CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 202346

Name: Lidocaine Patch, 5%

Sponsor: Mylan Technologies Inc.

Approval Date: August 7, 2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 202346

APPROVAL

Mylan Technologies Inc.
781 Chestnut Ridge Road, P.O. Box 4310
Morgantown, WV 26504
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 25, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch, 5%.

Reference is also made to your amendment dated May 6, 2015. The May 6, 2015, submission constituted a complete response to our April 24, 2015, Action Letter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is **approved**, effective on the date of this letter. The Division of Bioequivalence has determined your Lidocaine Patch, 5%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lidoderm Patch, 5%, of Teikoku Pharma USA, Inc. (Teikoku).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted in

Apparatus:	V (Paddle over Disk)
Speed:	50 rpm
Medium:	10 mM Sodium Acetate Buffer, pH 4.0
Temperature:	32°C
Volume:	500 mL
Specifications:	1.5 h: (b) (4) %
	6 h: (b) (4) %
	12 h: (b) (4) %
	24 h: (b) (4) %

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special

Supplement – Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Teikoku's Lidoderm Patch, 5%, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,827,529 (the '529 patent), is scheduled to expire on October 27, 2015.

Your ANDA contains a paragraph IV certification to the '529 patent under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Lidocaine Patch, 5%, under this ANDA. You have notified the Agency that Mylan Technologies Inc. (Mylan) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that no action for infringement was brought against Mylan within the statutory 45-day period.

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 & 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.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

You have been requested to provide information after the ANDA has been approved. Any information submitted to meet the conditions requested in this letter is considered a "Post Approval Commitment Response." To alert the Office of Generic Drug staff to the fact that you

are providing post approval commitment information, please designate your submission in your cover letter as "POST APPROVAL COMMITMENT RESPONSE."

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 (FDFs) or active pharmaceutical ingredients (APIs) 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.

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 http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

Carol A. Holquist -S

Digitally signed by Carol A. Holquist -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300052464, cn=Carol A. Holquist -S
Date: 2015.08.07 15:06:49 -04'00'

Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

<u>OTHER ACTION LETTERS</u>

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 202346

COMPLETE RESPONSE

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated October 25, 2010, received October 26, 2010, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Topical Patch, 5%.

We acknowledge receipt of your amendments dated June 26, October 18, and October 25, 2013; November 5, 2014; January 7, February 19, and February 27, 2015.

The June 26, 2013, submission constituted a Complete Response to our June 3, 2013, action letter.

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

In an information request issued on 13-FEB-2015, we requested that you justify (b) (4) However, your response did not adequately address the quality concerns that were expressed in the information request. Please respond to the following concerns:

1) (b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

BIOEQUIVALENCE

The Division of Bioequivalence 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.

DISSOLUTION

The Division of Bioequivalence acknowledges that the firm will use the following in vitro drug release method and specifications for its product:

Apparatus:	V (Paddle over Disk)	
Speed:	50 rpm	
Medium:	10 mM Sodium Acetate Buffer, pH 4.0	
Temperature:	32°C	
Volume:	500 mL	
Specifications:	1.5 h:	(b) (4) %
	6 h:	(b) (4) %
	12 h:	(b) (4) %
	24 h:	(b) (4) %

CLINICAL

The Division of Clinical Review has completed its review and the data submitted to ANDA 202346 are adequate to demonstrate that the irritation potential of Mylan Technologies, Inc's Lidocaine Patch, 5% is no worse than that of the RLD.

The data also demonstrate minimal potential of Mylan's Lidocaine Patch, 5% to induce sensitization, as also in the case of the reference listed drug (RLD), Lidoderm® Patch.

The data also demonstrate that the adhesive performance of Mylan's Lidocaine Patch, 5% is at least as good as that of the RLD.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. 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.

LABELING

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated February 27, 2015.

Please continue to monitor available labeling resources such as 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.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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**
> **CHEMISTRY**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. 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 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

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

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 (FDFs) or active pharmaceutical ingredients (APIs) 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.

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 Andrew Potter, Regulatory Project Manager, at (240) 402-9266.

Sincerely yours,

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

ANDA 202346

COMPLETE RESPONSE

Mylan Technologies, Inc.
Attention: S. Wayne Talton
Vice President, Global Regulatory Operations

110 Lake St.
St. Albans, VT 05478

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated October 25, 2010, received October 26, 2010, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch, 5%.

We acknowledge receipt of your amendments dated November 10, and December 15, 2010; February 8, March 8, July 1, and August 29, 2011; March 8 (two submissions), August 9, October 5, and November 7, 2012.

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

The deficiencies presented below are minor deficiencies:

A. Deficiencies:

1. (b) (4)

Following this page, 2 Pages Withheld in Full as (b)(4)

22. (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters and in-process material attributes
- Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's **Generic Drugs: Information for Industry** webpage: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

BIOEQUIVALENCE

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and has identified the following deficiencies.

1. For the bioequivalence (BE) study LIDO-1037, you reported the "apparent dose" delivered. However, the validity of your reported data for the "apparent dose" delivered cannot be confirmed as the study report did not include the complete analytical report, validation report, and the detailed experimental procedures. Please

provide this information. Please provide your analysis to show that the "apparent dose" delivered for your test product was comparable to the reference product.

2. We note that a number of subjects in the study LIDO-1037 were evaluated with adhesion score as 1 or 2 at some time points during the study. According to the protocol, score 1 means >=75% to <90% adhered (some edges only lifting off the skin) and score 2 means >=50% to 75% adhered (less than half the system lifting off the skin). You submitted the adhesion scores at 3 time points (4, 8 and 12 hours (± 10 minutes) after patch application) for each patch applied for all the subjects. However, you did not provide statistical summary data of the adhesion scores for the test and reference patches (Mean, SD, Minimum, Median, Maximum, confidence interval etc.) and the acceptance criterion for comparable adhesion of the test and reference products. Please provide this information.

3. The FDA's Office of Scientific Investigations (OSI) previously conducted an inspection at the analytical site, Mylan Pharmaceutical Inc (3711 Collins Ferry Rd, Morgantown, WV 26505), for a different application. This analytical site is the same as that used for the BE study LIDO-1037 in your application. The FDA Form 483 issued to the analytical site at the end of the inspection noted the following:

1) *Stability of processed samples was determined with only mid level QCs during pre-study validation for the audited studies. Processed stability was not evaluated with low and high QC concentrations.*

2) *Failure to document all aspects of study conduct.*

   No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes during the audited studies.

Please address the impact of each of these findings on the study in your current application.

4. You approved the bioanalytical method validation report on June 15, 2010, after the completion date of the sample analysis on June 9, 2010 for the study LIDO-1037. The analytical method is considered validated only after the method validation report is approved by signatory authority. For future submission, please ensure a validated analytical method is used for study sample analysis.

5. For better understanding for your formulation and dissolution method development and optimization, please provide individual concentration and pharmacokinetic data of pilot study LIDO-09254 and the dissolution testing data for all formulations used in this study, if available.

CLINICAL

The Division of Clinical Review has completed its review and the data submitted to ANDA 202346 are adequate to demonstrate that the irritation potential of Mylan Technologies, Inc's Lidocaine Patch, 5% is no worse than that of the RLD.

The data also demonstrate minimal potential of Mylan's Lidocaine Patch, 5% to induce sensitization, as also in the case of the reference listed drug (RLD), Lidoderm® Patch.

The data also demonstrate that the adhesive performance of Mylan's Lidocaine Patch, 5% is at least as good as that of the RLD.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. 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

LABELING

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated (November 7, 2012).

Please continue to monitor available labeling resources such as 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

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a MINOR AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION – MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Product Quality (CMC), Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to. Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. 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 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

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

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 dose forms (FDFs) or active pharmaceutical ingredients (APIs) 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.

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 Esther Chuh, Pharm.D., Regulatory Project Manager, at (240) 276-8530.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
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/

ROBERT L WEST

06/03/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

<u>LABELING</u>

Cut along dotted lines

NDC 0378-9055-16 **Rx only**

Lidocaine Patch 5%

1 Patch

(10 x 14 cm)

9055:4

Each adhesive patch contains:
Lidocaine, USP . . . . . 140 mg
(50 mg per gram adhesive) in polyisobutylene adhesive matrix.

DOSAGE: For dosage and full prescribing information, read accompanying product information.

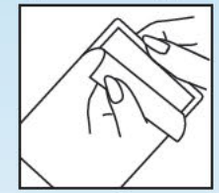
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]

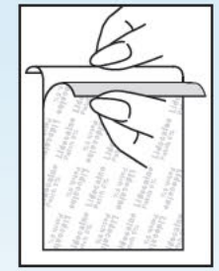
WARNING: Keep used and unused patches out of the reach of children, pets and others.

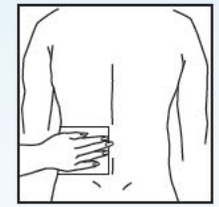
Mylan®

661

DIRECTIONS FOR USE:
Do not store patch outside of sealed envelope.







- Cut the pouch at the top and both sides along the dotted lines.
- Peel open the pouch and remove the patch with the transparent release liner.
- Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.
- Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
- Apply immediately after removal from the pouch.
- Apply up to three (3) Lidocaine Patch 5% patches at one time to cover the most painful area. Apply patches only once for up to 12 hours in a 24-hour period (12 hours on and 12 hours off). Remove patch if irritation occurs.

9055:4

Lidocaine Patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

Mylan®
Mylan.com

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

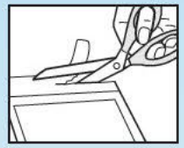
N 3 0378-9055-16 3

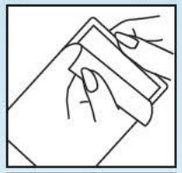
099

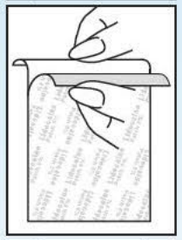
Lidocaine Patch 5%

30 Patches

DIRECTIONS FOR USE:
Do not store patch outside of sealed envelope.







- Cut the pouch at the top and both sides along the dotted lines.
- Peel open the pouch and remove the patch with the transparent release liner.
- Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.
- Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
- Apply immediately after removal from the pouch.
- Apply up to three (3) Lidocaine Patch 5% patches at one time to cover the most painful area. Apply patches only once for up to 12 hours in a 24-hour period (12 hours on and 12 hours off). Remove patch if irritation occurs.

Lidocaine Patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

M9055-93-30C:R3

Mylan®

30 Patches

Lidocaine Patch 5%

Lidocaine Patch 5%

30 Patches

Mylan®

NDC 0378-9055-93

PUSH IN
PULL UP

NDC 0378-9055-93

Rx only

Lidocaine Patch 5%

30 Patches

30 Envelopes
Containing 1
Patch Each

Each adhesive patch contains:
Lidocaine, USP 140 mg (50 mg per gram adhesive) in a polyisobutylene adhesive matrix.

Usual Dosage: See package insert for complete prescribing information.

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

WARNING: Keep used and unused patches out of the reach of children, pets and others.

Mylan®

Mylan®

30 Patches

Lidocaine Patch 5%

N 3 0378-9055-93 4

6.448DPLATE:R1

LIDO:R2

130102

Lidocaine Patch 5%

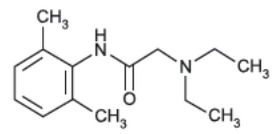
Lidocaine Patch 5%

℞ only

Prescribing Information

DESCRIPTION: Lidocaine patch 5% is comprised of an adhesive material containing 5% lidocaine, USP, which is applied to a pigmented polyethylene/polyester backing film printed with brown ink and covered with a silicone coated polyester film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm × 14 cm.

Lidocaine is chemically designated as 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-acetamide, has an octanol: water partition ratio of 43 at pH 7.4, and has the following structure:



Each adhesive patch contains 140 mg of lidocaine, USP (50 mg per gram adhesive) in a polyisobutylene adhesive matrix.

CLINICAL PHARMACOLOGY: Pharmacodynamics: Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.

The penetration of lidocaine into intact skin after application of lidocaine patch 5% is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

Pharmacokinetics: ***Absorption:*** The amount of lidocaine systemically absorbed from lidocaine patch 5% is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three lidocaine patch 5% patches were applied over an area of 420 cm^2 of intact skin on the back of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The results are summarized in Table 1.

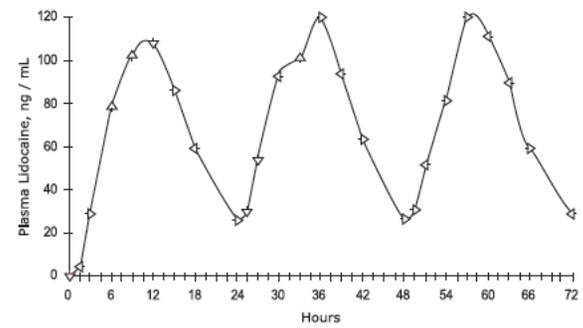
Table 1 Absorption of lidocaine from lidocaine patch 5%

Normal volunteers
(n = 15, 12-hour wearing time)

Lidocaine Patch 5%	Application Site	Area (cm^2)	Dose Absorbed (mg)	C_{max} (mcg/mL)	T_{max} (hr)
3 patches	Back	420	64 ± 32	0.13 ± 0.06	11 hr

When lidocaine patch 5% is used according to the recommended dosing instructions, only 11 ± 4% of the dose applied is expected to be absorbed. At least 82% (115 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 mcg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for 3 days, indicated that the lidocaine concentration does not increase with daily use. The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1.

Figure 1
Mean lidocaine blood concentrations after three consecutive daily applications of three lidocaine patch 5% patches simultaneously for 12 hours per day in healthy volunteers (n = 15).



Distribution: When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.6 SD, n = 15). At concentrations produced by application of lidocaine patch 5%, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 mcg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.

Metabolism: It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats. The blood concentration of this metabolite is negligible following application of lidocaine patch 5%. Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.

Excretion: Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 SD, n = 15).

CLINICAL STUDIES: Single-dose treatment with lidocaine patch 5% was compared to treatment with vehicle patch (without lidocaine), and to no treatment (observation only) in a double-blind, crossover clinical trial with 35 post-herpetic neuralgia patients. Pain intensity and pain relief scores were evaluated periodically for 12 hours. Lidocaine patch 5% performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours.

Multiple-dose, 2-week treatment with lidocaine patch 5% was compared to vehicle patch (without lidocaine) in a double-blind, crossover clinical trial of withdrawal-type design conducted in 32 patients, who were considered as responders to the open-label use of lidocaine patch 5% prior to the study. The constant type of pain was evaluated but not the pain induced by sensory stimuli (dysesthesia). Statistically significant differences favoring lidocaine patch 5% were observed in terms of time to exit from the trial (14 versus 3.8 days at p-value < 0.001), daily average pain relief, and patient's preference of treatment. About half of the patients also took oral medication commonly used in the treatment of post-herpetic neuralgia. The extent of use of concomitant medication was similar in the two treatment groups.

INDICATION AND USAGE: Lidocaine patch 5% is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin.

CONTRAINDICATIONS: Lidocaine patch 5% is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

WARNINGS: Accidental Exposure in Children: Even a used lidocaine patch 5% contains a large amount of lidocaine (at least 115 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used lidocaine patch 5%, although the risk with this formulation has not been evaluated. It is important for patients to store and dispose of lidocaine patch 5% out of the reach of children, pets and others. (See HANDLING AND DISPOSAL)

Excessive Dosing: Excessive dosing by applying lidocaine patch 5% to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS: Systemic Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 mcg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of lidocaine patch 5%, the average peak blood concentration is about 0.13 mcg/mL, but concentrations higher than 0.25 mcg/mL have been observed in some individuals.

PRECAUTIONS: General: ***Hepatic Disease:*** Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.

Allergic Reactions: Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, lidocaine patch 5% should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Non-intact Skin: Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. Lidocaine patch 5% is only recommended for use on intact skin.

External Heat Sources: Placement of external heat sources, such as heating pads or electric blankets, over lidocaine patch 5% patches is not recommended as this has not been evaluated and may increase plasma lidocaine levels.

Eye Exposure: The contact of lidocaine patch 5% with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Drug Interactions: ***Antiarrhythmic Drugs:*** Lidocaine patch 5% should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Local Anesthetics: When lidocaine patch 5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** A minor metabolite, 2,6-xylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of lidocaine patch 5%.

Mutagenesis: Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test.

Impairment of Fertility: The effect of lidocaine patch 5% on fertility has not been studied.

Pregnancy: ***Teratogenic Effects:*** *Pregnancy Category B.* Lidocaine patch 5% has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lidocaine patch 5% should be used during pregnancy only if clearly needed.

Labor and Delivery: Lidocaine patch 5% has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should lidocaine patch 5% be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Nursing Mothers: Lidocaine patch 5% has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk:plasma ratio of lidocaine is 0.4. Caution should be exercised when lidocaine patch 5% is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Application Site Reactions: During or immediately after treatment with lidocaine patch 5%, the skin at the site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Allergic Reactions: Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Other Adverse Events: Due to the nature and limitation of spontaneous reports in postmarketing surveillance, causality has not been established for additional reported adverse events including:

Asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia, lightheadedness, metallic taste, nausea, nervousness, pain exacerbated, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.

Systemic (Dose Related) Reactions: Systemic adverse reactions following appropriate use of lidocaine patch 5% are unlikely, due to the small dose absorbed (see CLINICAL PHARMACOLOGY: Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

OVERDOSAGE: Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS: Systemic Reactions), drug blood concentration should be checked. The management of overdose includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine.

In the absence of massive topical overdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects, or overdosage from other sources of lidocaine or other local anesthetics.

The oral LD_{50} of lidocaine HCl is 459 (346 to 773) mg/kg (as the salt) in non-fasted female rats and 214 (159 to 324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg, respectively, in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species.

DOSAGE AND ADMINISTRATION: Apply lidocaine patch 5% to intact skin to cover the most painful area. Apply the prescribed number of patches (maximum of 3), only once for up to 12 hours within a 24 hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. (See HANDLING AND DISPOSAL) Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides.

When lidocaine patch 5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Lidocaine patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

HANDLING AND DISPOSAL: Hands should be washed after the handling of lidocaine patch 5%, and eye contact with lidocaine patch 5% should be avoided. Do not store patch outside the sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them. Lidocaine patch 5% should be kept out of the reach of children.

HOW SUPPLIED: Lidocaine patch 5% is available as the following:

Carton of 30 patches, packaged into individual child-resistant envelopes.

