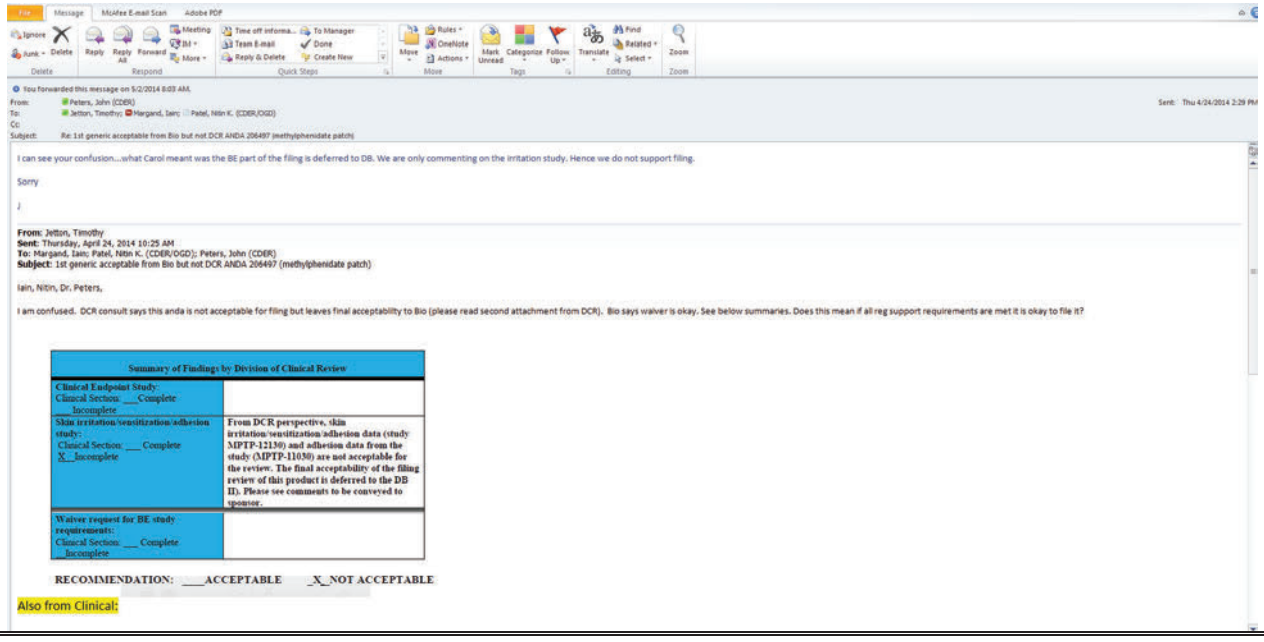
1. Edit Application Property Type in DARRTS where applicable for

a. First Generic Received
☐ Yes ☒ No
b. Market Availability
☒ Rx ☐ OTC
c. Pepfar
☐ Yes ☒ No
d. Product Type
☐ Small Molecule Drug
e. USP Drug Product (at time of filing review)
☐ Yes ☒ No

2. Edit Submission Patent Records in DAARTS
☐ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
☐ Yes
4. EER (internal notation: RSB to submit at time of filing)
☐ Yes
5. GDUFA Obligation Met (Filing Fee, Type II DMF Fee, and Facility Fee)
☐ Yes - (internal notation-if not met contact: cder-om-collection@fda hhs.gov)
6. DMF Complete Assessment
☐ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. RTR due to DCR see email below



I can see your confusion...what Carol meant was the BE part of the filing is deferred to DB. We are only commenting on the irritation study. Hence we do not support filing.

Sorry

From: Jetton, Timothy
Sent: Thursday, April 24, 2014 10:25 AM
To: Hargand, Iain; Patel, Nitin K. (CDER/OGD); Peters, John (CDER)
Subject: 1st generic acceptable from Bio but not DCR ANDA 206497 (methylphenidate patch)

Iain, Nitin, Dr. Peters,

I am confused. DCR consult says this anda is not acceptable for filing but leaves final acceptability to Bio (please read second attachment from DCR). Bio says waiver is okay. See below summaries. Does this mean if all reg support requirements are met it is okay to file it?

Summary of Findings by Division of Clinical Review	
Clinical Endpoint Study: Clinical Section: ___Complete ___Incomplete	
Skin irritation/sensitization/adhesion study: Clinical Section: ___Complete X__Incomplete	From DCR perspective, skin irritation/sensitization/adhesion data (study MPTP-12130) and adhesion data from the study (MPTP-11030) are not acceptable for the review. The final acceptability of the filing review of this product is deferred to the DB II). Please see comments to be conveyed to sponsor.
Waiver request for BE study requirements: Clinical Section: ___ Complete ___Incomplete	

RECOMMENDATION: ___ACCEPTABLE _X_NOT ACCEPTABLE

Also from Clinical:

ANDA 206497

Mylan Technologies, Inc.
Attention: Joseph J. Sobecki
110 Lake Street
St. Albans, VT 05478

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 13, 2013, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methylphenidate Transdermal Patch, 10mg/9hrs, 15mg/9hrs, 20mg/9hrs & 30mg/9hrs.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

From Department of Clinical Review perspective, your data from a skin irritation/sensitization/adhesion study (MPTP-12130) and the adhesion study (MPTP-11030) are not acceptable for receiving your ANDA. The submission is incomplete. Data requested below are the combined requests of the DCR and the statistical reviewers.

The following additional information is requested for the review:

For the Study MPTP-12130:

1. Adverse events in a SAS dataset (.xpt file)

2. Concomitant medications in a SAS dataset (.xpt file)

3. The frequency table for proportion of subjects with a meaningful degree of detachment. See below for an example.

		Adhesion score				
Product	N	100 (100% adhesion), N (%)	95 N (%)	85 N (%)	75 N (%)	<75, N (%)
A						
B						

4. The frequency table for mean days until removed or moved due to a significant irritation during induction period. See below for an example.

Irritation data			
Product	Combined irritation score (dermal response + other effects) > 3	Patches removed due to unacceptable degree of irritation	Mean days until patch was removed due to unacceptable degree or irritation
A			
B			

5. The frequency table for combined irritation scores (irritation and other effect scores) during re-challenge Period

6. Adhesion evaluation result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the reference product is less than or equal to 0 as recommended in the draft guidance for this product

7. The description and composition of Study MPTP-12130 test product Lot R6D0023. It is unclear whether the formulation provided in section "3.2.P.1 Description and Composition" is for this lot or not.

8. A list of subjects included in the evaluable population per treatment for adhesion analysis in a SAS .xpt file

9. A list of subjects excluded from the evaluable population per treatment (if any) and reason for exclusion for adhesion analysis in a SAS .xpt file

10. Adverse events in a SAS .xpt file

11. Concomitant medications in a SAS .xpt file

12. Adhesion scores in a SAS xpt file

13. Adhesion evaluation result demonstrating that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the RLD (30 mg/9 hours) is less than or equal to 0 as recommended in the draft guidance for this product

14. Table with proportion of subjects with meaningful degree of detachment (see comment #3 above for an example)

15. The description and composition of Study MPTP-11030 test product Treatments A (Lot R6C0003) and B (Lot R6C0004). It is unclear whether the formulation provided in section "3.2.P.1 Description and Composition" is for this lot or not.

Thus, your application will not be received within the meaning of Section 505(j) of the Act.

Since FDA has refused to receive this ANDA for reasons other than failure to pay Generic Drug User Fees, in accordance with Section 744B(a)(3)(D) of the Act, you are eligible to receive a refund of 75 percent of the filing fee for this application. To initiate the refund, e-mail CDERcollections@fda.hhs.gov with your Tax ID number (required for all domestic companies) or DUNS Number (required for all foreign companies), and the address where the refund is to be sent. This information is **required**, and FDA cannot process a refund without it.