NDC 0378-9055-93

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

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

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

REVISED JANUARY 2015
LIDO:R2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

LABELING REVIEWS

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

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	3/10/2015
ANDA Number(s)	202346
Review Number	4th
Applicant Name	Mylan Technologies, Inc.
Established Name & Strength(s)	Lidocaine Patch 5%
Proposed Proprietary Name	None
Submission Received Date	2/27/2015
Labeling Reviewer	Betty Turner
Labeling Team Leader	Malik Imam

Review Conclusion

☒ ACCEPTABLE – No Comments. (**post approval comments with next supplement review)**

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the 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.

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

1. GENERAL COMMENTS
2. CONTAINER LABEL
3. CARTON LABELING
4. PRESCRIBING INFORMATION
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Choose an item. all differences annotated and explained.

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 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the next supplement review).

POUCH and CARTON, Directions for Use- We encourage you to revise “pouch” to read “envelope” in order to be consistent with the insert labeling.

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. Include the previous review(s) finalized date(s).

Reviewer Comments:

The previous labeling review was completed on 11/25/2012. The revisions requested for the Pouch and Carton (i.e., to revise "pouch" to read "envelope" in order to be consistent with the insert labeling. The revisions were not made to the proposed labeling. We will ask the firm to make the changes post approval.

In the amendment dated 8/29/2011 Mylan responded to labeling deficiencies regarding the strength of the patch. (see comment and firm's response below).

CARTON – (30 patches per carton)

FDA COMMENT: Please explain why your pouch and carton label states "Lidocaine, USP 140 mg (50 mg per gram adhesive)..." while the reference listed drug (RLD), Lidoderm states "Lidocaine 700 (50 mg per gram adhesive)..." Why does your patch deliver 140 mg per patch while the RLD delivers 700 mg of lidocaine per patch?

MYLAN'S RESPONSE: The Mylan patch contains 140 mg per patch but *delivers* the same dose as the RLD that contains 700 mg per patch. Both patches are formulated at the same drug concentration (i.e. 50 mg lidocaine per gram adhesive, or 5%), and are the same size (i.e. 140 cm^2). However, given that the RLD claims to deliver only 3 ± 2% of the 700 mg of lidocaine contained in the patch, the Mylan patch was developed to contain only the amount of lidocaine needed for the patch to be therapeutically equivalent to the RLD. This was done by keeping the same lidocaine concentration in the adhesive matrix (i.e. 5%), but reducing the thickness of the adhesive layer from 100 mg/cm^2 (about 1.0 mm thick) to 20 mg/cm^2 (about 0.2 mm thick). The approach taken by Mylan in the development of the Lidocaine patch is aligned with the Agency's Guidance for Industry, *Residual Drug in Transdermal and Related Drug Delivery Systems*, August 2011, in that the amount of residual drug in transdermal products be minimized consistent with the current state of technology.

Therapeutic equivalence was confirmed in a single-dose, fasting, two-way crossover, *in vivo* bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, Lidoderm® Patch 5% (LIDO-1037). Thus, Mylan's Lidocaine Patch 5% and the RLD deliver at the same rate and extent, thereby, producing bioequivalent plasma concentration vs. time profiles. Please refer to Section 5.3.1.2 (Sequence 0000) for more information concerning this study.

FDA COMMENT 4b: CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption,

Your labeling states "...only 11 ± 4% of the dose applied is expected to be absorbed. At least 82% (115 mg) of lidocaine.." while the RLD's states "...only 3 ± 2% of the dose applied is

expected to be absorbed. At least 95% (665 mg) of lidocaine..". Why is your drug product's absorption profile different than the RLD's? Please submit the rationale.

MYLAN'S RESPONSE 4b: The absorption of lidocaine is no different from the Mylan Lidocaine Patch 5% or the RLD as demonstrated by the single-dose, fasting, two-way crossover, *in vivo* bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, Lidoderm® Patch 5% (LIDO-1037). The differences noted by the reviewer relate to the lower total amount of drug in the Mylan Lidocaine patch compared to the RLD. This results in different amounts of residual drug in the patches between the two products as illustrated in the following table.

	Mylan Lidocaine Patch 5%	**RLD***
Total Lidocaine per Patch	140 mg	700 mg
Lidocaine Dose Absorbed	15 mg ± 6**	21 mg ± 11
Fraction of the original dose absorbed	15 ± 6 mg / 140 mg = **11 ± 4%**	21 ± 11 mg / 700 mg = **3 ± 2%**
Minimum Residual Lidocaine	140 mg – 25 mg*** = **115 mg**	**665 mg**
Minimum Residual Lidocaine (%)	115 mg / 140 mg = **82%**	665 mg / 700 mg = **95%**

*Note: These values were taken from the RLD labeling that states a Dose Absorbed of 64 ± 32 mg for three-patch wear, or about 21 ± 11 mg absorbed per patch, and residual drug of at least 95% (665 mg).

**Note: From residual patch analyses performed as part of LIDO-1037.

***Note: The maximum depletion measured in the residual patch analysis from LIDO-1037 was 23.8 mg, which was rounded to 25 mg for use in the labeling.

Click here to enter text.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
YES

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

Reviewer Comments:

The firm submitted this gratuitous labeling amendment to update their labeling in accordance with the most recently approved labeling for the RLD. The pouch, carton and insert labeling were revised according to the labeling for the reference listed drug labeling approved January 7, 2015.

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).

Reviewer Comments: NA

Click here to enter text.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in SharePoint Repository files? NO
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check all that apply)
MOST RECENTLY APPROVED MODEL LABELING-NDA *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 020612/S-012 **Supplement Approval Date:** 01/07/2015 **Proprietary Name:** LIDODERM **Established Name:** lidocaine patch 5%. **Description of Supplement:** This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, provides for the addition of the statements "Lidoderm may not stick if it is wet. Avoid contact with water such as bathing, swimming or showering." to the **DOSAGE AND ADMINISTRATION** section of the Package Insert, Overwrap Envelope, and Carton labeling.
MOST RECENTLY APPROVED MODEL LABELING-ANDA **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **BPCA or PREA TEMPLATE (Describe):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**

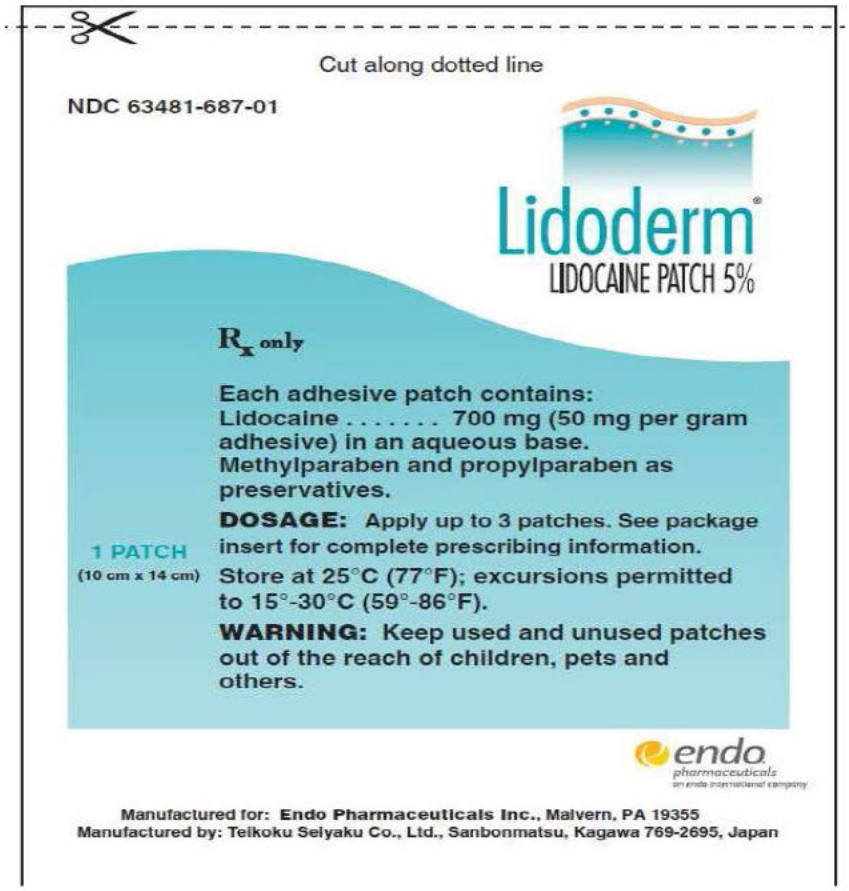
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

Click here to enter text.

3.3 MODEL CONTAINER LABELS

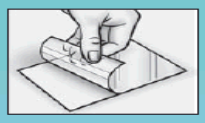
Model labels and carton labeling. [Insert or paste images below]



DIRECTIONS FOR USE

Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.



Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over LIDODERM patches is not recommended.

LIDODERM may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

3 63481-687-017

211374

LOT:

EXP:

NDC 63481-687-06

Lidoderm®

LIDOCAINE PATCH 5%

R_x only

30 PATCHES

30 Envelopes
Containing 1 Patch Each

Each adhesive patch contains:
Lidocaine 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.

Usual Dosage: Apply up to 3 patches. See package insert for complete prescribing information.

Store at 25˚C (77˚F); excursions permitted to 15˚-30˚C (59˚-86˚F).

WARNING: Keep used and unused patches out of the reach of children, pets and others.

endo pharmaceuticals
an endo international company

Manufactured for: **Endo Pharmaceuticals Inc.**, Malvern, PA 19355
Manufactured by: Teikoku Seiyaku Co., Ltd., Sanbonmatsu, Kagawa 769-2695, Japan

3.4 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	3/10/2015	No	NA	NA
PF	3/10/2015	No	NA	NA

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/10/2015.

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
5827529	Oct 27, 2015	U-486	EXTERNAL PREPARATION FOR APPLICATION TO THE SKIN CONTAINING LIDOCAINE-DRUG RETAINING LAYER PLACED ON SUPPORT AND COMPRISES ADHESIVE GEL BASE 1-10% BY WEIGHT OF LIDOCAINE	PIV	10/22/201	NONE

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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
Click here to enter text.					

Reviewer Assessment:

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

Reviewer Comments:

No information is carved out of the labeling.

Click here to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED? **NO**
Are there changes to the manufacturing statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each adhesive patch contains 140 mg of idocaine,USP (50 mg per gram adhesive) in a polyisobutylene adhesive matrix.	Each adhesive patch contains 140 mg of lidocaine, USP (50 mg per gram adhesive) in a polyisobutylene Adhesive matrix.	**No change to this section**

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	**Currently Proposed**	**Assessment**
HOW SUPPLIED: Lidocaine patch 5% is available as the following: Carton of 30 patches, packaged into ndividual child-resistant envelopes. NDC 0378-9055-93 **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room emperature.]**	**HOW SUPPLIED:** Lidocaine patch 5% is available as the following: Carton of 30 patches, packaged into ndividual child-resistant envelopes. NDC 0378-9055-93 **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]** For more information, call Mylan Pharmaceuticals,Inc. at 1-877-446-3679 (1-877-4-INFO-RX).	**Mylan added a contact number for more information.**

Table 7: Manufactured by statement		
Previously Labeling Review	**Currently Proposed**	**Assessment**
Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. OCTOBER 2012 LIDO:R1	**Mylan Pharmaceuticals Inc.** Morgantown, WV 26505 U.S.A. REVISED JANUARY 2015 LIDO:R2	**Updated revision date and number.**

5. COMMENTS FOR CHEMISTRY REVIEWER

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

Reviewer Comments:

On 9/19/2012 an email communication was sent to the chemist to ask if cutting the patch will affect the delivery system. The chemist response was that he doesn't think the patch cutting would affect the delivery system.

Click here to enter text.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:
None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

If this review is acceptable, then all pertinent labeling pieces must be entered for both tables.

For each row, 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 Date**	**Recommendation**
Container	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patch	Final	1 patch	11/7/2012	Satisfactory
Carton	Final	30 Pouches	2/27/2015	Satisfactory
(Other) Pouch	Final	1 pouch/envelope	2/27/2015	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Date**	**Recommendation**
Prescribing Information	Final	REVISED JANUARY 2015 **LIDO:R2**	2/27/2015	Satisfactory
Medication Guide	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements		Click here to enter text.	2/27/2015	Satisfactory

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	202346
Date of Submission:	November 7, 2012
Applicant's Name:	Mylan Technologies Inc.
Established Name and Strength:	Lidocaine Patch 5%

Labeling Comments below are considered:

☒ No Comments **(**Labeling Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated November 7, 2012.

Please continue to monitor available labeling resources such as 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

Note RPM - Labeling comments end here

REMS required?

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No

Elements to assure safe use (ETASU) (505-1(f)(3)) ☐ Yes ☒ No

Implementation system if certain ETASU (505-1(f)(4)) ☐ Yes ☒ No

Timetable for assessment (505-1(d)) ☐ Yes ☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

	Date submitted	Final or Draft	Recommendation
POUCH	11/7/2012	Final	Acceptable for approval
PATCH	11/7/2012	Final	Acceptable for approval
CARTON	11/7/2012	Final	Acceptable for approval
PHYSICIAN INSERT	11/7/2012	Final	Acceptable for approval
SPL	11/7/2012		Acceptable for approval

REVISIONS NEEDED POST APPROVAL? Yes.

POUCH and CARTON: We encourage you to revise "pouch" to read "envelope" in order to be consistent with the insert labeling.

The above post-approval comment is annual reportable and will be communicated to the firm to Juliane Foley at (802) 527-9345 once the review has been signed off.

NOTES/QUESTIONS TO THE CHEMIST:

From: Li, Xihao
Sent: Wednesday, September 19, 2012 3:06 PM
To: Turner, Betty
Subject: RE: ANDA 202346 Lidocaine Patch 5% -Mylan

Hi Betty,

I don't think the patch cutting would affect the delivery system.

Thanks,
Xihao

From: Turner, Betty
Sent: Wednesday, September 19, 2012 1:25 PM
To: Li, Xihao
Subject: ANDA 202346 Lidocaine Patch 5% -Mylan

Hello Xihao,

I am currently the labeling reviewer for ANDA 202346 Lidocaine Patch 5%.

According to the Dosage and Administration section of the insert labeling, "Patches may be cut into smaller sizes with scissors prior to removal of the release liner." Will cutting the patch affect the delivery system?

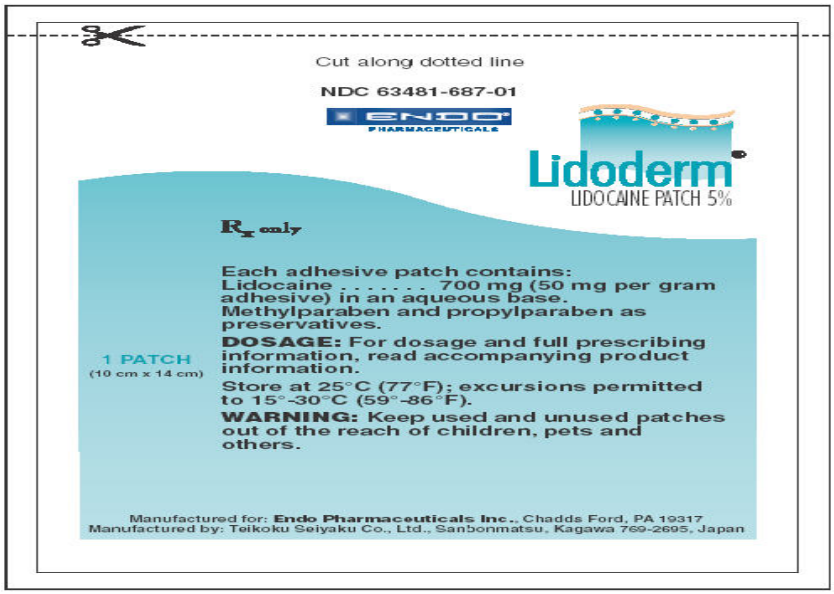
I look forward to your comments.

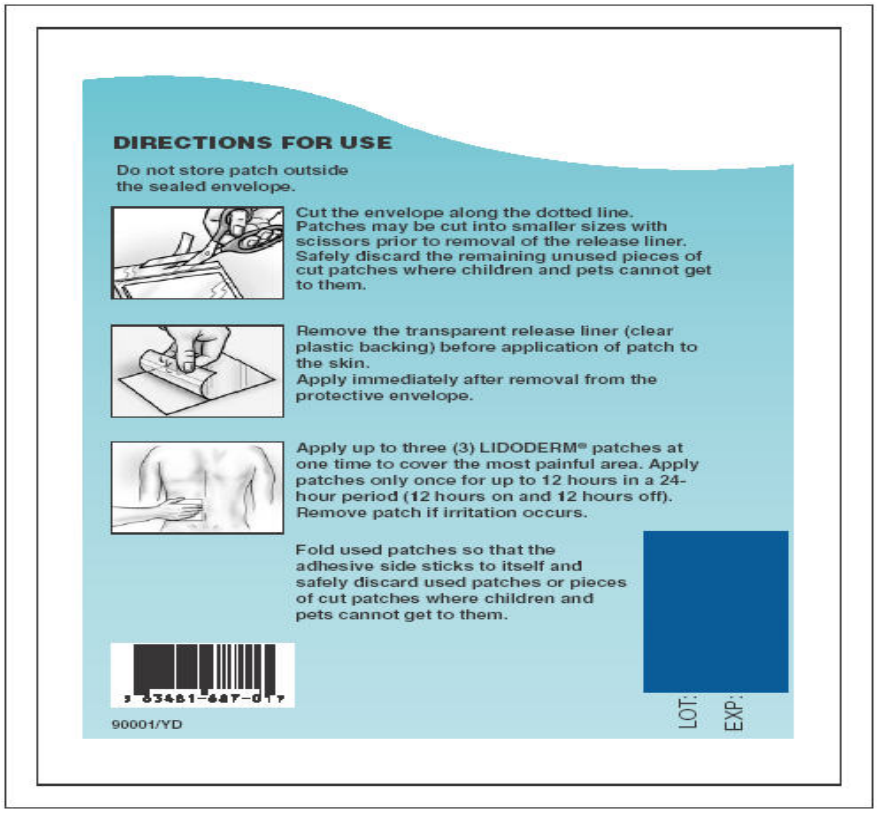
Thanks,

Betty
(240) 276-8728

FOR THE RECORD:

1. **MODEL LABELING**
   The reference listed drug for this product is Lidoderm Patch, 5% of Teikoku Pharma USA, Inc. NDA 020612/S-011; approved April 13, 2010. S-011 provided for a new subsection, External Heat Sources to the PRECAUTIONS section.