You may either amend your application by providing a complete response to the Refuse to Receive letter or withdraw your application under 21 CFR 314.99. Submission of a complete

DIVISION OF CLINICAL REVIEW CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA#	206497
DRUG NAME	Methylphenidate Transdermal System, 10mg/9hrs (1.1 mg/hr), 15mg/9hrs (1.6 mg/hr), 20mg/9hrs (2.2 mg/hr), & 30mg/9hrs (3.3 mg/hr)
DOSAGE FORM	Transdermal System
APPLICANT NAME	Mylan Technologies, Inc.
REFERENCE LISTED DRUG (RLD)	Daytrana® Transdermal System, 3.3 mg/hr, Noven Pharms Inc.
NDA	021514
PRIMARY REVIEWER	Sunny Tse, Ph.D. Division of Clinical Review Office of Generic Drugs
SECONDARY REVIEWER	Carol Y. Kim, PharmD. Division of Clinical Review Office of Generic Drugs
TERTIARY REVIEWER	John R. Peters, M.D. Director Division of Clinical Review Office of Generic Drugs
REQUESTED BY **REQUESTED DATE**	Edward Washington Regulatory Support Team Office of Generic Drugs 12/23/2013

Summary of Findings by Division of Clinical Review	
Clinical Endpoint Study: Clinical Section: ___Complete ___ Incomplete	
Skin irritation/sensitization/adhesion study: Clinical Section: ___ Complete X__Incomplete	**From DCR perspective, skin irritation/sensitization/adhesion data (study MPTP-12130) and adhesion data from the study (MPTP-11030) are not acceptable for the review. The final acceptability of the filing review of this product is deferred to the DB II). Please see comments to be conveyed to sponsor.**
Waiver request for BE study requirements: Clinical Section: ___ Complete __Incomplete	

RECOMMENDATION: ____ACCEPTABLE _X_NOT ACCEPTABLE

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 206497 **FIRM NAME** **Mylan Technologies, Inc.**

DRUG NAME Methylphenidate Transdermal System Patch 10 mg/9hrs (1.1 mg/hr), 15 mg/9hrs (1.6 mg/hr), 20 mg/9hrs (2.2 mg/hr) & 30 mg/9hrs (3.3 mg/hr)

DOSAGE FORM **Transdermal System Patch**
SUBJ: Request for examination of: Bioequivalence Study and Request for Waiver

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Patrick Nwakama
Reviewer

_____ Date: _____
Moheb Makary
Team Leader

_____ Date: _____
Ethan M. Stier
Director, Division of Bioequivalence 2

GDUFA DMF COMPLETENESS ASSESSMENT CHECKLIST

For evaluation of initial COMPLETENESS for review of a Type II Drug Master File which has paid the required GDUFA DMF fee.

(b) (4)

[redacted]

Primary Reviewer: Kun Shen Email: Kun.Shen@fda.hhs.gov Date: 12/16/2013	Review Recommendation for Initial Completeness Assessment ☑ COMPLETE ☐ INCOMPLETE

1. Has the GDUFA fee been paid? Enter date paid: 2/26/2013 Payment ID: (b) (4) [redacted]

☑ Yes ☐ No

2. Is the DMF active?

☑ Yes ☐ No

If no, DMF is INCOMPLETE per policy. Issue Incomplete Letter to DMF holder.

3. Has the DMF been reviewed, after November 30, 2007, for chemistry, manufacturing and controls (CMC) by FDA in the context of a review of a prior application?

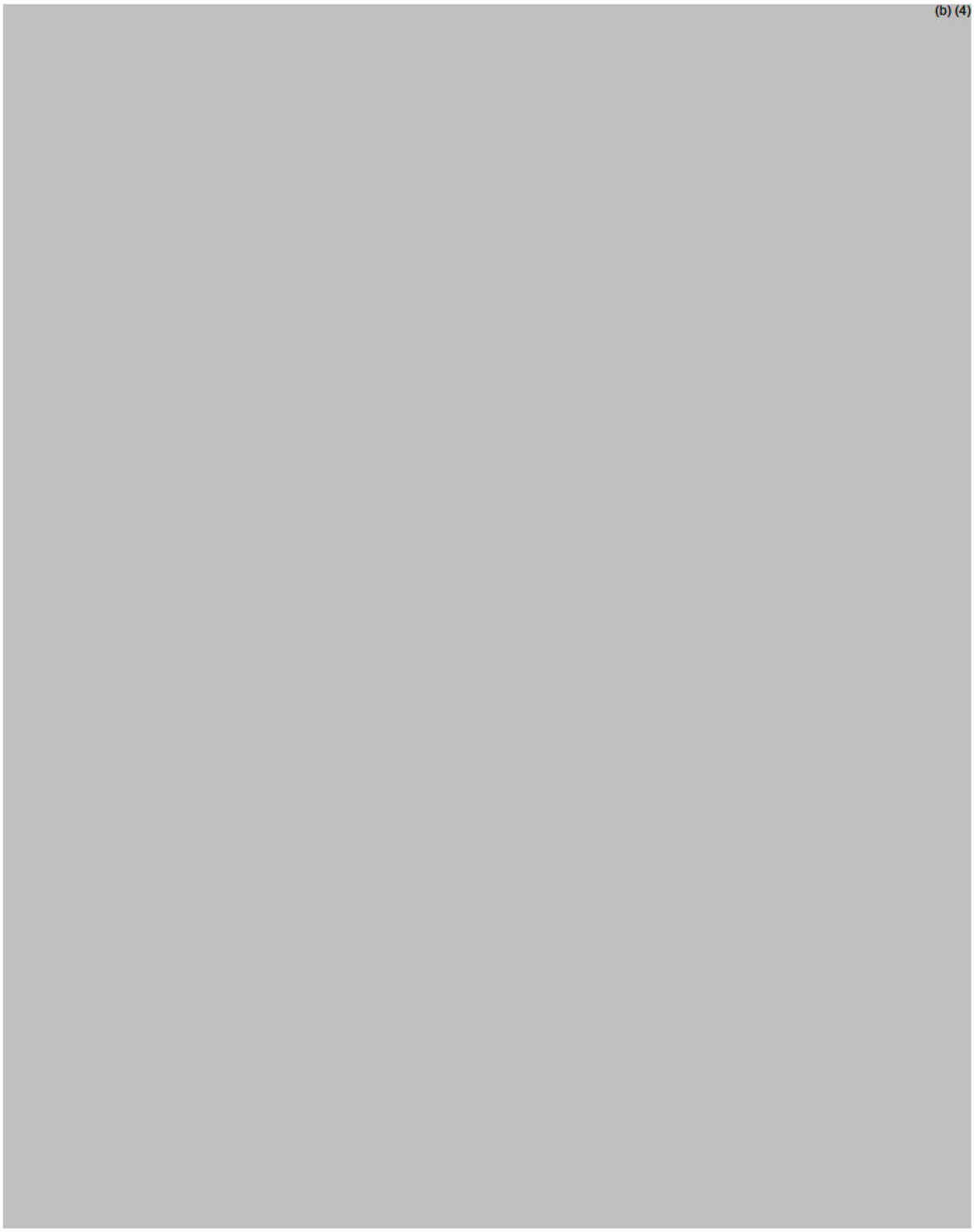
☑ Yes ☐ No

If "yes," the DMF is COMPLETE per policy. If "no," review DMF with checklist.

ADDITIONAL COMMENTS REGARDING THE DMF:

Agent:
Contact Person:
Phone Number:
Fax Number:
Email:

Most recent CMC review date: 8/15/13.