DIRECTIONS FOR USE
Do not store patch outside the sealed envelope.
Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.
Remove the transparent release liner (clear plastic backing) before application of patch to the skin. Apply immediately after removal from the protective envelope.
Apply up to three (3) LIDODERM® patches at one time to cover the most painful area. Apply patches only once for up to 12 hours in a 24-hour period (12 hours on and 12 hours off). Remove patch if irritation occurs.
Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.
LOT:
EXP:
90001/YD


Lidoderm
LIDOCAINE PATCH 5%
ENDO PHARMACEUTICALS
NDC 63481-687-06
Rx only
Each adhesive patch contains:
Lidocaine 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.
Usual Dosage: See package insert for complete prescribing information.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
WARNING: Keep used and unused patches out of the reach of children, pets and others.
Manufactured for: Endo Pharmaceuticals Inc., Chadds Ford, PA 19317
Manufactured by: Takeda Sagami Co., Ltd., Sanbommatsu, Sagamihara 799-2696, Japan
30 PATCHES
30 Envelopes
Containing 1 Patch Each
Directions for Use
Do not store patch outside the sealed envelope.
Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.
Remove the transparent release liner (clear plastic backing) before application of patch to the skin. Apply immediately after removal from the protective envelope.
Apply up to three (3) Lidoderm® patches at one time to cover the most painful area. Apply patches only once for up to 12 hours in a 24-hour period (12 hours on and 12 hours off). Remove patches if irritation occurs.
Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.
90001/YD

2. **USP- 35:**
USP: Not compendial, [redacted] (b) (4) November 23, 2012

PF: None (checked November 23, 2012

Medwatch:
Lidoderm (lidocaine) patch
Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – April 2010

PRECAUTIONS
General
- External Heat Sources: Placement of external heat sources, such as heating pads or electric blankets, over Lidoderm patches is not recommended as this has not been evaluated and may increase plasma lidocaine levels.

3. **PATENT AND EXCLUSIVITY:** (checked August 27, 2012, September 27, and November 23, 2012)
Patent Data – NDA 020612

No	Expiration	Use Code	Use	**How filed**	**Labeling Impact**
5411738	May 2, 2012	-		PIII	No Impact
5601838	May 2, 2012	U-488	Method for reducing pain associated with herpes-zoster and post herpetic neuralgia	PIII	No Impact
5741510	Mar 30, 2014			PIV	No Impact
5827529	Oct 27, 2015	U-486	External preparation for application to the skin containing lidocaine-drug retaining layer placed on support and comprises adhesive gel base 1-10% by weight of lidocaine	PIV	No Impact

Exclusivity Data– NDA 020612

Code	Reference	Expiration	**Labeling impact**
None			

On 3/14/11, Endo sued Mylan in District Court of Delaware: Case 1:11-cv-00220-UNA for infringement of ‘510 patent.

PATENT AMENDMENT UPDATE (April 16, 2012)

Mylan submits this patent amendment to notify the Agency that the Endo Action was dismissed in its entirety by the District of Delaware on April 2, 2012 and there is no thirty month stay of approval for this ANDA. A copy of the order ("Order") dismissing the Endo Action is attached for your reference.

The Order states that the District of Delaware "is ***unable*** to rule on the issues related to infringement [of the '510 patent] as pled in Endo's complaint" and, thus, the Endo Action was dismissed. Order at fn.2 (emphasis added).

4. **INACTIVE INGREDIENTS**

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 53 (Volume 1.1).

Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Lidocaine Patch 5%

Components	Pharmaceutical Function	% w/w	mg per patch
Active Ingredient			
Lidocaine, USP	Active Ingredient	5.00	140.00
Inactive Ingredients			
Polyisobutylene (b) (4)	Adhesive	(b) (4)	(b) (4)
Theoretical Total Matrix		100.00	(b) (4)
Components of the Delivery and Packaging System			
Pigmented Polyethylene / Polyester Film (MEDIFLEX® 1501)	Backing	NA	(b) (4)

Components	Pharmaceutical Function	% w/w	mg per patch
Brown Ink (b) (4)	Imprinting Ink	NA	(b) (4)
Silicone Coated Polyester Film (MEDIRELEASE® 2249)	Release Liner	NA	

(b) (4)

Mylan's patch is 10 cm x 14 cm and the RLD's patch is 10 cm x 14 cm.

5. **MANUFACTURING FACILITY**
Mylan Technologies
110 Lake Street
St. Albans, VT 05478

6. **FINISHED PRODUCT DESCRIPTION [2.3.P.5.1- original submission]**

RLD: Patch, packaged into individual child-resistant envelopes.

ANDA: A (b) (4) patch consisting of a pigmented backing film randomly printed with "Lidocaine Patch 5%" in brown ink, and adhesive matrix layer and a clear removable release liner. Each individual patch is packaged in a sealed pouch, imprinted with lot number and expiration date. (b) (4)

Lidicaine patch 5% is available as the following: Carton of 30 patches, packed into individual child-resistant envelopes.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

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

8. **PRODUCT LINE**

RLD: child resistant patch in carton of 30 patches

ANDA: child resistant patch in carton of 30 patches

9. **CONTAINER/CLOSURE 2.3.P.7**
Lidocaine Patch 5% is packaged as a single patch within a child resistant pouch formed by (b) (4)

The final market package for Mylan's Lidocaine Patch 5% consists of Thirty (30) sealed pouches in a single carton.

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

10. **BIOAVAILABILITY/BIOEQUIVALENCE-** Incomplete as of June 20, 2012.

11. **BACKGROUND INFORMATION ABOUT CP DOCKET 2006P-0552 (Lidoderm).**
The findings of the CP could be read in DARRTS under L. Schultheis clinical review dated 12/03/07. In essence FDA found that clinical trials are NOT necessary for a generic product of Lidoderm. The information below is from L. Schultheis' review:

Therefore, in the case of Lidoderm, we believe that plasma levels will adequately reflect skin levels of lidocaine, and are sufficient to establish bioequivalence between the innovator and a generic product having the same formulation, provided that adequate pharmacokinetic information for both products is available. We disagree with the petitioner's conclusion that clinical trials are necessary for a generic product of Lidoderm having the same formulation of lidocaine to demonstrate efficacy.

12. **SPL DATA ELEMENTS**
The firm did submit SPL. Note that Mylan did not list inactive ingredients such as polyisobutylene (probably because of the lack of UNI code). Because this product could not be fully approved until May 2012, the SPL DLE may need to be revisited.

Revised 11/6/12 and found acceptable.

13. **AF dated 8/29/2011**
Mylan response to the labeling deficiencies;

PATCH

MYLAN'S RESPONSE: Mylan acknowledges that our proposed patch printing was found acceptable as submitted in draft. Mylan will submit final printed labeling closer to the time in which we anticipate receipt of final approval.

CARTON – (30 patches per carton)

FDA COMMENT: Please explain why your pouch and carton label states "Lidocaine, USP 140 mg (50 mg per gram adhesive)..." while the reference listed drug (RLD), Lidoderm states "Lidocaine 700 (50 mg per gram adhesive)..." Why does your patch deliver 140 mg per patch while the RLD delivers 700 mg of lidocaine per patch?

MYLAN'S RESPONSE: The Mylan patch contains 140 mg per patch but *delivers* the same dose as the RLD that contains 700 mg per patch. Both patches are formulated at the same drug concentration (i.e. 50 mg lidocaine per gram adhesive, or 5%), and are the same size (i.e. 140 cm^2). However, given that the RLD claims to deliver only 3 ± 2% of the 700 mg of lidocaine contained in the patch, the Mylan patch was developed to contain only the amount of lidocaine needed for the patch to be therapeutically equivalent to the RLD. This was done by keeping the same lidocaine concentration in the adhesive matrix (i.e. 5%), but reducing the thickness of the adhesive layer from 100 mg/cm^2 (about 1.0 mm thick) to 20 mg/cm^2 (about 0.2 mm thick). The approach taken by Mylan in the development of the Lidocaine patch is aligned with the Agency's Guidance for Industry, *Residual Drug in Transdermal and Related Drug Delivery Systems*, August 2011, in that the amount of residual drug in transdermal products be minimized consistent with the current state of technology.

Therapeutic equivalence was confirmed in a single-dose, fasting, two-way crossover, *in vivo* bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, Lidoderm® Patch 5% (LIDO-1037). Thus, Mylan's Lidocaine Patch 5% and the RLD deliver at the same rate and extent, thereby, producing bioequivalent plasma concentration vs. time profiles. Please refer to Section 5.3.1.2 (Sequence 0000) for more information concerning this study.

FDA COMMENT 4b: CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption,

Your labeling states "...only 11 ± 4% of the dose applied is expected to be absorbed. At least 82% (115 mg) of lidocaine.." while the RLD's states "...only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine..". Why is your drug product's absorption profile different than the RLD's? Please submit the rationale.

MYLAN'S RESPONSE 4b: The absorption of lidocaine is no different from the Mylan Lidocaine Patch 5% or the RLD as demonstrated by the single-dose, fasting, two-way crossover, *in vivo* bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, Lidoderm® Patch 5% (LIDO-1037). The differences noted by the reviewer relate to the lower total amount of drug in the Mylan Lidocaine patch compared to the RLD. This results in different amounts of residual drug in the patches between the two products as illustrated in the following table.

	Mylan Lidocaine Patch 5%	**RLD***
Total Lidocaine per Patch	140 mg	700 mg
Lidocaine Dose Absorbed	15 mg ± 6**	21 mg ± 11
Fraction of the original dose absorbed	15 ± 6 mg / 140 mg = **11 ± 4%**	21 ± 11 mg / 700 mg = **3 ± 2%**
Minimum Residual Lidocaine	140 mg – 25 mg*** = **115 mg**	**665 mg**
Minimum Residual Lidocaine (%)	115 mg / 140 mg = **82%**	665 mg / 700 mg = **95%**

*Note: These values were taken from the RLD labeling that states a Dose Absorbed of 64 ± 32 mg for three-patch wear, or about 21 ± 11 mg absorbed per patch, and residual drug of at least 95% (665 mg).
**Note: From residual patch analyses performed as part of LIDO-1037.
***Note: The maximum depletion measured in the residual patch analysis from LIDO-1037 was 23.8 mg, which was rounded to 25 mg for use in the labeling.

Date of Review: November 23, 2012

Primary Reviewer: Betty Turner

Team Leader: Chi-Ann Y Wu

Following this page, 5 Pages of Draft Labeling have been Withheld in Full as (b)(4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BETTY B TURNER
11/25/2012

CHI-ANN Y WU
11/25/2012
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202346

Date of Submission: August 29, 2011

Applicant's Name: Mylan Technologies, Inc.

Established Name: Lidocaine Patch 5%

Labeling Deficiencies:

GENERAL COMMENTS:

i. Please note your labeling was submitted in draft. Please submit your Pouch, Patch, Carton and Insert labeling in final print.

ii. Please provide your labeling in the Structured Product Labeling (SPL) format.

Revise your labeling, as instructed above, and submit final printed labeling electronically

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No. Electronic submission in draft

Pouch Labels: Acceptable in draft as submitted in 10/25/10 e-submission

Patch Labels: Acceptable in draft as submitted in 10/25/10 e-submission

Carton Labels: (30 patches/carton):
Acceptable in draft as submitted in 10/25/10 e-submission

Professional Package Insert Labeling:
Acceptable in draft as submitted in 10/25/10 e-submission

SPL: See comment above.

Revisions needed post-approval:

NOTES TO THE CHEMIST:

From: Turner, Betty
Sent: Wednesday, September 19, 2012 1:25 PM
To: Li, Xihao
Subject: ANDA 202346 Lidocaine Patch 5% -Mylan

Hello Xihao,

I am currently the labeling reviewer for ANDA 202346 Lidocaine Patch 5%.

According to the Dosage and Administration section of the insert labeling, "Patches may be cut into smaller sizes with scissors prior to removal of the release liner." Will cutting the patch affect the delivery system?

I look forward to your comments.

Thanks,

Betty
(240) 276-8728

FOR THE RECORD: Please note the first cycle review was completed by Thuyanh Vu, labeling reviewer. Portions of this review were taken from the review completed 8/11/11 in DARRTS.

1. MODEL LABELING:

The reference listed drug for this product is Lidoderm Patch, 5% of Teikoku Pharma USA, Inc. NDA 020612/S-011; approved April 13, 2010. S-011 provided for a new subsection, External Heat Sources to the PRECAUTIONS section.

Cut along dotted line

NDC 63481-687-01

ENDO PHARMACEUTICALS

Lidoderm®

LIDOCAINE PATCH 5%

℞ only

1 PATCH
(10 cm x 14 cm)

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.

DOSAGE: For dosage and full prescribing information, read accompanying product information.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Keep used and unused patches out of the reach of children, pets and others.

Manufactured for: **Endo Pharmaceuticals Inc.**, Chadds Ford, PA 19317
Manufactured by: Teikoku Seiyaku Co., Ltd., Sanbonmatsu, Kagawa 769-2695, Japan

DIRECTIONS FOR USE

Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.

Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
Apply immediately after removal from the protective envelope.

Apply up to three (3) LIDODERM® patches at one time to cover the most painful area. Apply patches only once for up to 12 hours in a 24-hour period (12 hours on and 12 hours off). Remove patch if irritation occurs.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

3 63481-687-01

90001/YD

LOT:

EXP:

2. **MEDWATCH:**
Lidoderm (lidocaine patch) is not on the MedWatch site, checked on August 5, 2011, and September 17, 2012.

3. **PATENT AND EXCLUSIVITY:** (Checked August 27, 2012 and September 17, 2012)

PATENT DATA – NDA 020612					
Patent No	**Expiration**	**Use Code**	**Description**	**Patent Certification**	**Labeling Impact**
5411738	May 2, 2012	-		PIII	No Impact
5601838	May 2, 2012	U-488	Method for reducing pain associated with herpes-zoster and post herpetic neuralgia	PIII	No impact
5741510	Mar 30, 2014			PIV	No impact
5827529	Oct 27, 2015	U-486	External preparation for application to the skin containing lidocaine-drug retaining layer placed on support and comprises adhesive gel base	PIV	No impact

			1-10% by weight of lidocaine		

EXCLUSIVITY DATA – NDA 020612			
Code	**Expiration**	**Reference**	**Labeling Impact**
None			

On 3/14/11, Endo sued Mylan in District Court of Delaware: Case 1:11-cv-00220-UNA for infringement of '510 patent.

PATENT AMENDMENT UPDATE (April 16, 2012)

Mylan submits this patent amendment to notify the Agency that the Endo Action was dismissed in its entirety by the District of Delaware on April 2, 2012 and there is no thirty month stay of approval for this ANDA. A copy of the order ("Order") dismissing the Endo Action is attached for your reference.

The Order states that the District of Delaware "is ***unable*** to rule on the issues related to infringement [of the '510 patent] as pled in Endo's complaint" and, thus, the Endo Action was dismissed. Order at fn.2 (emphasis added).

4. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM:** 2.3.P.3
Mylan Technologies
110 Lake Street
St. Albans, VT 05478

5. **INACTIVE INGREDIENTS:** 2.3.P.1
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 53 (Volume 1.1).

Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Lidocaine Patch 5%

Components	Pharmaceutical Function	% w/w	mg per patch
Active Ingredient			
Lidocaine, USP	Active Ingredient	5.00	140.00
Inactive Ingredients			
Polyisobutylene (b) (4)	Adhesive	(b) (4)	
(b) (4)			
Theoretical Total Matrix		100.00	(b) (4)
Components of the Delivery and Packaging System			
Pigmented Polyethylene / Polyester Film (MEDIFLEX® 1501)	Backing	NA	(b) (4)

Components	Pharmaceutical Function	% w/w	mg per patch
Brown Ink (b) (4)	Imprinting Ink	NA	(b) (4)
Silicone Coated Polyester Film (MEDIRELEASE® 2249)	Release Liner	NA	

(b) (4)

Mylan's patch is 10 cm x 14 cm and the RLD's patch is 10 cm x 14 cm.

6. **DRUG PRODUCT DESCRIPTION [2.3.P.5.1- original submission]:**
NDA: Patch, packaged into individual child-resistant envelopes.

ANDA: A (b) (4) patch consisting of a pigmented backing film randomly printed with "Lidocaine Patch 5%" in brown ink, and adhesive matrix layer and a clear removable release liner. Each individual patch is packaged in a sealed pouch, imprinted with lot number and expiration date. (b) (4) (b) (4)

7. **STORAGE TEMPERATURE STATEMENT COMPARISON** – 2.3.P.8

NDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

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

USP: Not compendial, (b) (4)

8. **PACKAGING CONFIGURATION:**
RLD: child resistant patch in carton of 30 patches

ANDA: child resistant patch in carton of 30 patches.

9. **CONTAINER CLOSURE:** 2.3.P.7
Lidocaine Patch 5% is packaged as a single patch within a child resistant pouch formed by (b) (4)

The final market package for Mylan's Lidocaine Patch 5% consists of Thirty (30) sealed pouches in a single carton.

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

[redacted]

10. **FINISHED PRODUCT DESCRIPTION:**
Lodocaine patch 5% is available as the following: Carton of 30 patches, packed into individual child-resistant envelopes.

11. **BIOAVAILABILITY/BIOEQUIVALENCE-** Incomplete as of June 20, 2012.

12. **BACKGROUND INFORMATION ABOUT CP DOCKET 2006P-0552 (Lidoderm).**
The findings of the CP could be read in DARRTS under L. Schultheis clinical review dated 12/03/07. In essence FDA found that clinical trials are NOT necessary for a generic product of Lidoderm. The information below is from L. Schultheis' review:

Therefore, in the case of Lidoderm, we believe that plasma levels will adequately reflect skin levels of lidocaine, and are sufficient to establish bioequivalence between the innovator and a generic product having the same formulation, provided that adequate pharmacokinetic information for both products is available. We disagree with the petitioner's conclusion that clinical trials are necessary for a generic product of Lidoderm having the same formulation of lidocaine to demonstrate efficacy.

13. Firm did submit SPL. Note that Mylan did not list inactive ingredients such as polyisobutylene (probably because of the lack of UNI code). Because this product could not be fully approved until May 2012, the SPL DLDE may need to be revisited.

14. **AF dated 8/29/2011**

Mylan response to the labeling deficiencies;

PATCH

MYLAN'S RESPONSE: Mylan acknowledges that our proposed patch printing was found acceptable as submitted in draft. Mylan will submit final printed labeling closer to the time in which we anticipate receipt of final approval.
CARTON – (30 patches per carton)

FDA COMMENT: Please explain why your pouch and carton label states "Lidocaine, USP 140 mg (50 mg per gram adhesive)..." while the reference listed drug (RLD), Lidoderm states "Lidocaine 700 (50 mg per gram adhesive)..." Why does your patch deliver 140 mg per patch while the RLD delivers 700 mg of lidocaine per patch?

MYLAN'S RESPONSE: The Mylan patch contains 140 mg per patch but *delivers* the same dose as the RLD that contains 700 mg per patch. Both patches are formulated at the same drug concentration (i.e. 50 mg lidocaine per gram adhesive, or 5%), and are the same size (i.e. 140 cm^2). However, given that the RLD claims to deliver only 3 ± 2% of the 700 mg of lidocaine contained in the patch, the Mylan patch was developed to contain only the amount of lidocaine needed for the patch to be therapeutically equivalent to the RLD. This was done by keeping the same lidocaine concentration in the adhesive matrix (i.e. 5%), but reducing the thickness of the adhesive layer from 100 mg/cm^2 (about 1.0 mm thick) to 20 mg/cm^2 (about 0.2 mm thick). The approach taken by Mylan in the development of the Lidocaine patch is aligned with the Agency's Guidance for Industry, *Residual Drug in Transdermal and Related Drug Delivery Systems*, August 2011, in that the amount of residual drug in transdermal products be minimized consistent with the current state of technology.

Therapeutic equivalence was confirmed in a single-dose, fasting, two-way crossover, *in vivo* bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, Lidoderm® Patch 5% (LIDO-1037). Thus, Mylan's Lidocaine Patch 5% and the RLD deliver at the same rate and extent, thereby, producing bioequivalent plasma concentration vs. time profiles. Please refer to Section 5.3.1.2 (Sequence 0000) for more information concerning this study.

FDA COMMENT 4b: CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption,

Your labeling states "...only 11 ± 4% of the dose applied is expected to be absorbed. At least 82% (115 mg) of lidocaine.." while the RLD's states "...only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine..". Why is your drug product's absorption profile different than the RLD's? Please submit the rationale.

MYLAN'S RESPONSE 4b: The absorption of lidocaine is no different from the Mylan Lidocaine Patch 5% or the RLD as demonstrated by the single-dose, fasting, two-way crossover, *in vivo* bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, Lidoderm® Patch 5% (LIDO-1037). The differences noted by the reviewer relate to the lower total amount of drug in the Mylan Lidocaine patch compared to the RLD. This results in different amounts of residual drug in the patches between the two products as illustrated in the following table.

	Mylan Lidocaine Patch 5%	**RLD***
Total Lidocaine per Patch	140 mg	700 mg
Lidocaine Dose Absorbed	15 mg ± 6**	21 mg ± 11
Fraction of the original dose absorbed	15 ± 6 mg / 140 mg = **11 ± 4%**	21 ± 11 mg / 700 mg = **3 ± 2%**
Minimum Residual Lidocaine	140 mg – 25 mg*** = **115 mg**	**665 mg**
Minimum Residual Lidocaine (%)	115 mg / 140 mg = **82%**	665 mg / 700 mg = **95%**

*Note: These values were taken from the RLD labeling that states a Dose Absorbed of 64 ± 32 mg for three-patch wear, or about 21 ± 11 mg absorbed per patch, and residual drug of at least 95% (665 mg).
**Note: From residual patch analyses performed as part of LIDO-1037.
***Note: The maximum depletion measured in the residual patch analysis from LIDO-1037 was 23.8 mg, which was rounded to 25 mg for use in the labeling.

15. REMS:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

Date of Review: September 18, 2012 Date of Submission: August 29, 2011

Primary Reviewer: Betty Turner

Team Leader: Chi-Ann Y Wu

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BETTY B TURNER
09/19/2012

CHI-ANN Y WU
09/19/2012
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202346 Date of Submission: October 25, 2010

Applicant's Name: Mylan Technologies, Inc.

Established Name: Lidocaine Patch 5%

Labeling Deficiencies:

1. PATCH

   Acceptable in draft.

2. CARTON – (30 patches per carton)

   Please explain why your pouch and carton label states “Lidocaine, USP 140 mg (50 mg per gram adhesive)...” while the reference listed drug (RLD), Lidoderm states “Lidocaine 700 (50 mg per gram adhesive)...” Why does your patch deliver 140 mg per patch while the RLD delivers 700 mg of lidocaine per patch?

3. POUCH

   See CARTON statement.

4. INSERT

   a. See CARTON statement.

   b. CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption,

      Your labeling states “...only 11 ± 4% of the dose applied is expected to be absorbed. At least 82% (115 mg) of lidocaine...” while the RLD’s states “...only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine...” Why is your drug product’s absorption profile different than the RLD’s? Please submit the rationale.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No

Pouch Labels:

Patch Labels :

Carton Labels (30 patches/carton):

Professional Package Insert Labeling:

SPL:

Revisions needed post-approval: No

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Lidoderm Patch
NDA Number: 20612/S-011
NDA Drug Name: Lidoderm Patch
NDA Firm: APP
Date of Approval of NDA Insert and supplement #: S-011: approved 4/13/2010
Has this been verified by the MIS system for the NDA? YES
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING – Lidoderm Patch, 5% of Teikoku Pharma USA, Inc. (NDA 20612/S-011; approved 4/13/10). S-011 provided a new subsection, External Heat Sources to the PRECAUTIONS section.

   This is a 1st generic.

2. PATENT DATA

   200612

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5411738	May 2, 2012	--		PIII	No Impact

5601838	May 2, 2012	U-488	Method for reducing pain associated with herpes-zoster and post herpetic neuralgia	PIII	No impact
5741510	Mar 30, 2014			PIV	No impact
5827529	Oct 27, 2015	U-486	External preparation for application to the skin containing lidocaine-drug retaining layer placed on support and comprises adhesive gel base 1-10% by weight of lidocaine	PIV	No impact

No Exclusivities

On 3/14/11, Endo sued Mylan in District Court of Delaware: Case 1:11-cv-00220-UNA for infringement of '510 patent.

3. INACTIVE INGREDIENTS [2.3.P.1-original submission]

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 53 (Volume 1.1).

Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Lidocaine Patch 5%

Components	Pharmaceutical Function	% w/w	mg per patch
Active Ingredient			
Lidocaine, USP	Active Ingredient	5.00	140.00
Inactive Ingredients			
Polyisobutylene (b) (4)	Adhesive	(b) (4)	
(b) (4)			
Theoretical Total Matrix		100.00	(b) (4)
Components of the Delivery and Packaging System			
Pigmented Polyethylene / Polyester Film (MEDIFLEX® 1501)	Backing	NA	(b) (4)

Components	Pharmaceutical Function	% w/w	mg per patch
Brown Ink (b) (4)	Imprinting Ink	NA	(b) (4)
Silicone Coated Polyester Film (MEDIRELEASE® 2249)	Release Liner	NA	

Mylan's patch is 10 cm x 14 cm and the RLD's patch is 10 cm x 14 cm.

4. MANUFACTURER [2.3.P.3-original submission]

Mylan Technologies
110 Lake Street
St. Albans, VT 05478

5. DRUG PRODUCT DESCRIPTION [2.3.P.5.1-original submission]

NDA: Patch, packaged into individual child-resistant envelopes.

ANDA: A (b) (4) patch consisting of a pigmented backing film randomly printed with "Lidocaine Patch 5%" in brown ink, and adhesive matrix layer and a clear removable release liner. Each individual patch is packaged in a sealed pouch, imprinted with lot number and expiration date. (b) (4) (b) (4)

6. CONTAINER/CLOSURE [2.3.P.7.1-original submission]

Lidocaine Patch 5% is packaged as a single patch within a child resistant pouch formed by (b) (4)

The final market package for Mylan's Lidocaine Patch 5% consists of Thirty (30) sealed pouches in a single carton.

The primary packaging for Mylan's Lidocaine Patch 5% is a pouch formed by (b) (4) (b) (4) Mylan has demonstrated that the primary container/closure system for Lidocaine Patch 5% is Child Resistant per the testing required in 16 C.F.R. PART 1700. The study report is included in Section 3.3.

Figure 1. Diagram of Primary Container/Closure System for Lidocaine Patch 5%

(b) (4)

(b) (4)

7 STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

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

USP: Not compendial, (b) (4)

8. PACKAGING CONFIGURATIONS

RLD: child resistant patch in carton of 30 patches

ANDA: child resistant patch in carton of 30 patches

9. Background information about CP Docket 2006P-0552 (Lidoderm). The findings of the CP could be read in DAARTS under L. Schultheis clinical review dated 12/3/07. In essence FDA found that clinical trials are NOT necessary for a generic product of Lidoderm. Below is from L. Schultheis' review:

Therefore, in the case of Lidoderm, we believe that plasma levels will adequately reflect

skin levels of lidocaine, and are sufficient to establish bioequivalence between the innovator and a generic product having the same formulation, provided that adequate pharmacokinetic information for both products is available. We disagree with the petitioner's conclusion that clinical trials are necessary for a generic product of Lidoderm having the same formulation of lidocaine to demonstrate efficacy.

10. Firm did submit SPL. Note that Mylan did not list inactive ingredients such as polyisobutylene (probably because of the lack of UNI code). Because this product could not be fully approved until May 2012, the SPL DLDE may need to be revisited.

11. MedWatch: Lidoderm (lidocaine patch) is not on the MedWatch site, checked on August 5, 2011.

Date of Review: August 5, 2011 **Date of Submission: October 25, 2010**

Primary Reviewer: Thuyanh Vu **Date:**

Team Leader: **Date:**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
08/08/2011

JOHN F GRACE
08/11/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

MEDICAL REVIEWS

Clinical Consultation

Lidocaine Transdermal System, 5% (Mylan Technologies, Inc.)

Drug Product:	Lidocaine Transdermal System, 5%
Drug Class:	6040400 (Local Anesthetics, Topical)
Chemical Name:	acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)
ANDA:	202346
ANDA Sponsor:	Mylan Technologies, Inc.
Reference Listed Drug:	Lidoderm
RLD Sponsor:	Teikoku Pharma USA (NDA N020612, approval date 19 Mar, 1999)
Reviewer:	Trueman Sharp MD, MPH Medical Officer, DCR, OGD
Secondary Reviewer:	Lesley-Anne Furlong, MD Deputy Division Director, DCR, OGD
To:	CMC/Chemistry 5, Robert Berendt Ph.D.
Reason for Consult:	To obtain a clinical assessment of observed differences between Mylan generic and RLD lidocaine 5% patch
Materials Reviewed:	• consult plus supplementary email and conversations • ANDA submission • CMC reviews # 1 and #2 of the ANDA • Mylan responses to reviews • current draft CMC response #3 to Mylan • DCR review of ANDA submission • Sample test and RLD patches • FDA Draft Guidance on Lidocaine (Patch/Topical) of May 2007 • available eCTD documents from RLD, N020612
Date of Submission:	3/28/2014
Date of Completion:	6/16/2014
Conclusion:	It is our opinion that the increased stickiness, the three cuts required to open the pouch, the decreased thickness, and the stiffer liner will not result in clinical safety or efficacy issues.

1 Executive Summary:

This review addresses a CMC request for DCR to evaluate concerns regarding a proposed lidocaine patch from a clinical perspective. A summary of the background of this request is as follows:

Mylan Technologies, Inc. submitted an ANDA on 25 Oct, 2010, for a lidocaine transdermal system (patch). The proposed patch uses a different formulation from the reference listed drug (RLD) that results in the test patch having different physical properties. On 3 Jun, 2013, the Office of Generic Drugs (OGD) issued a complete response letter listing 22 CMC and five bioequivalence deficiencies. The Division of Clinical Review (DCR) did not have any clinical bioequivalence deficiencies: The clinical studies for skin irritation, sensitization, and adhesion were adequate to show that the irritation/sensitization potential and adhesion performance for the test product were noninferior to the RLD. Among the CMC deficiencies, however, were concerns about (b) (4)

On 26 Jun, 2013, Mylan responded to the issues raised in the complete response. This response is currently undergoing CMC review. On 31 Mar, 2013, the CMC team consulted DCR requesting a clinical assessment of continued concerns regarding (b) (4) (b) (4)

The CMC team further clarified the consult request by email. Specifically:

(b) (4)

CMC provided separately a draft of their most recent evaluation of the applicant's response (CMC Review #3 draft) as well as samples of the RLD and test patches.

To address the consult, DCR evaluated the provided samples (six test and three RLD patches) and reconsidered the data available from the clinical trials reported in the ANDA. DCR also reviewed other relevant documents (as noted above).

It is our opinion that the increased stickiness, the need to cut on three sides rather than one side to open the pouch, the thinner patch, and the less flexible liner will not cause clinical safety or efficacy issues. However, if patients fail to cut as directed on three sides

of the packaging, the test product may be difficult to remove from the pouch and product quality complaints are a possibility.

2 Recommendation:

We conclude that the three cuts required to open the test product pouch, the decreased thickness of the patch, and the stiffer liner should not raise clinical safety or efficacy issues. (See the Discussion section for our evaluation.)

.

3 Regulatory Background:

The RLD (LIDODERM; NDA N020612; Teikoku Pharma USA) was approved on 19 Mar, 1999, for the treatment of post-herpetic neuralgia. The RLD is distributed in the U.S. by ENDO Pharmaceuticals. A review of the documents available in DARRTS does not indicate there have been any substantial changes to the RLD. (However, the original approval pre-dated the eCTD and there are few documents available in DARRTS and the eCTD.)

As shown below, one generic has been approved for this drug product (Watson Pharmaceuticals Inc.; approved 8/23/2012) and a number of others are under review.

This ANDA was submitted by Mylan on October 25, 2010, and accepted for filing on 10 January, 2011. The filing had been preceded by correspondence and meetings with OGD to seek advice on proposed changes in formulation and labeling, and their clinical development plan. Since the filing, FDA asked Mylan for additional information concerning long-term frozen stability, additional clinical study data, clarification on a variety of formulation issues, clarifications in study design, and changes in labelling. A complete response was sent to Mylan on 6/3/2013, listing 22 CMC and five bioequivalence deficiencies. Mylan provided a Minor Complete Response Amendment on 26 June, 2013, and samples of the most recent test and RLD patches on 18 October, 2013. At the present time, a second complete response for the CMC and Bioequivalence issues raised is under review.

3.1 DARRTS and OGD Database Listings for This Product:

There are entries in DARRTS related to Lidocaine patches: three NDAs (Table 1), 12 INDs (Table 2), 8 ANDAs (Table 3), 4 protocols (Table 4) and 28 Controlled Correspondences (Table 5).

APPEARS THIS WAY ON ORIGINAL

Table 1: List of NDAs related to Lidocaine patches

Appl No	Product Name	Submitter	Dosage Form	Responsible Organization	Current Status	Status Date
020575	LIDOCAINE	NOVEN PHARMACEUTICALS INC	PATCH, CONTROLLED RELEASE	CDER/ODE II/DAAAP	Approved	5/21/1996
021504	LIDOSITE TOPICAL SYSTEM	VYTERIS INC	PATCH, CONTROLLED RELEASE	CDER/ODE II/DAAAP	Approved	5/6/2004
021623	Synera (Lidocaine 70 mg and Tetracaine 70 mg) Topical Patch	GALEN SPECIALTY PHARMA US LLC	PATCH	CDER/ODE II/DAAAP	Approved	6/23/2005

Searched on 6/11/2014, search terms "lidocaine patch"; CDER: Center for Drug Evaluation and Research; ODEII: Office of Drug Evaluation II, DAAAP: Division of Anesthetics, Analgesia and Addiction Products, OGD: Office of Generic Drugs

Table 2: List of INDs related to Lidocaine patches

Appl No	Product Name	Type of IND	Submitter	Dosage Form	Responsible Organization	Current Status	Status Date

(b) (4)

[redacted]

(b) (4)

Table 3: List of ANDAs related to Lidocaine patches

Appl No	Product Name	Submitter	Dosage Form	Responsible Organization	Current Status	Status Date
(b) (4)						
202346	LIDOCAINE	MYLAN TECHNOLOGIES INC	PATCH	CDER/OGD	Pending	6/27/2013
(b) (4)						
200675	LIDOCAINE	WATSON LABORATORIES INC	PATCH	CDER/OGD	Approved	8/23/2012

Searched on 6/11/2014, search terms "lidocaine patch"; CDER: Center for Drug Evaluation and Research; ODEII: Office of Drug Evaluation II, DAAAP: Division of Anesthetics, Analgesia and Addiction Products, OGD: Office of Generic Drugs

Table 4: List of Protocols related to Lidocaine patches in the DBE Protocol Database

Protocol No	Drug Name	Dosage Form	Submitter	Responsible Organization	Completed Date
05-030	Lidocaine, 5%	Transdermal Patch	Mylan Pharm.	OGD	5/15/2006
09-006	Lidocaine	(b) (4)			
09-039	Lidocaine				
09-046	Lidocaine				

Searched on 6/12/2014, search terms "lidocaine patch," DBE: Division of Bioequivalence, OGD:Office of Generic Drugs

Table 5: List of Controlled Correspondence related to Lidocaine patches in the OGD Controlled Correspondence Database

Ctl No	Title	Description	From	Status	Date Closed
04-236	Lidocaine Patch	(b) (4)			
04-243	Lidocaine Patch 5%				
04-185	Lidocaine Patch				
04-936	Lidocaine Patch 5%				
06-1410	Lidocaine Patch				
06-0581	Lidocaine Patch				
06-0374	Lidocaine Patch				
06-0217	Lidocaine Patch				
06-0223	Lidocaine Patch				
06-0612	Lidocaine Patch				
06-1542	**Lidocaine Patch**				
06-1508	Lidocaine Patch				
06-1258	Lidocaine Patch				
06-1594	**Lidocaine Patch**				

		(b) (4)
06-1596	Lidocaine Patch	
09-0618	**Lidocaine patch**	
09-0620	Lidocaine patch formulation	
07-1554	Lidocaine Patch	
08-0827	Lidocaine patch inactive ingredients/formulation	
08-0840	Formulation/inactive ingredients lidocaine patch	
09-0641	Acceptability of inactive ingredients Lidocaine patch	
08-1157	Lidocaine patch fornulation	
11-0271	Formulation lidocaine patch	
11-0307	Inactive ingredients in lidocaine patch	
11-0315	Fromulation lidocaine patch	
11-0564	Lidocaine patch content	
11-0664	Formulation Lidocaine patch	
11-0564A	Lidocaine patch content	

Searched on 6/12/2014, search terms "lidocaine patch," DBE: Division of Bioequivalence, OGD: Office of Generic Drugs

3.2 Current Guidances/Draft Guidances:

Draft Guidance on Lidocaine (Patch/Topical) of May 2007

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf

3.3 Orange Book:

Table 6: Orange Book currently marketed prescription entries for Lidocaine patches

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020612	AB	Yes	LIDOCAINE	PATCH; TOPICAL	5%	LIDODERM	TEIKOKU PHARMA USA
A200675	AB	No	LIDOCAINE	PATCH; TOPICAL	5%	LIDOCAINE	WATSON LABS INC

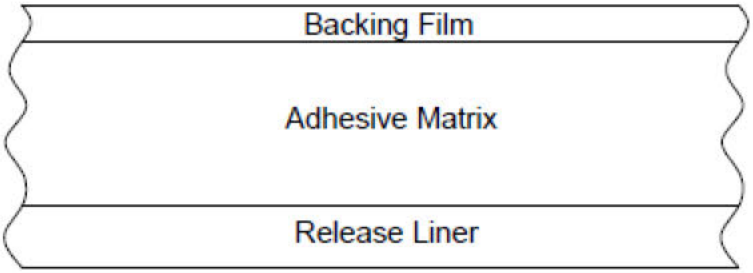
Searched on 6/12/2014

3.4 Patch Design and Formulation:

Mylan's Lidocaine Patch 5% contains an active pharmaceutical ingredient dispersed in a pressure-sensitive adhesive matrix. Mylan's Lidocaine Patch 5% is bioequivalent to Teikoku Pharma's LIDODERM® (Lidocaine Patch 5%) distributed in the US by Endo Pharmaceuticals.