MODULE 1: ADMINISTRATIVE

		COMMENT (S)
1.1	**1.1.2** **Signed and Completed Application Form (356h)** (Rx/OTC Status) Rx (original signature) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf **** PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 29: MANUFACTURING STEPS AND/OR TYPE OF TESTING****	
1.2	**Cover Letter** Yes	

	Is the drug product subject to REMS requirements? ☒ Yes ☐ No Refer to the link below to determine if the product is a REMS product. **http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm** If the product is subject to REMS, send an email to Mary Dempsey informing her the ANDA has been submitted	
1.2.1	**Form FDA 3674 (PDF)** B	
*	**Table of Contents** (paper submission only) Select	
1.3.2	**Field Copy Certification** 21CFR 314.94(d)(5) (original signature) Select	
1.3.3	**Debarment Certification-GDEA** (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) Yes 2. List of Convictions statement (original signature) Yes	
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Yes Disclosure Statement (Form FDA 3455) Select	
1.3.5	**Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **Patent Certification [**21 CFR 314.94 (a)(12)/505(j)(2)(A)(vii)] 1. Patent number(s) 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ Statement of Notification (21 CFR 314.95/505(j)(2)(B)) ☐ 3. Expiration of Patent(s): a. Pediatric exclusivity submitted? Select b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: State marketing intentions?	

Patent and Exclusivity Search Results from query on Appl No 021514 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021514	001	6210705	Sep 30, 2018		Y	U - 727	
N021514	001	6348211	Sep 30, 2018		Y	U - 727	
N021514	001	8632802	Oct 7, 2025		Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

Patent and Exclusivity Search Results from query on Appl No 021514 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021514	002	6210705	Sep 30, 2018		Y	U - 727	
N021514	002	6348211	Sep 30, 2018		Y	U - 727	
N021514	002	8632802	Oct 7, 2025		Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

Patent and Exclusivity Search Results from query on Appl No 021514 Product 003 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021514	003	6210705	Sep 30, 2018		Y	U - 727	
N021514	003	6348211	Sep 30, 2018		Y	U - 727	
N021514	003	8632802	Oct 7, 2025		Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

Patent and Exclusivity Search Results from query on Appl No 021514 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021514	004	6210705	Sep 30, 2018		Y	U - 727	
N021514	004	6348211	Sep 30, 2018		Y	U - 727	
N021514	004	8632802	Oct 7, 2025		Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes b. Type II DMF# (b) (4) c. Type III DMF authorization letter(s) for container closure Select d. Type III or V DMF authorization letter(s) for sterile product sterilization process Select 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) Select	
1.12.4	**Request for Comments and Advice** - Proprietary name requested N/A If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes Select 2. No - contact the firm to submit the request as a separate electronic amendment.	
1.12.11	**Basis for Submission** NDA#: NDA 21514 Ref Listed Drug: DAYTRANA Firm: NOVEN PHARMACEUTICALS INC **ANDA suitability petition required?** Select If Yes, provide petition number and copy of approved petition **ANDA Citizen's Petition Required?** Select If Yes, provide petition number and copy of petition	
1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients Select 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD	
1.12.14	**Environmental Impact Analysis Statement** (cite 21CFR 25.31 and 25.15(d), if applicable) Yes	
1.12.15	**Request for Waiver** (cite 21 CFR 320.22 or 320.24(b)(6)) Request for Waiver of In-Vivo BA/BE Study(ies) Yes	

Contains Nonbinding Recommendations

Draft Guidance on Methylphenidate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Methylphenidate

Form/Route: Film, Extended Release/Transdermal

Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints Study
   Design: Single-dose, fasting, two-treatment, two-period crossover in vivo
   Strength: 30 mg/9 hr
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: The transdermal patch should be applied to the hip, as recommended in the approved reference listed drug (RLD) and worn for 9 hours.

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2. Type of study: Skin Irritation, Sensitization and Adhesion Study
   Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 10 mg/9 hr
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Methylphenidate in plasma, using an achiral assay for *d*- and *l*-methylphenidate (PK study only)

Bioequivalence based on (90% CI): Methylphenidate (PK study only)

Waiver request of in vivo testing: 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr based on (i) acceptable bioequivalence studies on the 30 mg/9 hr strength, (ii) proportional similarity of the 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr formulations to the 30 mg/9 hr strength, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Additional comments regarding the skin irritation, sensitization and adhesion study:

1. The Office of Generic Drugs (OGD) recommends evaluating skin irritation, sensitization and adhesion in a single study. To support approval, the test product must be no more irritating than the RLD, be no more sensitizing than the RLD and adhere at least as well as the RLD. Each parameter is to be evaluated with a separate analysis. The primary endpoints should be considered as co-primary endpoints, e.g., for each of them, the study must demonstrate that the test product is no worse than the RLD. The analysis for each parameter and the primary endpoint(s) and any

Reference ID: 3503991

1.14.1	**Draft Labeling** (Multi Copies N/A for E-Submissions) **1.14.1.1** 4 copies of draft for paper submission only (each strength and container) Yes **1.14.1.2** Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated **1.14.1.3** 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically **1.14.1.4** Labeling Comprehension Studies Refer to Pharmacy Bulk Package Sterility Assurance Table (for PBP's only) See link below for table: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf	
	Listed Drug Labeling **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated Yes **1.14.3.3** RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label Yes	

MODULE 2: Quality Overall Summary

		COMMENT (S)
2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** Yes **Word Processed e.g., MS Word** Yes **Additional information regarding QbR may be found at the following link:** http://www fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971 htm **Question based Review (QbR)** Yes **2.3.S Drug Substance (Active Pharmaceutical Ingredient)** Yes 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability **2.3.P Drug Product** Yes 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product **Oral Solids**: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft *Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation* (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	

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MODULE 2.7: Clinical Summary

		COMMENT (S)
2.7	**Clinical Summary (Bioequivalence)**Model BE Data Summary Tables **http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf** **** In addition to the standard tables, see the link above for tables specifically designed for in-vitro binding studies **** **http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM364105.pdf** **E-Submission: PDF** Yes **Word Processed: e.g., MS Word** Yes **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Yes Table 4. Bioanalytical Method Validation Yes Table 6. Formulation Data Yes Table 10. Study Information Yes Table 11. Product Information Yes Table 17. Comparative Physiochemical Data of Ophthalmic Solution Products N/A **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution Yes (include complete comparative In Vitro Dissolution Data (individual) with Certificate of Analysis [CoA] for Test and Reference products including: potency, assay, content uniformity, date of manufacture and lot number) Table 9. Reanalysis of Study Samples Yes Table 12. Dropout Information Yes Table 13. Protocol Deviation Yes Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analysis Yes **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Yes Table 3. Statistical Summary of the Comparative BA Data: 1. Unscaled Average – Table A 2. Reference-scaled Average BE Studies – Tables A **and** B BE Studies Select Table 16. Composition of Meal Used in Fed Bioequivalence Study Select **2.7.1.4 Appendix** Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples Yes **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Yes **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies Yes	

MODULE 3: 3.2.S DRUG SUBSTANCE

<table>
<tr><td></td><td></td><td>COMMENT (S)</td></tr>
<tr><td>3.2.S.1</td><td>General Information) Yes
(Do not refer to DMF)
3.2.S.1.1 Nomenclature
3.2.S.1.2 Structure
3.2.S.1.3 General Properties</td><td></td></tr>
<tr><td>3.2.S.2</td><td>Manufacturer
Drug Substance (Active Pharmaceutical Ingredient)
Must correlate to the establishment information submitted in annex to Form FDA 356h.
1. Name and Full Address(es)of the Facility(ies) Yes
2. Contact name, phone and fax numbers, email address Yes
3. U.S Agent’s name (if applicable) Yes
4. Specify Function or Responsibility Yes
5. Type II DMF number for API (b) (4)
6. CFN, FEI or DUNS numbers (if available)</td><td></td></tr>
<tr><td>3.2.S.3</td><td>Characterization Yes