Mylan's Lidocaine Patch 5% contains three layers. The (b) (4) backing (b) (4) is a pigmented polyethylene / polyester laminate film. The (b) (4) is the polyisobutylene adhesive matrix containing the active pharmaceutical ingredient, Lidocaine, USP. The (b) (4) is a transparent polyester film coated with silicone release agent. The release liner is removed from the patch and discarded prior to use.

Figure 1: Schematic Diagram of Mylan's Lidocaine Patch 5%



Mylan's Lidocaine Patch 5% – A 140 cm^2 patch that contains 140 mg of Lidocaine, USP. It is a (b) (4) patch consisting of a pigmented backing film randomly printed with "Lidocaine Patch 5%" in brown ink, an adhesive matrix layer and a clear removable release liner. Each individual patch is packaged in a sealed, printed pouch.

Table Ia: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Adhesive Matrix

Components	Pharmaceutical Function	% w/w	mg/ patch	Maximum Level listed in the FDA *IID*[1] (mg)	Quality Standards
Active Ingredients					
Lidocaine, USP	Active Ingredient	5.00	140.00	NA	DMF (b) (4) and Mylan Specification
Inactive Ingredients					
Polyisobutylene (b) (4)	Adhesive	(b) (4)		119[2]	(b) (4) (b) (4)
Theoretical Total Matrix		100.00	(b) (4)		

[1]FDA's electronic Inactive Ingredients Database (IID) for Approved Drug Products (last updated July 15, 2010) for transdermal/topical route of administration. All excipient levels are either below the maximum level listed in the IID for this dosage form or a comprehensive review of the safety is provided. 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]Polyisobutylene is listed in the IID at 119 mg. Due to the physical size of Mylan's Lidocaine Patch 5% (140 cm^2), the amount of polyisobutylene in the patch exceeds the maximum level listed in the IID. Mylan has provided safety information for polyisobutylene in Section 3.3 to demonstrate that the level of this component in the formulation does not affect the safety of the proposed drug product.

Table Ib: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Other Components of Mylan's Lidocaine Patch 5%.

Components	Pharmaceutical Function	mg/ patch	Maximum Level listed in the FDA *IID*[1] (mg)	Quality Standards
Pigmented Polyethylene / Polyester Film (MEDIFLEX® 1501)	Backing	(b) (4)		Mylan DMF 11404 and Mylan Specifications
Brown Ink (b) (4)	Imprinting Ink			(b) (4)
Silicone Coated Polyester Film (MEDIRELEASE® 2249)	Release Liner			Mylan DMF 14652 and Mylan Specifications

(b) (4)

Table IIa: Quantitative Composition of Adhesive Matrix Components of Mylan's Lidocaine Patch 5%

Components	% w/w	Basis Weight (g/m^2)[6]	mg/patch	kg per batch (b) (4)
Active Ingredients				
Lidocaine, USP	5.00	(b) (4)	140.00	(b) (4)
Inactive Ingredients				
Polyisobutylene (b) (4)	(b) (4)			
Total	**100.00**	(b) (4)		

[6] Basis weight is provided in units of grams per square meter (g/m^2)

Table IIb: Quantitative Composition of Other Components of Mylan's Lidocaine Patch 5%

Components	Basis Weight (g/m^2)	mg/patch
Pigmented Polyethylene/ Polyester Film (MEDIFLEX® 1501)	(b) (4)	
Brown Ink (b) (4)		
Silicone Coated Polyester Film (MEDIRELEASE® 2249)		

Batch records for the production batch size of the master laminate and finished product are provided in Section 3.2.P.3.3.

Container/Closure System:

Each Mylan Lidocaine Patch 5% is packaged in a (b) (4) flat pouch with rounded corners that is imprinted with lot # and manufacture date. (b) (4) (b) (4) (b) (4) Thirty (30) sealed pouches of Mylan's Lidocaine Patch 5% are placed in a carton along with labeling.

4 Label:

The most recent label for the RLD was approved on 04/13/2010 and may be found at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020612s011lbl.pdf.

There is no Black Box Warning.

4.1 Indications:

LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia.

(b) (4)

5 Discussion:

- The primary and secondary reviewer for this consult opened six Mylan patches (three from lot 6E0143 and three from lot R6B0039) as well as three RLD patches (lot number 81058). We found that if the Mylan test patch pouches were opened following the instructions of the RLD patch (only one cut is made along the top of the pouch) the patches did indeed seem sticky and were difficult to remove from the pouch. However, if the Mylan instructions were followed (which require cutting along three sides of the pouch) then there was minimal sticking and we experienced no difficulty in removing the patch from the pouch.
- It was our opinion that the instructions and the markings on the Mylan pouch were clear and easy to follow. However, we acknowledge that we may not be representative of the typical patient under usual conditions of patch use.
- We could find no mention of difficulties with the test patch in the ANDA studies. The study report from the adhesion and sensitization study (LIDO-1046), states, "products were opened with scissors according to the instructions on the product packaging. The adhesive surface of the patch was not touched during application and the lidocaine patch was applied immediately after opening the packaging, cutting the patch into 4 equal sections and removing the protective liner." There were similar statements in the other two studies performed (LIDO-1037 and LIDO-1044). No

issues were noted in the study reports of difficulties removing the Mylan patches from their pouches. However, it is of note that this was not a question explicitly addressed by any of the studies. Also, in all three of the studies it appears the pouches were opened in the research setting with the assistance of the researchers.

- Whether an individual who has previously used the RLD patch and is accustomed to making just one cut of the pouch would have difficulty switching over to a new pouch with different instructions is difficult to assess. As noted above, it was our opinion that the instructions and the markings on the Mylan pouch were clear and easy to follow. However, we may not be representative of the typical patient under typical conditions of patch use.
- Switching between RLD and the test product may not be an issue encountered by some patients. Post-herpetic neuralgia, the main indication for this patch, generally lasts for a finite period of time in most patients (usually 1-3 weeks) and it is likely many patients would not have to switch patches in this amount of time. However, some patients with post-herpetic neuralgia need treatment for a prolonged period of time. (b) (4) Of note, if patients did switch patches they could conceivably switch from the generic to the RLD as well.
- Whether a patient who is familiar with the RLD patch might perceive a thinner patch as being unsatisfactory is a matter of conjecture. Some patients may prefer the thinner patch and some may prefer the thicker patch. We did not see the test patch being thinner as an issue with respect to the ease of use.
- Whether a patient who is familiar with the RLD patch might perceive a less flexible release liner as being unsatisfactory is also a matter of conjecture. Based on the three samples provided, we did not see the less flexible release liner as a concern. Once the liner is removed, the patch appeared to be flexible enough to apply.

6 Conclusions and Recommendations:

- It is our opinion that the increased stickiness, the three cuts required to open the pouch, the decreased thickness, and the stiffer liner should not be significant issues for patients, either with respect to their ability to use the product or as a matter of perception compared to the RLD.

7 References:

None

8 Appendix:

None

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/s/

TRUEMAN W SHARP
06/16/2014

LESLEYANNE FURLONG
06/16/2014

Review of Skin Irritation, Sensitization and Adhesion Studies

ANDA #202346

Lidocaine Patch, 5%

Mylan Technologies, Inc.

Nicole Lee, Pharm.D.
Clinical Reviewer
Division of Clinical Review
Office of Generic Drugs

Dates of submissions reviewed:
October 26, 2010; July 1, 2011 (amendment); August 9, 2012 (amendment); October 9, 2012 (amendment)

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Review of a Skin Irritation, Sensitization and Adhesion Study for ANDA #202346

Executive Summary

Lidocaine Patch, 5% (Lidoderm®, approved 3/19/1999) is indicated for relief of pain associated with post-herpetic neuralgia. Mylan Technologies, Inc. (Sponsor) submitted ANDA 202346 on 10/26/2010 for a generic formulation of Lidocaine Patch 5%. This review focuses on the studies submitted to ensure that the skin irritation and sensitization potential of this proposed generic topical patch product are no greater than those of the RLD and that the generic product adheres to the skin as well as the RLD over the intended duration of wear.

Mylan conducted two separate studies, #LIDO-1046 for skin irritation and sensitization and #LIDO-1044 for adhesion only. Study #LIDO-1046 was an open-label, multiple-dose, randomized application site, two-treatment, three-phase, one-period human dermal safety study. A total of 240 patients were enrolled in the study. Study #LIDO-1044 was an open-label, single dose, randomized, one-period, two-treatment study which enrolled 24 patients.

According to the sponsor's data, these studies demonstrate that Mylan's Lidocaine Patch is no more irritating than the RLD and has no more potential to cause sensitization than that expected with use of the reference listed product Lidoderm®. Adhesion data from study #LIDO-1044 demonstrated that its adherence is no worse than that of the RLD.

According to the FDA statistical review, the test patch was found to be non-inferior to the reference patch for irritation, sensitization and adhesion.

I. Approval Recommendation

The data submitted to ANDA 202346, for irritation, sensitization and adhesion of Mylan's Lidocaine Patch are adequate to demonstrate that it is no more irritating and has no greater potential to cause sensitization than the reference listed drug (RLD), Lidoderm® Patch. In addition, the study has demonstrated that it adheres at least as well as the RLD. This application is therefore recommended for approval from a clinical bioequivalence perspective.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Study #LIDO-1046 was an open-label, multiple dose, randomized application site, two-treatment, three-phase study of Mylan's Lidocaine Patch, 5%, versus the RLD, Lidoderm® Patch, 5%. Each subject received one-fourth (1/4) cut patch of each of the two test formulations and one-fourth (1/4) cut patch of the reference product applied simultaneously to separate sites every 24 hours and worn for a 12-hour period each day for 21 days. Following a 14-day rest

period on Day 36, during the challenge phase, subjects that completed the induction phase received one-fourth (1/4) cut patch of each of the two test formulations and one-fourth (1/4) cut patch of the reference product applied to naïve skin sites on the back for 48 hours. This study compared skin irritation and sensitization potential of Mylan's test product with the reference product.

Treatments Administered:
Test Product: One-fourth (1/4) Lidocaine Topical Patch, 5%, Lot No. R6B0017, Mylan
Reference Product: One-fourth (1/4) Lidoderm® Patch, 5%, Lot No. 97278, expired 08/2010, Endo

B. Skin Irritation Evaluation

The data submitted to ANDA 202346 for irritation of Mylan's Lidocaine Transdermal System demonstrates that it is no more irritating than the reference listed drug.

The upper 90% confidence interval of the least-squares mean being < 0 indicates Mylan's patch is non-inferior to Lidoderm®.

Further irritation data found in the application was as follows:

- Two (2) subjects had their patches moved to at least a 2nd site due to maximum irritation reached for the Test Product. Three (3) subjects had their patches moved to at least a 2nd site due to maximum irritation reached for the Reference Product.
- The number of subjects who had a score of 0 or 1 was 673 for the Test product and 672 for the Reference product.
- The number of subjects who had a score of 3 or 5 was 5 for the Test product and 7 for the Reference product.
- Per the sponsor, the least-squares mean cumulative irritation score for Test Treatment A was 0.654 vs. 0.741 for Reference Treatment B.

According to the FDA statistical analysis, the non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μT -1.25μR) was less than zero (-0.2383) and the non-inferiority test was passed for test patch versus reference patch. Therefore, the irritation potential of the test patch is not worse than that of the reference patch.

C. Skin Sensitization Evaluation

One subject, subject (b) (6)) had an irritation score of 5 at the 24 hour of the challenge phase. The score resolved to 2 at the 48 and 72 hour challenge phase measurements. In addition, the induction scores reached a 5 at patch number 10 out of 21. This would suggest that the scores seen in the challenge phase are due to irritation, not sensitization.

According to the FDA statistical analysis, no evidence of sensitization reactions were observed after the 24 hour challenge phase since neither treatment produced an irritation score greater than 2 at the 48 and 72 hour in the challenge phase of the study. Therefore, no subjects were identified

as potentially sensitized. No evidence of sensitization reactions were observed after the 24 hour challenge phase since neither treatment produced an irritation score greater than 2 in the challenge phase of the study. Therefore, no subjects were identified as potentially sensitized.

D. Skin Adhesion Evaluation

Based on the mean cumulative adhesion scores, Treatment A-test (0.55) demonstrated better adhesive characteristics compared to Treatment B-reference (0.92), over a single application period of 12 hrs.

The frequency distribution of the adhesion score were as follows:

	Scores				
Product	0	1	2	3	4
Test	12	10	1	1	0
Reference	4	9	6	1	4

Based on this data, the adhesiveness of the test product was not inferior to that of Lidoderm®.

According to the FDA statistical analysis, Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μT -1.25μR) was less than zero (-0.2834) and the non-inferiority test was passed for test versus reference patch. Therefore, the adhesion potential of the test is non-inferior to that of the reference.

E. Adverse Events

There were a total of two thousand, nine hundred seventy-three (2973) additional AEs reported by two hundred thirty-six (236) subjects over the course of the study. The AEs were mild and moderate in severity. There was on (1) serious adverse events (SAEs) reported.

- Eight hundred thirty-seven (837) AEs including: application site anesthesia, application site erythema, application site pain, application site paresthesia, application site pruritis, application site warmth, and pruritis, were considered probably related to the sponsor's Lidocaine Patch 5%. There was one (1) AE (skin irritation) considered unlikely/remotely related to Mylan's Lidocaine Patch 5%.
- Six hundred six (606) AEs including: pain, pruritis, skin burning sensation, and skin irritation were considered unrelated/not related to Mylan's Lidocaine Patch 5%.
- Eight hundred fourteen (814) AEs including: application site erythema, application site pain, application site paresthesia, application site pruritis, myalgia, and pruritis were considered probably related to RLD. There was one (1) AE (skin irritation) considered unlikely/remotely related to Lidoderm® Patch 5%.
- Six hundred five (605) AEs including: application site pain, pain, pruritis, skin burning sensation, and skin irritation were considered unrelated/not related to RLD

There were no deaths reported for this study. There was one SAE reported over the course of the study. Subject (b) (6) experienced appendicitis on 13 May 2010 (Day 16 of induction period). The

SAE (appendectomy) was severe and considered to be unrelated/not related to Mylan's Lidocaine Patch 5% and/or Lidoderm® Patch 5%.

III. Formulation

Mylan's Lidocaine Patch 5% [redacted] (b) (4) The [redacted] (b) (4) backing [redacted] (b) (4) is a pigmented polyethylene / polyester laminate film. The [redacted] (b) (4) is the polyisobutylene adhesive matrix containing the active pharmaceutical ingredient, Lidocaine, USP. The [redacted] (b) (4) is a transparent polyester film coated with silicone release agent. The release liner is removed from the patch and discarded prior to use. Mylan's Lidocaine Patch 5% – A 140 cm^2 patch that contains 140 mg of Lidocaine, USP. It is a [redacted] (b) (4) patch consisting of a pigmented backing film randomly printed with "Lidocaine Patch 5%" in brown ink, an adhesive matrix layer and a clear removable release liner. Each individual patch is packaged in a sealed, printed pouch.

Component	Function	Test (% w/w)	Reference* (% w/w)
Lidocaine	Active	5.00	5
Polyisobutylene [redacted] (b) (4)	Adhesive	[redacted] (b) (4)	

[redacted] (b) (4)

(b) (4)

Reviewer's comments:

According to the sponsor, Mylan recognized LIDODERM® (lidocaine patch 5%) is an extremely complex formulation composed of many inactive ingredients. Due to this complexity and in deference to the LIDODERM® Orange Book patents, Mylan did not consider adhesive gel formulations that contained water or a water retaining agent. Rather, Mylan chose to develop a simpler generic formulation using traditional transdermal adhesive technology.

The RLD formulation has many excipients and a high amount of drug (700mg). The majority of the drug never leaves the patch. The sponsor chose to develop a different formulation (b) (4) (b) (4) *with reduced amount of drug (140mg), however, to maintain the same drug concentration (5%) and the same patch size. The firm needs to provide evidence that proposed drug product is bioequivalent and delivers the same amount as the RLD based on residual drug analysis per the BE review.*

(b) (4) *Polyisobutylene* (b) (4) (b) (4) *used in Mylan's Lidocaine Patch 5% are outside the IIG limits for the transdermal route of administration.* (b) (4) *The backing and release liner component materials used in Mylan's Lidocaine Patch 5% are not listed in the IIG but are present in Mylan's other FDA approved products. The level of Pigmented Polyethylene is* (b) (4) *than previously approved product and the level of Silicone Coated Polyester Film is* (b) (4) *than previously approved product. These excipients are not in direct contact with skin. In a consult dated April 4, 2011 from the Division of Anesthesia, Analgesia and Addition Products, the levels of the Polyisobutylenes and levels of excipients comprising the backing film and release liner were found acceptable.*

Clinical Review

I. Introduction and Background

Lidocaine Patch, 5% is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin. Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. LIDODERM® (lidocaine patch 5%) is comprised of an adhesive material containing 5% lidocaine, which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner

is removed prior to application to the skin. The size of the patch is 10 cm x 14 cm. Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base.

A. Drug Established Name, Drug Class,

Established Name: Lidocaine Patch
Drug Class: Amide-type local anesthetic

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug: Lidoderm Patch, 5%, Teikoku Pharma USA
NDA number: 020612
Date of Approval: March 19, 1999

- **Approved Indication(s):** Indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin

- **Dosing Regimen:** Apply Lidoderm to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner.

Identity of Products:
Test: Lidocaine Topical Patch 5%, Lot No. R6B0017, Mylan Technologies, Inc.
Reference: Lidoderm Patch, manufactured by Endo Pharmaceuticals, Inc., Lot No. 97278, Expiration date: 08/2010

C. Regulatory Background

ANDA 200675, Watson Laboratories, Inc. was approved on 8/23/2012.

DARRTS lists the following submissions for Lidocaine Patch, 5%:

Application	Sponsor	Responsible Organization	Status	Status Date
(b) (4)				
ANDA-202346 (current application)	Mylan Technologies, Inc.	OGD	Pending	10/26/2010

Controls/Protocols

There are 5 protocols listed in the Office of Generic Drugs (OGD) database:

Protocol No	Drug Name	Firm	Letter Date	Completed Date	Comments
09-006	Lidocaine	(b) (4)			
09-039	Lidocaine				
10-005	Lidocaine, 5%				
05-030	Lidocaine, 5%	Mylan Pharm.	6/20/2005	5/15/2006	
09-046	Lidocaine	(b) (4)			

There are 48 Controlled Correspondence Documents listed in the OGD database:

Control No.	Title	Description	Status	Doc Date	From
04-1062	Lidocaine Transdermal system	(b) (4)			
04-185	Lidocaine Patch				
04-218	Lidocaine				
04-236	Lidocaine Patch				
04-243	Lidocaine Patch 5%				

04-936	Lidocaine Patch 5%	(b) (4)			
05-1377	Lidocaine Topical Film				
06-0217	Lidocaine Patch				
06-0223	Lidocaine Patch				
06-0374	Lidocaine Patch				
06-0519	Lidocaine Topical Patch				
06-0581	Lidocaine Patch				
06-0612	Lidocaine Patch				
06-1258	Lidocaine Patch				
06-1337	Lidocaine Topical Patch				
06-1410	Lidocaine Patch				
06-1457	5% lidocaine topical patch				
06-1508	Lidocaine Patch	Inquiry in relation to the recent bioequivalence recommendation	Closed 9/7/2012	10/17/2006	ENDO

06-1536	Topical Lidocaine	(b) (4)			
06-1542	Lidocaine Patch				
06-1575	Lidocaine Topical Patch				
06-1594	Lidocaine Patch	Request for BE recommendations	Closed 1/3/2007	10/20/2006	Mylan
06-1596	Lidocaine Patch	(b) (4)			
06-1661	Lidocaine Topical Patch				
06-1777	Lidocaine Topical Patch				
07-0053	Lidocaine Topical Patch				
07-0063	Lidocaine Transdermal Patch				
07-0212	Lidocaine Transdermal Patch				
07-1393	Lidocaine Topical Patch Inactive				
07-1554	Lidocaine Patch				
08-	Lidocaine				

0827	patch inactive ingredients/formulation	(b) (4) [redacted]
08-0840	Formulation/inactive ingredients lidocaine patch	
08-1048	Lidocaine topical patch	
08-1157	Lidocaine patch formulation	
09-0618	Lidocaine patch	
09-0620	Lidocaine patch formulation	
09-0641	Acceptability of inactive ingredients Lidocaine patch	
11-0271	Formulation lidocaine patch	
11-0307	Inactive ingredients in lidocaine patch	
11-0315	Formulation lidocaine	

	patch	(b) (4)
11-0344	Lidocaine transdermal patch	
11-0564	Lidocaine patch content	
11-0564A	Lidocaine patch content	
11-0664	Formulation Lidocaine patch	
12-0398	Lidocaine Topical Patch	
12-0399	Lidocaine Topical Patch	
12-0400	Lidocaine Topical Patch	
12-0401	Lidocaine Topical Patch	

D. Guidance

The current Draft Guidance for Lidocaine (patch/topical; 6 pages, May 2007) can be found at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf

The draft guidance general recommendations are attached in Appendix A.

Reviewer's comments: *The studies submitted are consistent with the draft guidance except for the fact that the firm conducted the induction period with patches worn for 12 hours per 24 hours instead of the full 24 hours. An information request was sent to the firm to clarify this issue on 6/20/2012. The response was found acceptable.*

E. Other Relevant Information

On June 20, 2012, a Request for Information was sent to the firm with the following comments:

1. Please submit a justification as to why the skin irritation and sensitization study was conducted with patches worn for 12 hours per 24 hours instead of the full 24 hours as recommended in the FDA Bioequivalence Draft Guidance: "…applied continuously to the same sites and replaced with a new one-fourth patch 3 times weekly."
2. Currently validated sensitization studies use at least a 24 hour contact exposure to induce a reaction. Please provide evidence and documentation that the 12-hour induction period for 21 days is sufficient to elicit acceptable sensitization data.
3. The source data for skin irritation/sensitization scores for each subject could not be located in your Case Report Forms. Please provide the source documentation of each irritation dermal response score, other effect score, and sensitization score for each subject.

On August 9, 2012 the firm submitted the following responses:

1. **Please submit a justification as to why the skin irritation and sensitization study was conducted with patches worn for 12 hours per 24 hours instead of the full 24 hours as recommended in the FDA Bioequivalence Draft Guidance: "…applied continuously to the same sites and replaced with a new one-fourth patch 3 times weekly."**

Firm's Response:

- The firm states that to be reflective of normal wear and to be consistent with the currently approved labeling for the reference listed drug, they chose the 12 hours per 24 hours of wear instead of the full 24 hours.
- They note that the FDA Draft Guidance for Lidocaine Patch allows for up to 24 hours detachment in any one of the sequential patch application periods. They state this provision suggests that intermittent application is acceptable for determination of comparable irritation or sensitization potential.
- The firm conducted 2 pilot clinical cumulative irritation studies which included testing of Lidoderm based on a continuous patch wear design, with application three times weekly and included testing of Lidoderm based on intermittent patch wear, aligned with the approved RLD label, both for 21 days. The data showed that a range of scores are achieved following either study design. According to the sponsor, the results illustrate that the intermittent wear study design is at least as provocative as (and trending to be more provocative than) the continuous wear study design. The pilot studies showed the following results:

Study LIDO-0929, n=12 subjects, Lidoderm® (lidocaine patch 5%), Intermittent wear

Scores	Study Day										
	1	3	5	7	9	11	13	15	17*	19	21
0	4	7	4	3	0	0	1	1	2	2	3
1	8	5	8	9	11	10	10	11	9	10	9
2	0	0	0	0	1	1	1	0	0	0	0
3	0	0	0	0	0	1	0	0	0	0	0

*one score was missing from Subject (b)(6)

Study LIDO-08173, n=36 subjects, Lidoderm® (lidocaine patch 5%), Continuous wear

Scores	Study Day								
	1	3	6	8	10	13*	15*	17*	20*
0	29	25	16	16	22	20	26	30	20
1	6	10	18	19	13	14	8	4	15
2	1	1	2	1	1	0	1	0	0
3	0	0	0	0	0	0	0	0	0

*Subject (b)(6) was missing scores for days 13 and 17; Subject (b)(6) was missing scores for days 13 through 20.

Reviewer's comments: *Based on the pilot cumulative irritation studies conducted by the firm, it was shown that both continuous and intermittent wear produced similar irritation results. Thus, this reviewer agrees that the study design for the cumulative irritation is acceptable.*

2. **Currently validated sensitization studies use at least a 24 hour contact exposure to induce a reaction. Please provide evidence and documentation that the 12-hour induction period for 21 days is sufficient to elicit acceptable sensitization data.**

Firm's Response:

- The firm states that the innovator demonstrated in their NDA for Lidoderm (NDA 020612) that lidocaine was not a sensitizer utilizing an intermittent study design, as opposed to a continuous application study design recommended in the FDA Bioequivalence Recommendation Guidance. In the Innovator's study, patches were cut to 1.3 cm x 1.3 cm and applied to the dorsal torso via occlusive dressing every other day for 3 consecutive weeks until a series of 9 x 24-hour exposures were completed (each patch was only worn for 24-hours at a time). This study was deemed acceptable for evidence of sensitization (or lack thereof) by a dermatology medical review officer from HFD-540.
- The FDA guidance allows periods of detachment of up to 24 hours during sequential patch applications. The original Lidoderm sensitization study utilized patches cut to 1.3 cm x 1.3 cm, whereas Mylan's study design utilized patches cut to 5 cm x 7 cm. However, subjects were exposed to more lidocaine more consistently and more continuously over time in the Mylan sensitization study than the Lidoderm sensitization study.
- The firm showed reports that Under normal exposure conditions, it is the amount of chemical exposed to the skin that is the important determinant in the development of

sensitization (Kimber et al., 2001[1]). Per Mylan's study design, subjects were exposed to lidocaine for 12 hours a day for 21 consecutive days to a 35 cm2 skin area for each treatment. Per Endo's study design, subjects were exposed to lidocaine for 24 hours a day for 9 days intermittently over 21 days to a 1.69 cm2 skin area. Clearly, subjects were exposed to more lidocaine over time in the Mylan sensitization study than the Endo sensitization study, with the cumulative exposure to lidocaine being both greater and more consistent.

- In addition, in a study performed by Basketter[2], et al., 2006, it was determined that the number of exposures to a test compound (p-phenylenediamine), not the exposure time, was significant for the development of a sensitization response. In one case report (Yuen et al., 2009), a 54-year old woman was determined to be sensitized to lidocaine after using a hemorrhoid cream containing lidocaine only once a year. In other cases, exposure to lidocaine was sporadic and of a fairly short duration; however sensitization still developed. administered via various routes of administration for varying lengths of exposure, (Yuen[3] et al., 2009; Hickey[4] et al., 2006; Gunson[5] et al., 2008; Fregert[6] et al., 1979; Amado[7] et al., 2007).

Reviewer's comments: *The intermittent study design of the NDA[8] was a single-center, 24-hour, repeat exposure test to 1.3 cm x 1.3 cm pieces of the Lidoderm Patch. The test material was applied to the skin of patients' dorsal torso via occlusive dressings every other day for 3 consecutive weeks until a series of 9 24-hour exposures were completed. Adverse skin reactions (i.e. erythema and edema) were evaluated and measured within 24 hours of their occurrence. If a subject experienced an adverse skin reaction to the test product, they were rechallenged at a previously unexposed skin site with the test material following a 10-14 day rest period. Repeat reactions if they occurred were scored at 24 and 48 hours post-application. No significant irritancy of any kind was reported during the course of this study. The Medical Officer stated that the reviews were appropriately conducted and that the Lidoderm Patch has a very low potential to cause topical irritancy or photoallergenicity. The team leader noted that the study was either conducted or reported incorrectly since all patients should have been challenged after a 2 week rest period. In addition, the team leader disagreed with the medical officer's review that the application provided substantial evidence of efficacy. However, there was no disagreement in regards to the study design. Based on the literature reports showing that sporadic exposure to lidocaine (once a year) was sufficient enough to elicit a sensitization reaction and the NDA intermittent study design ,this reviewer feels the firm's study design of*

[1] Kimber, DA et al. Skin Sensitization Testing in Potency and Risk Assessment. Toxicological Sciences. Vol. 59: 198-208 (2001)
[2] Basketter, DA et al. The Impact of Exposure Variables on the Induction of Skin Sensitization. Contact Dermatitis. Vol. 55: 178-185 (2006)
[3] Yuen, WY et al. Bullous Allergic Contact Dermatitis to Lidocaine. Contact Dermatitis. Vol. 61: 300-301 (2009)
[4] Hickey, JR et al. Delayed Hypersensitivity Following Intravenous Lidocaine. Contact Dermatitis. Vol. 54: 215-216 (2006)
[5] Gunson, TH et al. Allergic Contact Dermatitis to all Three Classes of Local Anaesthetic. Contact Dermatitis. Vol. 59: 126-127 (2008)
[6] Fregert, S. et al. Contact Allergy to Lidocaine. Contact Dermatitis. Vol. 5: 185-188 (1979)
[7] Amado, A. et al. Contact Allergy to Lidocaine: A Report of Sixteen Cases. Vol. 18(4): 215-220 (2007).
[8] NDA 20612, Medical Officer's Review dated 10/11/96 and Team Leader's Review dated 3/22/1997

patch applications at 12 hour intervals per 24 hours is sufficient enough for the determination of the sensitization potential of the test and reference products.

3. **The source data for skin irritation/sensitization scores for each subject could not be located in your Case Report Forms. Please provide the source documentation of each irritation dermal response score, other effect score, and sensitization score for each subject.**

Firm's Response*: The source data for the irritation and adhesion scores for this study were captured electronically via the Cetero Research Study Monitor system. The dermal irritation and adhesion evaluations were entered directly into the Study Monitor system by the Cetero Research Dermatology/Clinical Teams.*

Reviewer's comments*: In a separate amendment dated October 9, 2012, the firm sent in the SOPs of the electronic source documentation procedures as well as confirming that these procedures were used in several ANDAs that were approved (ANDA 200043, 090738 and 091427). This procedure is acceptable.*

II. Description of Clinical Data and Sources

CRO: Cetero Research

Study Center:

- Cetero Research- 4801 Amber Valley Parkway, Fargo, ND 58104

Study Period
Group I (Subjects 001-208):
Induction: 28 Apr 2010 – 18 May 2010
Challenge: 02 Jun 2010 – 07 Jun 2010

Group II (Subjects 209 – 240):
Induction: 06 May 2010 – 26 May 2010
Challenge: 10 June 2010 – 15 June 2010

Investigator(s): Alan K. Copa, Pharm.D

Enrollment: A total of 240 subjects were enrolled into the study.

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: October 26, 2010; amendment submitted on July 1, 2011

OSI Inspection: VAI- Cetero Research in Fargo, ND.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

An OSI inspection was requested. This reviewer also carefully reviewed data sets provided by the sponsor to verify appropriate adjudication of study patches among analysis groups. A statistical consultation was requested to verify the firm's data and calculations.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the sponsor, this study was conducted in accordance with the guidelines set forth by the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP)[1], the Code of Federal Regulations for Good Clinical Practice (21 CFR Parts 50 and 56), and the Declaration of Helsinki regarding the treatment of human subjects in a study.

D. Evaluation of Financial Disclosure

Form FDA 3454 was submitted by the sponsor certifying that the sponsor has not entered into any financial arrangements with the investigators of the clinical studies. Each investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor. None disclosed such interest. Finally, the sponsor certified that the investigator(s) were not the recipient of significant payments of any sort.

IV. Review of Skin Sensitization, Irritation, and Adhesion

A. Brief Statement of Conclusions

The data submitted to ANDA 202346, for irritation, sensitization and adhesion of Mylan's Lidocaine Patch are adequate to demonstrate that it is no more irritating and has no greater potential to cause sensitization than the reference listed drug (RLD), Lidoderm® Patch. In addition, the study has demonstrated that it adheres at least as well as the RLD. This application is therefore recommended for approval from a clinical bioequivalence perspective

B. General Approach to Review of the Comparative Skin Sensitization, Irritation, and Adhesion

The overall conduct of the study and the sponsor's data were reviewed to verify that their test patch cause no more irritation than the RLD. In addition, skin sensitization potential and adhesion performance were evaluated to verify that they are no worse than expected with use of the reference patch.

C. Detailed Review of Skin Irritation and Sensitization Study

Study #LIDO-1046

Title:
Comparative Evaluation of the Cumulative Irritation and Sensitization Potential of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers

Objective
The objective of this study was to evaluate the cumulative dermal irritation and contact sensitization potential of Mylan's lidocaine transdermal patch and Lidoderm® patch manufactured by Endo Pharmaceuticals Inc. following daily applications worn for 12 hours of each treatment (cut to ¼ size) simultaneously for three weeks in 200 healthy volunteers.

Study Design
An open-label, multiple dose, randomized application site, two-treatment, three-phase study

Study Population

Inclusion Criteria
Subjects could participate if they met the following inclusion criteria:

1. Age: 18 years and older.
2. Sex: Males and/or non-pregnant, non-lactating females.
    a. Women had a negative serum beta human chorionic gonadotropin (β-HCG) pregnancy test performed within 28 days prior to the start of the study.
    b. Women were not considered of childbearing potential if one of the following was reported and documented on the medical history:
        i. postmenopausal with spontaneous amenorrhea for at least one year, or
        ii. bilateral oophorectomy with or without a hysterectomy and an absence of bleeding for at least six months, or
        iii. total hysterectomy and an absence of bleeding for at least three months
3. Weight: At least 55 kg (121lbs) for men and 48 kg (106 lbs) for women with all subjects having a Body Mass Index (BMI) less than or equal to 35 kg/m^2 but greater than or equal to 19 kg/m^2.
4. Smoking Status: Only non-tobacco users were eligible to participate in this study. All subjects were judged by the principal or sub-investigator physician listed on the Form FDA 1572 as normal and healthy during a pre-study medical evaluation performed within 28 days of the initial dose of study medication, which included:
    a. a normal or non-clinically significant physical examination, including vital signs (blood pressure, heart rate, respiratory rate, and temperature)
    b. within normal limits or non-clinically significant laboratory evaluation results for the following tests (unless otherwise specified in the Exclusion Criteria):
        - *Serum Chemistries:*
            - Sodium
            - Potassium
            - Chloride
            - BUN
            - Iron
            - Albumin

        - Total Protein
        - AST/ALT
        - Alk. Phos.
        - Calcium
        - Creatinine
        - Total Bilirubin
        - Total Cholesterol/Triglyderides
        - Phosphate
        - Uric Acid
        - Glucose
    - *Hematology:*
        - Platelet Count
        - Leukocyte Count w/ Differential
        - Hematocrit
        - Red Blood Cell Count
        - Hemoglobin
    - *Urinalysis*
        - Appearance
        - Specific Gravity,
        - Protein
        - pH
        - Microscopic Examination (performed based on clinical judgment)
    - Additional tests may have been performed, if necessary, based on standard lab panels utilized by the clinical site.

c. Negative Hepatitis B and Hepatitis C tests
d. Negative HIV test
e. Normal or non-clinically significant 12-lead ECG

<u>Exclusion Criteria</u>
Subjects could not be enrolled if they met any of the following exclusion criteria:

1. Institutionalized subjects were not used.
2. Social habits:
    a. Use of any tobacco-containing products within 1 year of the start of the study.
    b. Ingestion of any vitamins or herbal products within 7 days prior to the initial dose of the study medication.
    c. Ingestion of any alcoholic food or beverage within the 24 hours prior to the initial dose of study medication.
    d. Any recent, significant change in dietary or exercise habits.
    e. History of drug and/or alcohol abuse within one year of start of study.
3. Medications:
    a. Use of systemic or topical analgesics or antihistamines within 72 hours of initial patch application or systemic or topical corticosteroids within 3 weeks of initial patch application.
    b. Use of other medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune

response to the product (e.g., cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy, analgesics) within 14 days of initial patch application.