Provide the following in tabular format as follows:

<table><tr><td>IUPAC Chemical Name</td><td>Code #</td><td>Chemical Structure</td><td>Process/ Degradation Impurity</td><td>Source/ Mechanism</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr></table>
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf</td><td></td></tr>
</table>

3.2.S.4 Control of Drug Substance (Active Pharmaceutical Ingredient)

3.2.S.4.1 Specification

Testing specifications and data from drug substance manufacturer(s) Yes

3.2.S.4.2 Analytical Procedures Yes

3.2.S.4.3 Validation of Analytical Procedures

(API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) Select

1. Spectra and chromatograms for reference standards and test samples Select
2. Samples-Statement of Availability and Identification of:

SAMPLE AVAILABILITY STATEMENT

Mylan commits to resolve any issues identified in the methods validation during review or after approval. Samples of the drug substance (see table below), reference standard and related material will be made available to the Agency upon request and/or at the time of the pre-approval inspection at the Mylan Technologies, Inc. facility.

Table 3.2.S.4.3/2: Sample availability

Drug Substance	Mylan Control Number	Supplier Lot Number
Methylphenidate	1106000630	1106000630
	1112000616	1112000616
	1208000854	1208000854

3.2.S.4.4 Batch Analysis

1. COAs specifications and test results from drug substance mfgr(s) Yes
2. Drug Product manufacturer's Certificates of analysis Yes

3.2.S.4.5 Justification of Specification Yes

Provide data in tabular format:

Chemical Name	Code#	MDD	IT	QT	TDI of Impurity	Proposed AC for Unspecified Impurities	Proposed AC for Specified Impurities	Justification if AC>QT for Specified Impurities

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

3.2.S.5 Reference Standards or Materials (Do not refer to DMF) Yes

3.2.S.6 Container Closure Systems Yes

3.2.S.7 Stability

1. Retest date or expiration date of API Yes

MODULE 3: 3.2.P DRUG PRODUCT

		COMMENT (S)
3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition with indication of the function of the inactive ingredient(s) Select 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) (provide justification in a tabular format) Select 3. Conversion from % to mg/dose values for inactive ingredients (if applicable) Select 4. Elemental iron: provide daily elemental iron calculation or statement of adherence to 21CFR73.1200 (calculation of elemental iron intake based on **maximum daily dose (MDD)** of the drug product is preferred if this section is applicable) Select 5. Injections: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the package configuration Select	

3.2.P.1 Description and Composition;

Mylan Technologies, Inc. (St. Albans, VT USA)

Table 3.2.P.1/1: Qualitative and Quantitative Unit Composition, Pharmaceutical Function, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Methylphenidate Transdermal Systems

Component	10 mg/ 9 hours (9.6 cm^2)	15 mg/ 9 hours (14.4 cm^2)	20 mg/ 9 hours (19.2 cm^2)	30 mg/ 9 hours (28.8 cm^2)	% w/w	Pharmaceutical Function	Maximum Level[1] Listed in FDA *Inactive Ingredient Database for Approved Drug Products*	Quality Standards
Active Ingredient								
Methylphenidate	(b) (4)							
Inactive Ingredients - Solid Matrix Reservoir and Skin Contact Adhesive Layers								
Hydrophobic Colloidal Silica NF	(b) (4)							
(b) (4) Mineral Oil NF	(b) (4)							
Polyisobutylene Adhesive	(b) (4)							
	(b) (4)							
	(b) (4)							
Total Matrix Weight								

3.2.P.1 Description and Composition;

Mylan Technologies, Inc. (St. Albans, VT USA)

Component	10 mg/ 9 hours (9.6 cm^2)	15 mg/ 9 hours (14.4 cm^2)	20 mg/ 9 hours (19.2 cm^2)	30 mg/ 9 hours (28.8 cm^2)	% w/w	Pharmaceutical Function	Maximum Level[1] Listed in FDA *Inactive Ingredient Database for Approved Drug Products*	Quality Standards
Inactive Ingredients – Backing Film, Release Liner, Printing Ink								
Ethylene-Vinyl Acetate / Polyester Film	(b) (4)							(b) (4)
Fluoropolymer-Coated Polyester Release Liner								
White Ink								
Total Drug Product Weight (excluding Release Liner)								

(b) (4)

From DCR review dated 2/14/14:

3.2.P.1 Description and Composition;

Mylan Technologies, Inc. (St. Albans, VT USA)

(b) (4)

Placebo formulation was not used in pivotal Study MPTP-12130.

Reviewer's Comments:

With the exception of hydrophobic colloidal silica, the formulation inactive ingredients were below the IID limit.

The sponsor provided data to support the use of hydrophobic colloidal silica at a maximum of (b) (4) *without change to the safety and efficacy of the test product.*[3]

The test product does not require Q1 and Q2 sameness.

3 ANDA 206497 in EDR[0000 (1) 12/13/2013 ORIG-1 /Multiple Categories/Subcategories Module 3.2.P.1 – Description and Composition of the Drug Product, page 3/6]

3.2.P.2	**Pharmaceutical Development** 1. Pharmaceutical Development Report Yes 2. Microbial Attributes a. Container/Closure Integrity Testing Report for Sterile Products b. Antimicrobial Effectiveness Testing for Multi-dose sterile products	
3.2.P.3	**Manufacture** **3.2.P.3.1 Drug Product** Must correlate to the establishment information submitted in annex to From FDA 356h for the finished dosage manufacturer and all outside contract testing laboratories. 1. Name and Full Address(es)of the Facility(ies) Yes 2. Contact name, phone and fax numbers, email address Yes 3. U.S Agent's name (if applicable) Yes 4. Specify Function or Responsibility Yes 5 CGMP Certification (from both applicant and drug product manufacturer if different entities) Yes 6. CFN, FEI or DUNS numbers (if available) **3.2.P.3.2 Batch Formula** Yes **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process and (for aseptic fill products) Facility Yes 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Yes 3. Master packaging records for intended marketing container(s) Select 4. If sterile product Select 5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes **3.2.P.3.4 Controls of Critical Steps and Intermediates** Yes **3.2.P.3.5 Process Validation and/or Evaluation** 1. Terminally Sterilized Product Select a. Validation of production terminal sterilization process b. Validation of depyrogenation of all product containers and closures c. Validation of container-closure package integrity 2. Aseptically Filled Product Select • Validation (bacterial retention studies) of sterilizing grade filter(s) • Validation of the sterilization of sterile bulk drug or product contact equipment, components, containers, and closures • Validation of depyrogenation of product containers and closures • Validation of aseptic filling process/line/room (media fills/process simulations) • Validation of container-closure package integrity	
3.2.P.4	**Controls of Excipients** (Inactive Ingredients) Source of inactive ingredients identified Select **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) Yes 2. Suppliers' COA (specifications and test results) Yes **3.2.P.4.2 Analytical Procedures** Select **3.2.P.4.3 Validation of Analytical Procedures** Select **3.2.P.4.4 Justification of Specifications:** 1. Applicant COA Yes	

3.2.P.5

Controls of Drug Product

3.2.P.5.1 Specification(s) Yes

3.2.P.5.2 Analytical Procedures Yes

3.2.P.5.3 Validation of Analytical Procedures

(if using USP procedure, must provide verification of USP procedure) Select

Samples - Statement of Availability and Identification of:

SAMPLE AVAILABILITY STATEMENT

Mylan commits to provide samples of Methylphenidate Transdermal Systems for the below listed exhibit batches and any necessary reference standards and related materials to the Agency upon request.