4. Diseases:
    a. History of any significant cardiovascular, hepatic, renal, pulmonary, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, psychological, musculoskeletal disease or malignancies unless deemed not clinically relevant by the Principal Investigator or Sub-investigator.
    b. Known history of prior tuberculosis infection, or any contact within the past 2 years with person with active tuberculosis.
    c. Acute illness at the time of either the pre-study medical evaluation or dosing.
    d. History of severe allergic reaction
5. Any reason which, in the opinion of a Principal Investigator or Sub-Investigator, would have prevented the subject from safely participating in the study.
6. Subjects who had received an investigational drug within 30 days prior to the initial dose of study medication and/or participated in any transdermal system or patch study for irritation or sensitization within the last 4 weeks.
7. Allergy or hypersensitivity to local anesthetics of the amide type, or to any other component of the lidocaine transdermal product.
8. Allergy or hypersensitivity to any tapes or adhesives (e.g., band-aids, medical tape).
9. Sunbathing or the use of tanning salons within 7 days prior to initial patch application.
10. Damaged skin in or around test sites that included sunburn, uneven skin tones, tattoos, scars or other disfigurations of the test site.
11. Use of perfumes, body lotions, powders or oils within 48 hours of initial patch application.

Reviewer's comments: *The guidance does not specify any inclusion/exclusion criteria. This reviewer feels the sponsor's inclusion/exclusion criteria are acceptable.*

Procedures/Observations, and safety measures

After screening evaluations had been performed, eligible subjects were scheduled to return to the clinical research unit for study entry.

Induction Phase

Subjects received the ¼ of lidocaine patch (Mylan) and ¼ of Lidoderm® patch simultaneously applied to a clean, dry area of the skin on the back according to the randomization scheme of the protocol. Patch application occurred every day for 21 days. The patch was worn for 12 hours. The twenty-one (21) applications (per patch) performed during this three-week phase were designated applications 1 through 21, respectively. If a subject developed an edematous reaction or a reaction of 3 or greater, according to the Irritation Rating Scale, the subject did not have any further patches applied to the same application site during the Induction phase of the study. In this case, any re-applications for Induction were made at a designated alternate site and appropriately documented and diagrammed. Medipore™ Soft Cloth Surgical Tape (3M) was applied to the two short edges of each dermal patch at the time of every application. Irritation evaluations occurred 30 to 40 minutes after each application was removed. Any evaluations made less than 30 minutes or greater than 40 minutes were documented as protocol deviations

Reviewer's comments: *As stated earlier, the firm conducted their induction phase with patches worn for 12 hours per 24 hours instead of the full 24 hours as recommended in the guidance. Based on the firm's response as stated previously in the review, the 12 hour wear is acceptable.*

Transdermal Wear Procedures

1. Subjects were instructed to keep the patches as dry as possible by avoiding showers, baths, soaking or swimming altogether during each wear period.
2. Subjects were instructed not to use tanning salons, saunas or sunbathe during the conduct of the study.
3. Subjects were not to apply heat sources of any kind (such as heating pads, electric blankets and tanning beds) to the patch.
4. Subjects engaged in normal activity for the duration of the study, avoiding vigorous exertion due to production of sweat decreasing patch adherence.
5. Subjects were to avoid wearing clothing which was constrictive around the application sites at any time during the study, in order to prevent adhesion of the patches from becoming compromised. This was documented in the informed consent forms.
6. Each subject kept a diary in which he/she recorded the length and number of baths or showers, any type of physical activity that would induce sweating, and any type of contact with water that may have affected patch adhesion. When reporting to the clinic for the applications and irritation evaluations, subjects brought their completed diary for the clinical staff to review. Diaries were collected at the end of each study week. These diaries became part of the case report forms submitted to the Sponsor at the conclusion of the study.
7. In the event that a patch fell off, it was given to a study monitor as soon as possible.
8. If less than 3 hours elapsed since the patch detachment, the patch was to be replaced by the clinical site staff and patch removal and irritation evaluation occurred at the previously scheduled time for the original application.
9. If more than 3 hours elapsed since the patch detachment, the subject was discontinued from the study.

Rest Phase

A rest period (no patch applications) of 14 days was to follow Induction application 21.

Challenge Phase

Following the Rest Phase, a Challenge application of ¼ of lidocaine patch (Mylan) and ¼ of a Lidoderm® patch simultaneously applied to a clean, dry area of the skin on the back (naïve site) according to the randomization scheme of the protocol. If the presence of residual reactions from the Induction sites made the Challenge application inadvisable, an alternative naïve site was used and documented on the subject's case report form. Patches were removed at 48 hours (±2 hours) after application. Irritation was assessed at 0.5, 24, 48 and 72 hours after removal of the patch, according to the irritation rating scale. Interpretation of a sensitization reaction was based on observation of an edematous reaction score of Grade 3 or greater and characterized by crescendo evolution of the reaction over 72 hours post-removal of the Challenge patch. This reaction was distinguished from an irritation reaction, which was anticipated to subside after patch removal.

***Reviewer's comments**: The FDA statistical reviewer is asked to identify subjects with a score of 2 or greater at 48 and/or 72 hours after challenge patch removal to identify possible sensitization reactions. If the subject had scores in the induction period that were at least as high as the scores in the challenge period, then the reaction should be considered irritation instead of sensitization.*

Endpoints

IRRITATION:
Dermal irritation was evaluated and scored at 30 to 40 minutes following each induction and challenge patch removal. Irritation reactions were graded using the following scoring system:

Scoring Scale for Evaluation of Induction and Sensitization Applications:

Dermal Response**:**

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; 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 site

Other Effects:

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

Sponsor's Statistical analysis plan
A one-sided hypothesis test was used to determine if the mean cumulative irritation score of Mylan's lidocaine patch 5% was equivalent to or better than the Lidoderm® patch (for the reference product). For the mean cumulative irritation scores, the null and alternative hypotheses were: H_0: $\mu_1/\mu_2 > 1.25$ and H_1: $\mu_1/\mu_2 \leq 1.25$, which (assuming $\mu_2 > 0$) can be written as: H_0: $\mu 1-1.25\mu_2 > 0$ and H_1: $\mu_1-1.25\mu_2 \leq 0$, where μ_1 is the mean cumulative irritation score for the test product and μ_2 is the mean cumulative irritation score for the reference product. The null hypothesis H_0 was rejected when the upper limit of the 90% confidence interval (that is the 95% upper confidence bound) for the quantity $\mu_1-1.25\mu_2$ was > 0. Mylan's lidocaine patch 5% was considered no worse than Lidoderm® Patch 5% in cumulative irritation, if the upper limit of the 90% confidence interval for the quantity $\mu_1-1.25\mu_2$ was ≤ 0.

Alternately, if the mean cumulative irritation score for the reference product was less than or equal to 1, the null and alternative hypotheses were: H_0: $\mu_1 > \mu_2 + 0.25$ and H_1: $\mu_1 \leq \mu_2 + 0.25$, where μ_1 is the mean cumulative irritation score for the test product and μ_2 is the mean cumulative irritation score for the reference product. The null hypothesis H_0 was rejected when the upper limit of the 90% confidence interval (that is the 95% upper confidence bound) for the quantity μ_1-μ_2 was > 0.25. Mylan's lidocaine patch 5% was considered no worse than Lidoderm® Patch 5% in cumulative irritation, if the upper limit of the 90% confidence interval for the quantity μ_1-μ_2 was ≤ 0.25.

A one-sided hypothesis test was used to determine if the dose limiting irritation (presented as number of days) of Mylan's lidocaine patch 5% was equivalent to or better than the Lidoderm® patch (for the reference product). For the mean number of days to dose limiting irritation, the null and alternative hypotheses were: H_0: $\mu_1/\mu_2 < 0.8$ and H_1: $\mu_1/\mu_2 \geq 0.8$, which (assuming $\mu_2 > 0$) can be written as: H0: $\mu 1 - 0.8\mu 2 < 0$ and H1: $\mu 1 - 0.8\mu 2 \geq 0$, where $\mu 1$ is the mean number of days until dose limiting irritation for the test product and $\mu 2$ is the mean number of days to dose limiting irritation for the reference product. The null hypothesis H_0 was rejected when the upper limit of the 90% confidence interval (that is the 95% upper confidence bound) for the quantity μ_1-$0.8\mu_2$ was < 0. Mylan's lidocaine patch 5% was considered no worse than Lidoderm® Patch 5% in mean number of days until dose limiting irritation, if the upper limit of the 90% confidence interval for the quantity μ_1-$0.8\mu_2$ was ≥ 0.

Discussion of Compliance

Patch application was to be completed under the direct supervision of the Cetero Research staff to ensure treatment compliance and proper patch application.

Demographics

Number enrolled: 240

Sex	Male	78
	Female	162
Age	Mean	32.2 ±12.1
Race	**Hispanic or Latino**	
	American Indian or Alaskan Native	0.42%
	White	2.50%
	Non Hispanic or Latino	
	Native Hawaiian or Other Pacific Islander	0.42%
	White, Asian	0.42%
	White, Black or African American, American Indian or Alaskan Native	0.42%
	White, Black or African American, Asian	0.42%
	Asian	0.83%
	White, Black or African American	0.83%
	White, American Indian or Alaskan Native	1.67%
	Black or African American	5.42
	White	86.68%

Results

Subject disposition:

Total number of subjects enrolled	240	100.00%
Number of premature discontinuations	22	9.17%
Discontinued by medical investigator due to AEs	1	0.42%
Subjects who elected to withdraw from study due to family emergency	1	0.42%
Subjects who elected to withdraw from study due to personal reasons	2	0.83%
Subjects who elected to withdraw from study due to schedule conflict	5	2.08%
Subjects were dropped from study due to non-compliance	13	5.42%

Summary of Subject Disposition

	Total
Randomized	240
Successfully Completed	218
Who Withdrew Consent	8
Discontinued by the Investigator	14
Discontinued by Sponsor	0
Included in Irritation Analysis	232
Included in Sensitization Analysis	218

Reviewer's comments: *The eight subjects that were excluded from the irritation analysis were those that did not have at last 16 valid irritation scores prior to discontinuation. The 22 subjects that were excluded from the sensitization analysis were those that were discontinued by the investigator (14) as well as those discontinued from the irritation analysis (8).*

Irritation: (per sponsor):

Cumulative Irritation Results (per sponsor)

Least-Squares Mean Cumulative Irritation		μ_1-1.25μ_2[1]	90% Confidence Interval[2]	μ_1-μ_2[3]	90% Confidence Interval[4]
Treatment A Mylan	Treatment B Lidoderm®				
0.654	0.741	-0.272	-0.305 – -0.239	-0.087	-0.116 –-0.06

[1] Estimated as Mylan least-squares mean – 1.25 x Lidoderm® least-squares mean.
[2] Upper 90% confidence interval < 0 indicates Mylan is non-inferior to Lidoderm®.
[3] Estimated as Mylan least-squares mean – Lidoderm® least-squares mean.
[4] Upper 90% confidence interval ≤0.25 indicates Mylan is non-inferior to Lidoderm®

Dose Limiting Irritation Results (per sponsor)

Least-Squares Mean Number of Days to Limiting Irritation*		μ_1-0.8μ_2[1]	90% Confidence Interval[2]
Treatment A Mylan	Treatment B Lidoderm®		
21.88	21.83	4.414	4.343 – 4.485

*If treatment did not produce dose-limiting irritation, the number of days was set to 22 days.
[1]Estimated as Mylan least-squares mean – 0.8 x Lidoderm® least-squares mean.
[2]Upper 90% confidence interval ≥ 0 indicates Mylan is non-inferior to Lidoderm

Frequency of Irritation Scores (Sum of Dermal Response and Other Effects Scores)

Frequency of Irritation Scores										
Time after initial patch application	Treatment A Mylan Lidocaine Patch 5%					Treatment B Lidoderm®				
Score	0	1	2	3	5	0	1	2	3	5
Day 7	67	154	10	1	0	44	176	11	1	0
Day 14	71	155	4	1	1	48	177	4	2	1
Day 21	73	153	4	1	1	68	159	2	2	1

Patients that had patches moved to at least a 2nd site due to maximum irritation reached at the previous patch site (per reviewer)

Test Patch (A)	(b) (6)
Reference Patch (C)	

FDA Statistical Review

Analysis for the mean cumulative irritation scores using mixed model

Test (Mean μ_T)	Reference (Mean μ_R)	Upper limit one-sided 95% CB (μ_T- 1.25μ_R)	Pass the Non-inferiority test
0.6541	0.7410	-0.2383	Yes

Frequency of irritation scores

Visit Day	Treatment	Score				
		0	1	2	3	5
Day 7	Test	67	154	10	1	0
	reference	44	176	11	1	0
Day 14	Test	71	155	4	1	1
	reference	48	177	4	2	1
Day 21	Test	73	153	4	1	1
	reference	68	159	2	2	1

Sensitization:

One subject, subject (b) (6) had an irritation score of 5 at the 24 hour of the challenge phase. The score resolved to 2 at the 48 and 72 hour challenge phase measurements. In addition, the

induction scores reached a 5 at patch number 10 out of 21. This would suggest that the scores seen in the challenge phase are due to irritation, not sensitization.

FDA statistical Review

No evidence of sensitization reactions were observed after the 24 hour challenge phase since neither treatment produced an irritation score greater than 2 at the 48 and 72 hour in the challenge phase of the study. Therefore, no subjects were identified as potentially sensitized.

Based on the 95% upper confidence bound for the difference in proportions, the test might exceed the reference by at most 2.03 percentage points with regard to the proportion of subjects who had sensitization.

Frequency of irritation scores for the challenge period

Evaluation day	Treatment	Irritation score			
		0	1	2	5
30 min	Test	115	98	5	0
	Reference	130	86	2	0
24 hour	Test	143	72	3	0
	Reference	141	74	2	1
48 hour	Test	194	22	2	0
	Reference	203	13	2	0
72 hour	Test	214	3	1	0
	Reference	216	1	1	0

D. Comparative Skin Sensitization Conclusion

One subject, subject (b) (6) had an irritation score of 5 at the 24 hour of the challenge phase. The score resolved to 2 at the 48 and 72 hour challenge phase measurements. In addition, the induction scores reached a 5 at patch number 10 out of 21. This would suggest that the scores seen in the challenge phase are due to irritation, not sensitization.

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No evidence of sensitization reactions were observed after the 24 hour challenge phase since neither treatment produced an irritation score greater than 2 in the challenge phase of the study. Therefore, no subjects were identified as potentially sensitized.

E. Comparative Irritation Conclusion

The data submitted to ANDA 202346 for irritation of Mylan's Lidocaine Transdermal System demonstrates that it is no more irritating than the reference listed drug.

The upper 90% confidence interval of the least-squares mean being < 0 indicates Mylan's patch is non-inferior to Lidoderm®.

The following table shows the irritation data:

	Score of 0 or 1	Score of 3 or 5	Least-squares mean cumulative irritation score	Number of Patches moved due to maximum irritation reached
Test	673	5	0.654	2
Reference	672	7	0.741	3

According to the FDA statistical analysis, the non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μT -1.25μR) was less than zero (-0.2383) and the non-inferiority test was passed for test patch versus reference patch. Therefore, the irritation potential of the test patch is not worse than that of the reference patch

F. Detailed Evaluation of Adhesion Study

Study # LIDO-1044

Title:
Single-Dose Adhesion Study of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers

Objective:
The primary objective of this study was to evaluate the adhesive properties of Mylan's lidocaine transdermal patch and Lidoderm® patch manufactured by Endo Pharmaceuticals Inc. following a 12-hour single-dose application in 24 healthy volunteers. A secondary objective was to assess acute dermal irritation after patch removal..

Study Design:
This was an open-label, single dose, randomized, one-period, two-treatment study investigating the adhesive properties of Mylan's Lidocaine Topical Patches 5% and Endo's Lidoderm® Lidocaine Patches 5% following a single application in 24 healthy adult subjects. Each subject wore two patches (one Lidoderm® and one Mylan patch) simultaneously for 12 hours. On study day 1, one Lidoderm® Patch 5% and one Mylan Lidocaine Topical Patch 5% were each applied to the subject's left back and right back, in a randomized fashion. Adhesion was assessed at 2, 4, 6, 8, 10 and 12 hours during the wear period.

Study Population:

Inclusion and exclusion criteria were identical to the Study LIDO-1046, except in inclusion #3, the weight for men was at least 60 kg (132 lbs) instead of 55 kg (121 lbs).

Procedures/Observations, and safety measures
Subjects were randomized to wear one Lidoderm patch and one Mylan lidocaine patch with the treatments applied to the subject's left back and right back, in a randomized fashion. Each subject wore two patches (1 Lidoderm and 1 Mylan patch) simultaneously for 12 hours. Subjects were housed at least 11 hours prior to patch application and until at least 1 hour after patch removal. Adhesion was assessed at 2, 4, 6, 8, 10 and 12 hours during the wear period.

Identity of Products:
Test: Lidocaine Topical Patch 5%, Lot No. R6B0017, Mylan Technologies, Inc.
Reference: Lidoderm Patch, Taikoku Seiyaku Co., Ltd., Lot No. 97278, Expiration date: 08/2010

Blinding/Randomization
This was an open-label study. Clinic staff, study monitors, and subjects were not blinded to the randomization scheme. The dermatologist or suitably trained personnel that performed the irritation scoring were blinded to the randomization scheme at the time of the evaluations. The randomization scheme used to assign each subject number to a treatment sequence was generated by Mylan Inc. The randomization scheme utilized a two-treatment, one period design and was generated prior to the first dosing period.

***Reviewer's comment**: It is unlikely that the evaluator could be entirely blinded to the sites of the test vs. reference product, since the patches themselves would have to be observed in order to assess adhesion. However, since this factor cannot be controlled since the evaluator must look at the patches to evaluate them, the data is acceptable.*

Concomitant Medications
The following are study prohibitions the subjects agreed to follow when they agreed to participate in the study:

1. Use of any medication, including over-the-counter products, for the 14 days prior to the initial dose of medication or during the study. If drug therapy other than that specified in the protocol was required during the time of adhesion and irritation assessments, the Pharmacokinetics/ Drug Metabolism Department at Mylan was consulted and a decision to continue or discontinue the subject was made based on the time the medication was administered and its pharmacology and pharmacokinetics.
2. Use of any vitamins or herbal products within seven days prior to the initial dose of the study medication or during the study.
3. Use of any medication known to induce or inhibit hepatic enzyme activity within 28 days prior to the initial dose of study medication or during the study.
4. Use of any hormonal contraceptives or hormone replacement therapy within three months prior to study medication dosing or during the study.
5. Use of any tobacco products within one year of start of study or during the study.
6. Any significant change in dietary or exercise habits throughout the duration of the study (except those imposed by the clinic confinement period of the study).
7. Use of any systemic or topical antihistamines, analgesics or corticosteroids throughout the duration of the study.