Table 3.2.P.5.3/2: Sample availability

Strength	Lot Number
10 mg/9 hrs (1.1 mg/hr)	R6D0023
15 mg/9 hrs (1.6 mg/hr)	R6D0035
20 mg/9 hrs (2.2 mg/hr)	R6D0036
30 mg/9 hrs (3.3 mg/hr)	R6D0014

3.2.P.5.4 Batch Analysis

Certificates of Analysis for Finished Dosage Form Yes

3.2.P.5.5 Characterization of Impurities Yes

Provide in tabular format as below:

IUPAC Chemical Name	Code #	Chemical Structure	Degradation Impurity	Source/ Mechanism

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

3.2.P.5.6 Justification of Specifications Yes

3.2.P.7

Container Closure System

1. Summary of Container/Closure System (if new resin, provide data) Select
2. Components Specification and Test Data Select
3. Packaging Configuration and Sizes
4. Container/Closure Testing (recommended additional testing for all plastic)Select
   a. Solid Orals: water permeation, light transmissionSelect
   b. Liquids: leachables, extractables, light transmissionSelect
5. Source of supply and suppliers address Select

3.2.P.8

3.2.P.8.1 Stability and Conclusions (Finished Dosage Form)

1. Stability Protocol submitted Yes
2. Expiration Dating Period for Marketed Packaging (b) (4)
3. Expiration Dating Period for Bulk Packaging (if applicable)

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (From Applicant and Drug Product Manufacturer, if different entities)

Post Approval Stability Protocol and Commitments Yes

3.2.P.8.3 Stability Data

1. Accelerated stability data
   a. Four (4) time points 0,1,2,3 Yes

-OR-

   b. . Refer to the Final Guidance for Industry *ANDAs: Stability Testing Drug Substances and Products*, dated June 2013 Select

Reference ID: 3503991

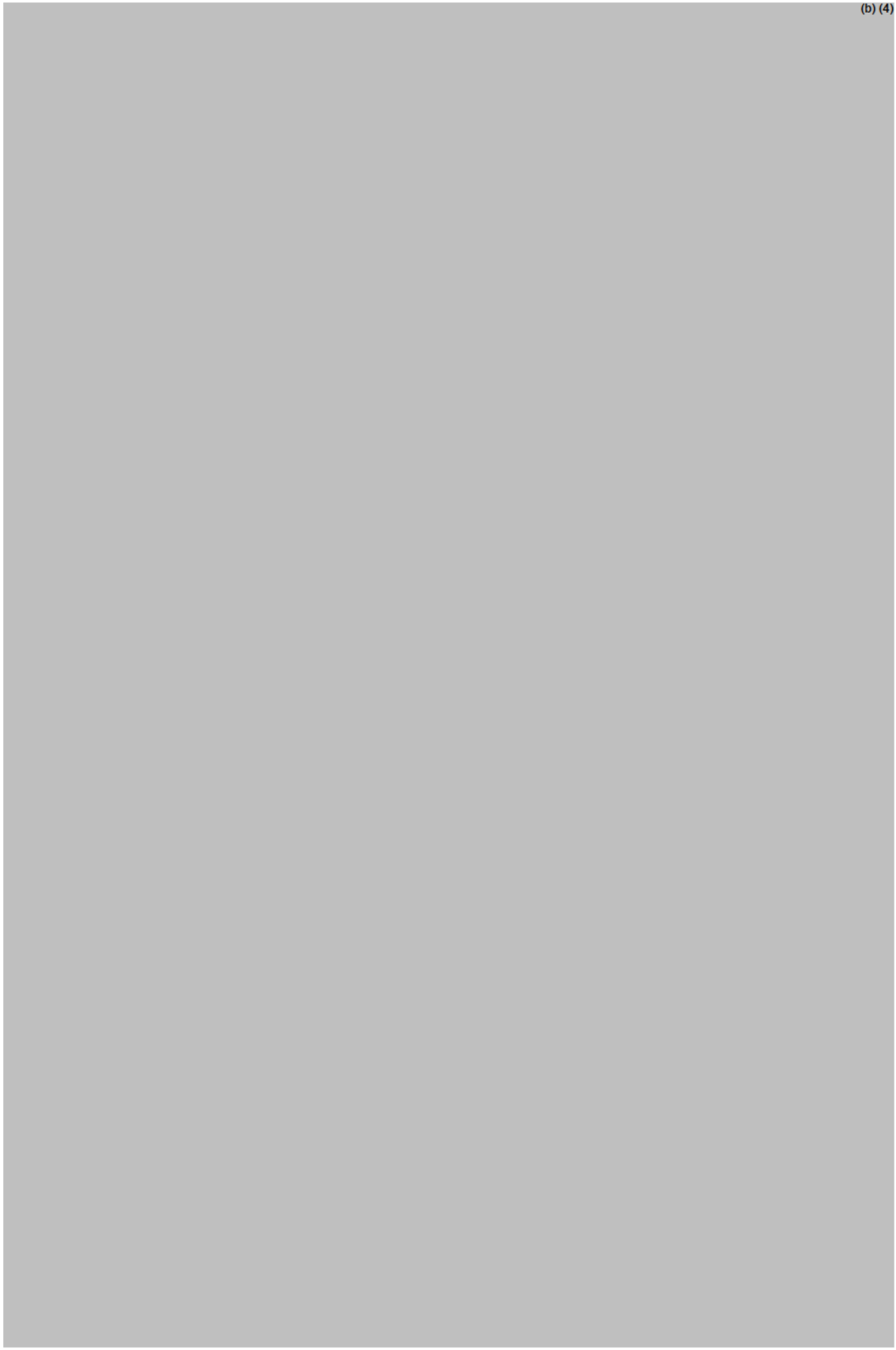
	c. For liquid and semi-solid products, upright and inverted/horizontal storage orientation Select 2. Batch numbers on stability records the same as the test batch Yes 3. Date accelerated stability study initiated Yes 4. Date accelerated stability sample(s) removed from stability chamber for each testing time point Yes	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

		COMMENT (S)
3.2.R Drug Substance	**3.2.R.1.S Executed Batch Records for drug substance (if available)** Select **3.2.R.2.S Comparability Protocols** Select **3.2.R.3.S Methods Validation Package** Select Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

		COMMENT (S)
3.2.R Drug Product	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation Select a. Theoretical Yield b. Actual Yield c. Packaged Yield Bulk Package Reconciliation for all bulk packaging considered a commercial container is required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: a. Bulk Package Label (1.14.1) Select b. Bulk Package Stability (3.2.P.8) 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months Select 2. If bulk is only warehoused for repackaging, provide RT stability data at 0,3,6 months Select c. Bulk Package Container and Closure information (3.2.P.7) Select **3.2.R.1.P.2 Information on Components** Select **3.2.R.2.P Comparability Protocols** Select **3.2.R.3.P Methods Validation Package** Select Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	


(b) (4)

MODULE 5: CLINICAL STUDY REPORTS

		COMMENT (S)
5.2	**Tabular Listing of Clinical Studies** Select	
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (proportionality of multiple strengths) Select b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers and strength of Products used in BE Study(ies)** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	
	See Module 2.7 Clinical Summary for placement of BA/BE Summary for tables 9 – 16. **The study data that support the BA/BE summary tables should be provided in the corresponding sections below:** **5.3.1.2 Comparative BA/BE Study Reports** **5.3.1.3 In Vitro-In-Vivo Correlation Study Reports (exception: all dissolution data should be placed in 2.7)** **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies** **Case Report Forms** should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging //www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4	**Literature References**	

	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** Division of Clinical Review Consult Complete ☐ Yes ☐ No	
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) Select 1. Study(ies) meets BE criteria (90% CI of 80-125) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** **Refer to the attached links for Nasal Product BE Tables:** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf **AND** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM271017.pdf Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** Division of Clinical Review Consult Complete ☐ Yes ☐ No	

Updated 1/24//2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIMOTHY G JETTON
05/09/2014

SHANNON L HILL
05/15/2014
Signing for Iain Margand

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 206497 **FIRM NAME** **Mylan Technologies, Inc.**

DRUG NAME Methylphenidate Transdermal System Patch 10 mg/9hrs (1.1 mg/hr), 15 mg/9hrs (1.6 mg/hr), 20 mg/9hrs (2.2 mg/hr) & 30 mg/9hrs (3.3 mg/hr)

DOSAGE FORM **Transdermal System Patch**
SUBJ: Request for examination of: Bioequivalence Study and Request for Waiver

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Patrick Nwakama
Reviewer

_____ Date: _____
Moheb Makary
Team Leader

_____ Date: _____
Ethan M. Stier
Director, Division of Bioequivalence 2

Item Verified:		YES	NO	Comments
Individual Product BE Recommendations		☒	☐	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf
RLD Product Appropriateness		☒	☐	Daytrana(R) Transdermal System (Lot No. R6D0014)
16 Biosummary Tables	Fast	☒	☐	Module 2.7.1 Tables 1 - 17
	Fed	☐	☒	
	Other	☐	☒	
Formulation (All Studies)		☒	☐	Module 2.7.1 Table 6
Individual Dissolution Data and Report		☒	☐	Module 2.7.1
Multimedia Dissolution Data and Report for ER Products (where applicable)		☒	☐	Module 2.7.1
Alcohol Dose Dumping Dissolution Data and Report (where applicable)		☐	☒	
Half-Tablet Dissolution Data and Report for Scored ER Tablets (where applicable)		☐	☒	
Certificate of Analysis of Test Product (Potency, Assay, Content Uniformity, Date of Manufacture, Lot Number)		☒	☐	Module 2.7.1 Table 11
Certificate of Analysis of Reference Product (Potency, Assay, Content Uniformity, Date of Expiry, Lot Number)		☒	☐	Module 2.7.1 Table 11
Bio Batch Size		☒	☐	Module 2.7.1 Table 11
BE Study Protocol	Fast	☒	☐	Module 5.3.1.2
	Fed	☐	☒	
	Other	☐	☒	
Non Standard Meal Menu	Fed	☐	☒	
Clinical Report	Fast	☒	☐	Module 5.3.1.2

	Fed	☐	☒	
	Other	☐	☒	
IRB Approval	Fast	☒	☐	Module 5.3.1.2
	Fed	☐	☐	
	Other	☐	☒	
Pre-Screening of Patients	Fast	☒	☐	Module 5.3.1.2
	Fed	☐	☒	
	Other	☐	☒	
Consent Form	Fast	☒	☐	Module 5.3.1.2
	Fed	☐	☒	
	Other	☐	☒	
Randomization Schedule	Fast	☒	☐	Module 5.3.1.2
	Fed	☐	☒	
	Other	☐	☒	
Test Article Inventory	Fast	☒	☐	Module 5.3.1.2
	Fed	☐	☒	
	Other	☐	☒	
Individual Adverse Event Report	Fast	☒	☐	Module 5.3.1.2
	Fed	☐	☒	
	Other	☐	☒	
Protocol Deviations	Fast	☒	☐	Module 5.3.1.2
	Fed	☐	☒	
	Other	☐	☒	
Individual and Mean Data & Graphs, Linear & Ln	Fast	☒	☐	Module 5.3.1.2, Study Report Body, Appendix 16.1.1
	Fed	☐	☒	

	Other	☐	☒	
SAS Datasets	Fast	☒	☐	Module 5.3.1.2 mptp-12012
	Fed	☐	☒	
	Other	☐	☒	
Statistical Report (Including SAS Output)	Fast	☒	☐	Module 5.3.1.2 mptp-12012
	Fed	☐	☒	
	Other	☐	☒	
Analytical SOP (Procedural SOP, Reanalysis SOP and Method Validation SOP)	Fast	☒	☐	Module 5.3.1.4, Attachment 2
	Fed	☐	☒	
	Other	☐	☒	
Long Term Storage Stability Data	Fast	☒	☐	Module 5.3.1.4 Validation Report Addendum 3; 121 days
	Fed	☐	☒	
	Other	☐	☒	
Pre-Study Validation Report	Fast	☒	☐	Module 5.3.1.4
	Fed	☐	☒	
	Other	☐	☒	
Within Study Analytical Report	Fast	☒	☐	Module 5.3.1.4
	Fed	☐	☒	
	Other	☐	☒	
Individual Samples Repeat Analysis Results (Include original and repeat values)	Fast	☒	☐	Module 5.3.1.4, Table 5
	Fed	☐	☒	
	Other	☐	☒	
Chromatograms, 20%	Fast	☒	☐	Module 5.3.1.4, Attachment 4
	Fed	☐	☒	
	Other	☐	☒	

Raw Numerical Data	Fast	☒	☐	Module 5.3.1.4
	Fed	☐	☒	
	Other	☐	☒	
Summary results provided by the firm indicate studies pass BE criteria		☒	☐	Module 2.7.1; Table 3
Waiver requests for other strengths / supporting data		☒	☐	Module 1.12; Section 1.12.15 (10 mg/9 hrs, 15 mg/9 hrs, 20 mg/9 hrs). All the three lower strengths are proportional similar to the 30 mg/9 hrs (28.8 cm2) strength and are eligible for waivers.

Test Formulation

Table 3.2.P.1/2: Qualitative Composition Statements – Methylphenidate Transdermal Systems

Components	Intermediate Laminate Composition		Finished Product mg/ system (area)			
	% w/w	g/m²	10 mg/ 9 hours (9.6 cm²)	15 mg/ 9 hours (14.4 cm²)	20 mg/ 9 hours (19.2 cm²)	30 mg/ 9 hours (28.8 cm²)
Solid Matrix Reservoir Layer						
Methylphenidate						(b) (4)
Hydrophobic Colloidal Silica NF						
(b) (4) Mineral Oil NF (b) (4)						
Polyisobutylene Adhesive (b) (4) (b) (4						
Solid Matrix Reservoir Subtotal	100.00%					(b) (4)
Skin Contact Adhesive Layer						
Hydrophobic Colloidal Silica NF (b) (4)						(b) (4)
(b) (4) Mineral Oil NF (b) (4)						
Polyisobutylene Adhesive (b) (4) (b) (4)						
Skin Contact Adhesive Subtotal	100.00%					(b) (4)
Backing, Release Liner, Printing Ink						
Ethylene-Vinyl Acetate (b) (4) Polyester Film (b) (4)						(b) (4)
(b) (4) Fluoropolymer-Coated Polyester Release Liner (b) (4)						
White Ink (b) (4)						

(b) (4) - *the Solid Matrix Drug Reservoir* (b) (4) *contains a methylphenidat* (b) (4)

Additional Comments regarding the ANDA: The firm conducted pivotal bioequivalence studies to evaluate the 1) pharmacokinetics, 2) adhesion, 3) cumulative irritation and 4) sensitization potential of the test vs. the RLD using exhibit batches of the test product - lot RD 0014 for MPTP-12012 (BE study) and lot R6D0023 for MPTP-12130 (Adhesion/Cumulative Irritation/Sensitization Study).

.

The firm conducted three BE studies (MPTP-11030, MPTP-1112, MPTP-12012) as summarized below:

1. Bioequivalence Study No. MPTP-11030 (Pilot)

The study MPTP-11030 was an irritation evaluator blinded, single-dose, randomized, three-period, three-treatment crossover bioequivalence. Treatment A (Mylan Lot#R6C0003); Treatment B (Mylan Lot#R6C0004), Treatment C (Daytrana®).

The bioequivalence of two formulations of Mylan's Methylphenidate Transdermal System, 30 mg/9 hours to Noven's Daytrana®, 30 mg/9 hours following a single 9-hour application was assessed. Statistical analyses of the data comparing Mylan's Methylphenidate Transdermal System, 30 mg/9 hr (**Treatment A, RC60003**) to Noven's Daytrana®, 30 mg/9 hours shows the upper 90% CIs limit for LCmax, LAUCI and LAUCT fall outside the acceptance range. In contrast, statistical analyses of the data comparing Mylan's Methylphenidate Transdermal System, 30 mg/9 hr (**Treatment B, RC60004**) to Noven's Daytrana®, 30 mg/9 hours demonstrated BE with the 90% CIs within 80 - 125% for LCmax, LAUCI and LAUCT. Based on the results from this study Mylan's Methylphenidate Transdermal System 30 mg/9 hours (**Treatment B, RC60004**) was **re-sized (from 34 cm^2 to 31.2 cm^2)** and a **pivotal** BE study conducted (MPTP-11125).

Component	Formulation 6.1105D:F2 Lot R6C0003		Formulation 6.1106D:F2 Lot R6C0004	
	30 mg/ 9 hrs (34 cm^2)	% w/w in component layer	30 mg/ 9 hrs (34 cm^2)	% w/w in component layer
Solid Matrix Drug Reservoir	[redacted]			
Methylphenidate				
Hydrophobic Colloidal Silica NF (b) (4)				
(b) (4) Mineral Oil NF (b) (4)				
Polyisobutylene Adhesive (b) (4)				
Skin Contact Adhesive				
Hydrophobic Colloidal Silica NF (b) (4)				
(b) (4) Mineral Oil NF (b) (4)				
Polyisobutylene Adhesive (b) (4)				
Total Matrix Weight				
Other Components				
Backing Film	Ethylene-Vinyl Acetate (b) (4) Polyester Film (b) (4)			
Release Liner	(b) (4) Fluoropolymer Coated Polyester Release Liner (b) (4)			
Imprinting Ink	White Ink (b) (4)			

Fasting Bioequivalence Study (MPTP-11030)

METHYLPHENIDATE TRANSDERMAL SYSTEM, 30 MG/9 HOURS (34 CM^2) Number of Subjects Completed = 24 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Parameter	**Test (A)**	**N**	**Reference C**	**N**	**Ratio***	**90% C.I.****
AUC0-t (ng×mL/hr)	190.94	19	155.78	19	1.23	112.23% - 133.87%
AUC∞ (ng×mL/hr)	200.93	19	165.96	19	1.21	111.45% - 131.52%
C_{max} (ng/mL)	19.70	19	16.54	19	1.19	109.21% - 129.98%
Parameter	**Test (B)**	**N**	**Reference C**	**N**	**Ratio***	**90% C.I.****
AUC0-t (ng×mL/hr)	177.50	22	155.78	22	1.14	104.87% - 123.80%
AUC∞ (ng×mL/hr)	186.88	22	165.96	22	1.13	104.16% - 121.73%
C_{max} (ng/mL)	17.63	22	16.54	22	1.07	98.23% - 115.71%

2. Bioequivalence Study No. MPTP-11125

The study MPTP-11125 was an irritation evaluator blinded, single-dose, randomized, two-period, two-treatment crossover bioequivalence study. Treatment B (Mylan Lot# R6C0004), Treatment C (Daytrana®). Statistical analyses of the data showed that the 90% CIs are within the acceptable BE range of 80.00% and 125.00% for LAUCI. The upper boundary of the 90% CIs for LCmax and LAUCT fall outside the upper CIs limit. Mylan's Methylphenidate Transdermal System 30 mg/9 hrs was **re-sized (from 31.2 cm^2 to 28.8 cm^2)** and a new pivotal BE study conducted (MPTP-12012).

Component	Formulation 6.1110D:F1 Lot R6C0016	
	30 mg/ 9 hrs (31.2 cm^2)	% w/w in component layer
Solid Matrix Drug Reservoir		(b) (4)
Methylphenidate		
Hydrophobic Colloidal Silica NF (b) (4)		
(b) (4) Mineral Oil NF (b) (4)		
Polyisobutylene Adhesive (b) (4)		
Skin Contact Adhesive		
Hydrophobic Colloidal Silica NF (b) (4)		
(b) (4) Mineral Oil NF (b) (4)		
Polyisobutylene Adhesive (b) (4)		
Total Matrix Weight		
Other Components		
Backing Film	Ethylene-Vinyl Acetate (b) (4) Polyester Film	
Release Liner	(b) (4) Fluoropolymer Coated Polyester Release Liner (b) (4)	
Imprinting Ink	White Ink (b) (4)	

Fasting Bioequivalence Study (MPTP-11125)

METHYLPHENIDATE TRANSDERMAL SYSTEM, 30 MG/9 HOURS (31.2 CM^2)
Number of Subjects Completed = 34; Dose (30 mg/9 hours)
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Parameter	Test	N	Reference	N	Ratio*	90% C.I.**
AUC0-t (ng×mL/hr)	157.30	34	138.20	34	1.14	102.69% - 126.15%
AUC∞ (ng×mL/hr)	166.46	34	149.31	34	1.11	101.60% - 122.34%
C_{max} (ng/mL)	17.27	34	14.80	34	1.17	103.61% - 131.32%

3. Bioequivalence Study No. MPTP-12012 (Pivotal Study)

The study MPTP-12012 was an irritation evaluator blinded, single-dose, randomized, three-period, two-treatment crossover BE study. In order to determine the intra-subject variability for the RLD, each subject received Daytrana® twice during the course of the study (reference-scaled). Statistical analysis of the data shows that the 90% CIs are within the acceptable BE limits of 80 - 125% for LAUCI, LAUCT and LCmax. This study demonstrates that Mylan's Methylphenidate Transdermal System, 30 mg/9 hours is BE to Noven's Daytrana® 30 mg/9 hours following application of a single 30 mg/9 hours patch under fasting conditions.

Table 67: Final Formulation of Methylphenidate Transdermal System

Component	Pharmaceutical Function	% w/w in component layer	30 mg/ 9 hrs (28.8 cm²)
Solid Matrix Reservoir			(b) (4)
Methylphenidate	Active		
Hydrophobic Colloidal Silica NF (b) (4)	(b) (4)		
(b) (4) Mineral Oil NF (b) (4)			
Polyisobutylene Adhesive (b) (4) (b) (4)			
Skin Contact Adhesive			
Hydrophobic Colloidal Silica NF (b) (4)			
(b) (4) Mineral Oil NF (b) (4)			
Polyisobutylene Adhesive (b) (4) (b) (4)			
Total			

Fasting Bioequivalence Study (MPTP-12012) – Reference Scaled Average Bioequivalence

METHYLPHENIDATE TRANSDERMAL SYSTEM, 30 MG/9 HOURS (28.8 CM^2) Number of Subjects Completed = 37; Dose (30 mg/9 hours) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC0-t (ng×mL/hr)	122.52	37	130.79	74	0.94	87.21% - 100.62%
AUC∞ (ng×mL/hr)	128.37	37	138.90	73	0.92	86.57% - 98.66%
C_{max} (ng/mL)	14.68	37	15.81	74	0.93	85.09% - 101.26%

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCT	0.93	86.98%	100.44%	0.0424	0.2058	-0.01145	ABE	Pass
LAUCI	0.92	85.89%	97.98%	0.0369	0.1921	-0.00410	ABE	Pass
LCMAX	0.93	84.51%	101.28%	0.0563	0.2373	-0.01317	ABE	Pass

Adhesion Results Summary for Study MPTP-12012

The firm assessed the Adhesion results according to the scoring system for adhesion defined in the study protocol. The mean data are summarized in the Table below.

Mean (± std. dev.) Adhesion Results for Transdermal System at 9 hours	
Mylan, Lot R6D0014	Daytrana®, Lot 58415
94.65% ± 4.67%	89.62% ± 12.40%

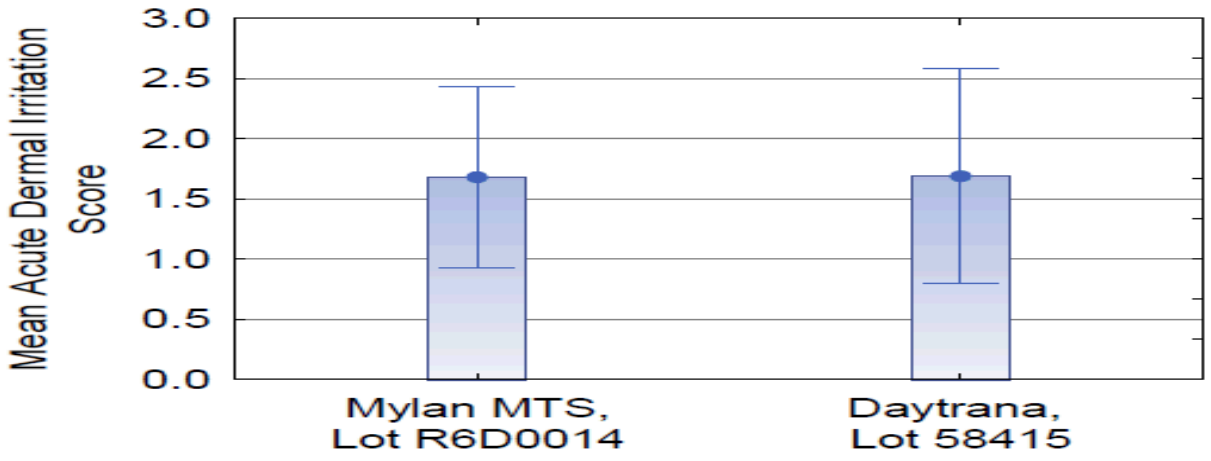
According to the firm, the results demonstrate that the adhesion of Mylan's Methylphenidate Transdermal System 30 mg/9 hrs (3.3 mg/hr) is comparable to Daytrana® 30 mg/9 hrs.

Irritation Results Summary for Study MPTP-12012

The firm tested irritation using the scale for irritation assessment defined in the study protocol. The frequency and mean data are summarized in Table and figure below.

Frequency of Irritation Scores at 30 Minutes after Patch Removal						
	Irritation Score					
Treatment	0	1	2	3	4	Total
Mylan, Lot R6D0014	5	3	28	1	0	37
Daytrana®, Lot 58415	10	12	45	5	2	74
Total	15	15	73	6	2	111

Mean (± std. dev.) Acute Dermal Irritation Score of the Patch	
Mylan, Lot R6D0014	Daytrana®, Lot 58415
1.68 ± 0.75	1.69 ± 0.89



The Application is acceptable for filing

Enter Review Productivity and Generate Report

Completed Assignment for 206497 ID: 21457

Reviewer: Nwakama, Patrick **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
21457	1/3/2014	Filing Checklist (REGULAR)	ANDA Filing Checklist	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

CHECKLIST for First Generic ANDA	
Checklist	1
Total	1

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/s/

PATRICK E NWAKAMA
01/17/2014

MOHEB H MAKARY
01/17/2014

ETHAN M STIER
01/19/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : December 20, 2013

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 206497 for Methyphenidate Transdermal System Patch 10 mg/9 hrs (1.1 mg/hr), 15 mg/9 hrs (1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr) to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Mylan Technologies Inc. has submitted ANDA 206497 for Methyphenidate Transdermal System Patch 10 mg/9 hrs (1.1 mg/hr), 15 mg/9 hrs (1.6 mg/hr), 20 mg/9 hrs (2.2 mg/hr) and 30 mg/9 hrs (3.3 mg/hr). The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. In order to accept an ANDA, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Mylan Technologies Inc. on December 13, 2013 for its Methyphenidate Transdermal System Patch product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

EDWARD WASHINGTON
12/23/2013

LATE CYCLE COMMUNICATIONS DOCUMENTS

Memorandum

To: ANDA 206497

From: Teena Thomas
Senior Regulatory Health Project Manager
Office of Bioequivalence
Office of Generic Drugs

Date: January 6, 2020

Subject: Product-Specific Guidance (PSG) on Methylphenidate

I. Background

In November 2019, the Agency announced the availability of a revised draft PSG entitled "Draft Guidance on Methylphenidate." This draft PSG provides product-specific recommendations for proposed generic drug products referencing Daytrana® (methylphenidate transdermal system, 1.1 mg, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr (NDA 021514).

Consistent with 21 CFR 320.24(a), the scientific recommendations reflected in this draft PSG represent FDA's determination of the most accurate, sensitive, and reproducible approach for conducting bioequivalence (BE) testing.

This memorandum describes whether such scientific recommendations impact the "adequate" BE and Clinical reviews of abbreviated new drug application (ANDA) 206497.

II. Discussion

The adequate **BE** review for this ANDA, completed April 19, 2016 is consistent with the scientific recommendations reflected in the Draft Guidance on Methylphenidate. Therefore, this guidance has no impact on the current BE review.

The adequate **Clinical** review for this ANDA, completed February 12, 2018 is consistent with the scientific recommendations reflected in the Draft Guidance on Methylphenidate. Therefore, this guidance has no impact on the current Clinical review.


APPEARS THIS WAY ON ORIGINAL

Teena
Thomas

Digitally signed by Teena Thomas
Date: 1/06/2020 10:24:28AM
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Memorandum

To: ANDA (b) (4)
ANDA 206497

From: Chitra Mahadevan, Pharm.D.
Senior Supervisory Project Manager
Office of Bioequivalence
Office of Generic Drugs

Date: November 7, 2018

Subject: Product-Specific Guidance (PSG) on Methylphenidate

I. Background

In October 2018, the Agency announced the availability of a revised draft PSG entitled "Draft Guidance on Methylphenidate." This draft PSG provides product-specific recommendations for proposed generic drug products referencing Daytrana® (Methylphenidate Extended Release Film), 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr, and 30 mg/9hr (NDA 021514).

Consistent with 21 CFR 320.24(a), the scientific recommendations reflected in this draft PSG represent FDA's determination of the most accurate, sensitive, and reproducible approach for conducting bioequivalence (BE) testing.

This memorandum describes whether such scientific recommendations impact the BE and Clinical reviews of abbreviated new drug applications (ANDAs) (b) (4) and 206497.

II. Discussion

(b) (4)

a. 206497

The adequate BE review for this ANDA, completed April 19, 2016, is consistent with the scientific recommendations reflected in the Draft Guidance on Methylphenidate. Therefore, this guidance has no impact on the current bioequivalence review.

The adequate clinical review for this ANDA, completed February 7, 2018, is consistent with the scientific recommendations reflected in the Draft Guidance on Methylphenidate. Therefore, this guidance has no impact on the current clinical review.

Chitra Mahadevan

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