8. Use of perfumes, body lotions, powders or oils prior to transdermal system application or during the wear period.
9. Excessive sweating, long showers, baths, saunas, and soaking in water or swimming during the transdermal wear period.
10. Sunbathing or the use of tanning salons during the conduct of the study.

Reviewer's comments: *This list is acceptable.*

Endpoints:

Adhesion Scores:

0	90% or more adhered (essentially no lift of 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	<50% adhered but not detached (more than half the system lifting off of the skin but not detached
4	0% adhered-Patch detached (patch completely off the skin)

Irritation scores were the same as those used for the Study LIDO-1046.

Demographics:

Parameters	Subjects N=24	Females N=17	Males N=7
Age	31.2 ±14.4	32.9 ±16.0	30.5 ±14.1
Weight (lbs)	68.8 ± 10.0	78.5 ±10.6	64.8 ± 6.5
Height (in.)	170.4 ± 9.3	182.7 ± 5.8	165.3 ± 4.2
BMI	23.7 ± 2.3	23.5 ± 2.6	23.7 ± 2.3

Results:

Summary of Descriptive Statistics for Cumulative Adhesion Evaluation Scores (PPPA Population, N=50) (per sponsor)

	Test Treatment A	Reference Treatment B
Mean	0.55	0.92
Median	0.42	0.67
SD	0.48	0.88
Minimum	0	0.67
Maximum	1.50	3.17

Number of Subjects for Evaluated Adhesion Score at Each Time Point (per sponsor), N=24

Treatment	Score	Hour 2	Hour 4	Hour 6	Hour 8	Hour 10	Hour 12
A	0	16	11	9	15	14	12
A	1	8	12	12	7	7	10
A	2	0	1	3	2	3	1
A	3	0	0	0	0	0	1

A	4	0	0	0	0	0	0
B	0	23	19	9	10	7	4
B	1	1	4	11	6	8	9
B	2	0	0	2	4	5	6
B	3	0	1	0	2	1	1
B	4	0	0	2	2	3	4

Treatment A: test
Treatment B: reference

Reviewer's comments: *Based on the mean cumulative adhesion scores, Treatment A-test (0.55) demonstrated better adhesive characteristics compared to Treatment B-reference (0.92), over a single application period of 12 hrs. According to the frequency distribution of the adhesion scores, there were 12 test patches vs. 4 reference patches that had a score of zero, 10 test patches vs. 9 reference patches had a score of one, 1 test patch and 6 reference patches had a score of two, 1 test patch vs. 1 reference patch had a score of three, and 0 test patches vs. 4 reference patches had a score of four at hour 12. Based on this data, the adhesiveness of the test product was not inferior to that of Lidoderm®.*

FDA Statistical Review

Analysis for the mean cumulative adhesion scores using mixed model

Test (mean)	Reference (mean)	Upper limit one-sided 95% CB (μ_T-1.25μ_R)	Pass the Non-inferiority test
0.5486	0.9167	-0.2834	Yes

Frequency of mean cumulative adhesion scores

Mean	0	0.167	0.333	0.5	0.667	0.833	1	1.167	1.333	1.5	2	2.167	2.667	3.167
Test	4	4	4	3	2	1	1	2	2	1	0	0	0	0
Reference	3	4	1	2	5	0	0	2	1	2	1	1	1	1

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was less than zero (-0.2834) and the non-inferiority test was passed for test versus reference patch. Therefore, the adhesion potential of the test is non-inferior to that of the reference.

Safety:
Five (5) subjects experienced a total of seven adverse events (AEs) over the course of the study. The AEs were mild in intensity. No SAEs were reported. The only adverse event (AE) reported was application site erythema which was reported by 4/24 (16.7%) subjects following application of Treatment A and 3/24 (12.5%) subjects following application of Treatment B.

Adhesion Conclusion

Based on the mean adhesive cumulative scores, the sponsor concluded that Treatment A (0.55) demonstrated better adhesive characteristics compared to Treatment B (0.92), over a single application period of 12 hrs.

Frequency Distribution of Adhesion Scores

	Adhesion Score				
	0	1	2	3	4
Test	12 (50%)	10 (42%)	1 (4%)	1 (4%)	0
Reference	4 (17%)	9 (38%)	6 (25%)	1 (4%)	4 (17%)

Based on this data, the adhesiveness of the test product was determined to be not inferior to that of Lidoderm®.

According to the FDA statistical analysis, the non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was less than zero (-0.2834) and the non-inferiority test was passed for test versus reference patch. Therefore, the adhesion potential of the test is non-inferior to that of the reference.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

No significant safety concerns were identified in this study.

B. Description of Adverse Events

There were a total of two thousand, nine hundred seventy-three (2973) additional AEs reported by two hundred thirty-six (236) subjects over the course of the study. The AEs were mild and moderate in severity. There was on (1) serious adverse events (SAEs) reported.

- Eight hundred thirty-seven (837) AEs including: application site anesthesia, application site erythema, application site pain, application site paresthesia, application site pruritis, application site warmth, and pruritis were considered probably related to the sponsor's Lidocaine Patch 5%. There was one (1) AE (skin irritation) considered unlikely/remotely related to Mylan's Lidocaine Patch 5%.
- Six hundred six (606) AEs including: pain, pruritis, skin burning sensation, and skin irritation were considered unrelated/not related to Mylan's Lidocaine Patch 5%.
- Eight hundred fourteen (814) AEs including: application site erythema, application site pain, application site paresthesia, application site pruritis, myalgia, and pruritis were considered probably related to RLD. There was one (1) AE (skin irritation) considered unlikely/remotely related to Lidoderm® Patch 5%.
- Six hundred five (605) AEs including: application site pain, pain, pruritis, skin burning sensation, and skin irritation were considered unrelated/not related to RLD

There were no deaths reported for this study. There was one SAE reported over the course of the study. Subject (b) (6) experienced appendicitis on 13 May 2010 (Day 16 of induction period). The SAE (appendectomy) was severe and considered to be unrelated/not related to Mylan's Lidocaine Patch 5% and/or Lidoderm® Patch 5%.

Frequently Reported Adverse Events by **Treatment A (Test)** (per sponsor), N=240

Adverse Event	Subjects who experienced indicated AE at least once by intensity		
	Mild	Moderate	Severe
Application site anesthesia	(b) (6)		
Application site erythema			
Application site pain			
Application site paresthesia			
Application site pruritus			
Application site warmth			
Pain			
Pruritus			
Skin burning sensation			
Skin irritation			
Total number of subjects reporting at least one AEs			

Frequently Reported Adverse Events by **Treatment B (Reference)** (per sponsor), N=240

Adverse Event	Subjects who experienced indicated AE at least once by intensity		
	Mild	Moderate	Severe
Application site erythema	(b) (6)		
Application site pain			
Application site paresthesia			
Application site pruritus			
Pain			
Pruritus			
Skin burning sensation			
Skin irritation			
Total number of			

subjects reporting at least one AEs			

VI. Relevant Findings From Division of Scientific Investigations and/or Other Consultant Reviews

OSI inspection:
VAI- Cetero Research, Fargo, ND

No FDA Form-483 was issued. However, the following verbal observations communicated to the firm:

1. Record review of computer generated pharmacy Drug Inventory control records for Study LIDO-1044 reveals the pharmacy's record of the randomization codes for placement of the patches on subjects has been "over" written manually and changed by pharmacy staff to reflect the correct placement as set in the protocol. The firm's SOPs and computer program, called "Study Monitor Program" are incomplete, in that; there is no current computer program that will print in and for pharmacy the protocol placement of the patches; and the SOPs fail to provide guidance for randomization documentation of dermatological studies. In addition, pharmacy has no applicable guidelines for the dermatology studies to follow.

2. Case document review for Subject (b) (6) for Study RI0-0159, LIDO-1046 shows a positive HCG on final-exit of study. The documents for the follow up of this pregnant subject were incomplete in that; documentation of final outcome of pregnancy was not in study files and SOPs are vague and do not address pregnancy follow up or guidance for where the final documentation should be placed when subjects are found pregnant at the end of a study. Subject's medical records noted a viable newborn delivered on (b) (6). The inspector explained to the management that case files should contain a complete final outcome-history of all subjects and the SOPs should address this matter.

The firm's management promised immediate correction, including possibly applying Fargo site-specific SOPs to both pharmacokinetic and dermatological studies. DBGC recommends that the studies be accepted for review.

***Reviewer's comments**: This reviewer agrees with the OSI comments and feels that the discrepancy would not significantly impact the results of the study.*

VII. Conclusion and Recommendation

A. Conclusion

The data submitted to ANDA 202346, for irritation, sensitization and adhesion of Mylan's Lidocaine Patch are adequate to demonstrate that it is no more irritating and has no greater

potential to cause sensitization than the reference listed drug (RLD), Lidoderm® Patch. In addition, the study has demonstrated that it adheres at least as well as the RLD.

B. Recommendation

This application is recommended for approval from a clinical bioequivalence perspective

APPEARS THIS WAY ON ORIGINAL

APPENDIX

Appendix A: Draft Guidance for Lidocaine (patch/topical; 6 pages, May 2007)
Recommended studies: 2 studies

1. Type of study: Fasting Design: Single-dose, in-vivo, using three topical patches
Strength: 5%; 700 mg/ patch
Subjects: Normal healthy males and females, general population.

2. Type of study: Skin irritation/sensitization study Design: Single-dose, in-vivo (preceded by an induction phase and a rest period)
Strength: 5%; 700 mg/ patch
Subjects: Normal healthy males and females, general population

Relevant additional comments regarding the BE study with clinical endpoint:

1. This product is intended to provide local pain relief of post-herpetic neuralgia at the application site. The RLD labeling directs that the patch should be cut to the appropriate size for the intended skin area to be treated. Therefore, your patch design must allow for the patch to be safely cut to a smaller size. In addition the active surface area of your patch should be comparable to that of the RLD.

2. Conduct the skin irritation and sensitization studies in healthy volunteers. Continuous same-site exposure is necessary to provide the maximal provocative exposure that is intended in the skin irritation and sensitization studies.

3. The clinical review team recommends that irritation and sensitization be evaluated in the same study. However, they should be evaluated with separate analyses. Primary endpoint(s) for each of these analyses need to be clearly defined prior to the start of the study. The two primary endpoints should be considered as co-primary endpoints, e.g., for each of them, the study must demonstrate that the test patches are no worse than the reference listed drug (RLD). In addition, the corresponding primary analysis for each primary endpoint needs to be specified in your protocol. Secondary endpoint(s) (if any) should also be clearly defined prior to the start of the study.

4. The OGD recommends that your patch have a design that can be cut to a smaller size as described in the labeling of the RLD. One-fourth of a test patch and one-fourth of the reference patch should be applied to the same individuals simultaneously for 21 days during the induction phase of the study. The patches should be applied continuously to the same sites and replaced with a new one-fourth patch 3 times weekly. The 21-day induction phase is to be followed by a 2-week rest period and then a single 48- hour challenge application of each one-fourth test system to a naïve site.

5. No make-up, creams, lotions, powders or other topical products should be applied to the skin area where the patch will be placed, as this could affect adhesive performance or induction of irritation.

6. Subjects should return for visits three times per week for irritation scoring and patch replacement during the induction phase. Scoring of skin reactions should be performed by a trained and blinded observer at each patch removal, using an appropriate scale. Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritation. An example of an appropriate irritation scale is as follows:

   DERMAL RESPONSE
   0 = no evidence of irritation
   1 = minimal erythema, barely perceptible
   2 = definite erythema, readily visible; 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 application site

   OTHER EFFECTS
   0 = no other observations
   1 = slight glazed appearance
   2 = marked glazed appearance
   3 = glazing with peeling and cracking
   4 = glazing with fissures
   5 = film of dried serous exudates covering all or part of the patch site
   6 = small petechial erosions and/or scabs

7. If the degree of irritation for a given patch is such that a new patch cannot be applied to the same site, then the product should be discontinued and the highest score observed prior to patch discontinuation should be carried forward for all remaining observations in the irritation analysis. Subsequent applications of the product may be applied to a different skin site in order to complete the induction phase for the skin sensitization evaluation.

8. To be valid for cumulative irritation analysis, the sequential patch applications for the particular product must not be detached from the skin for longer than 24 hours during the 21 day induction period (unless the patch was removed for an unacceptable degree of irritation).

9. Scoring of skin irritation should not be limited to reactions that appear to be related to only one component of the generic system. Any skin reaction should be included in the irritation analysis, regardless of the area of the patch associated with the reaction.

10. The cumulative irritation score, the total number of observations with a maximum irritation score for each product, the number of patches that were removed due to an unacceptable degree of irritation, and the number of days until sufficient irritation occurred to preclude patch application should be calculated for each test and reference product, and a statistical

analysis of the comparative results should be performed. In addition to the cumulative irritation scores, please provide a frequency chart showing the number of applications of each product with each irritation score on each study day. To support approval, the test product must be no more irritating than the reference product.

11. Subjects should be questioned about any itching, burning, pain or soreness at the application site. These symptoms should be recorded and compared between products.

12. To be included in the sensitization analysis, patches should be evaluated by a trained and blinded observer at 30 minutes, and at 24, 48 and 72 hours after removal of the challenge patch. Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of sensitization.

13. 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. Your protocol will need to include a clear objective definition of a sensitization reaction a priori. The test product should be no worse than the reference product with regard to the rate of sensitization.

14. If a patch completely detaches, it should be replaced within 24 hours and the subject should continue in the study. If a patch cannot be replaced within 24 hours or a subject does not know when the patch fell off, the subject should be excluded from both the irritation and sensitization analyses of that product. The subject should note the date and time of detachment as soon as it occurs.

15. If you are not relying upon adhesion data from the skin irritation and sensitization study to establish adequate adhesion performance of your product, then you may consider establishing criteria for using tape to reinforce any patches that are lifting during the study. In addition, you should consider replacing any detached patches within 24 hours to ensure valid cumulative irritation and sensitization induction.

16. Adhesion data should be collected during the course of the study to document that adhesion of the products is adequate for the intended induction of skin irritation and sensitization, even if you are not relying upon this study to establish adequate adhesive performance of your product.

17. Cutting patches to a smaller size is likely to change the shape as well as the size of the patch and may change adhesive performance of the patch. Therefore, adhesion data from your skin irritation and sensitization study may not be adequate to demonstrate that your to-be-marketed patch adheres at least as well as the RLD. Therefore, you should consider collecting adhesion data during your PK bioequivalence study, using an acceptable 5-point (0 to 4) scale. Reinforcement of the patches should therefore not be allowed in the PK study if it is also being used to demonstrate adequate adhesion, and you may need to increase the size of that study to allow for detached patches. Alternately, you may conduct a separate paired single-application adhesion study to demonstrate that your product adheres at least as well as the RLD.

18. For adhesion analysis, please provide adhesion scores for a single application of the intended duration of patch wear using a scale such as the following:

    0 = ≥ 90% adhered (essentially no lift off of 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 of the skin)
    3 = < 50% adhered by not detached (more than half the system lifting off of the skin without falling off)
    4 = patch detached (patch completely off the skin)

    For any patch that detaches, please carry forward a score consistent with detachment for all remaining observation periods.

19. The cumulative adhesion score and the time from application until patch detachment should be calculated for each test and reference product, and a statistical analysis of the comparative results should be performed. In addition to the mean cumulative adhesion scores, please provide a frequency chart showing the number of patches in each group with each adhesion score at each observation. Please also provide data regarding the number of patches that detached and duration of wear prior to detachment. To support product approval, the test product must adhere at least as well as the reference product.

20. Due to likely differences in appearance of the patches, blinding of the observer/evaluator may not be possible, especially for evaluation of patch adhesion, which requires direct observation of the patch itself. However, efforts should be made to blind the evaluation of irritation and sensitization.

21. The same investigator should perform all irritation evaluations and/or all patch adherence evaluations for each individual subject. The sponsor should consider training all investigators and potential alternates according to the protocol in order to ensure consistency in evaluations.

22. The study results should show that the proposed product does not produce any greater degree of irritation or sensitization than that produced by the RLD and that the adhesive performance over the intended duration of wear is at least as good as that of the RLD.

23. The analysis populations should be defined separately for irritation and sensitization and should be defined per product instead of per subject. Each property should have a separate test population and reference population for each product.

24. The Population Definitions for the Per-Protocol (PP) evaluation for each parameter should include the following:

    • Irritation Analysis– a product needs to be worn for the entire 3 weeks to be valid for the cumulative irritation evaluation OR if a patch is removed due to excessive irritation, it should be included using Last Observation Carried Forward (LOCF).

• Sensitization Analysis – all subjects that wear the product for the full 21 day induction phase and for 48 hours during the challenge phase and return for evaluation 24 hours after removal of the challenge patch (OR if the product is removed prior to 48 hours due to a sensitization reaction that caused the product to be removed) should be included using LOCF.

25. As the irritation and adhesive properties may be sensitive to climate changes, we prefer that the study be conducted in multiple centers with varying climate conditions

26. Please refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, please refer to the Guidance for Industry: "Handling and Retention of BA and BE Testing Samples" (May 2004). Retention samples should be randomly selected from each drug shipment by each study site prior to dispensing the medication to subjects. Samples must be randomly selected at each investigational site where the medication is dispensed and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples should not be returned to the sponsor at any time.

27. It is recommended that an independent party generates and holds the randomization code throughout the study in order to decrease the chance of unblinding and to minimize bias. The sponsor may generate the randomization code if not involved in packaging and labeling of study drugs.

28. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow verification of the treatment identity for each subject.

29. The OGD generally does not provide sample size recommendations. It is your responsibility to include sufficient patients in the study to demonstrate non-inferiority of skin irritation potential and adhesion performance of your product compared to the reference listed drug (RLD).

30. When submitting results of skin irritation, sensitization and adhesion studies in an ANDA, study data should be submitted in electronic format including the following information:

    a. A list of file names included in the CD or diskette(s) with a simple description of the content of each file. A document file containing a description of each dataset and an explanation of the variables included in each of the SAS datasets. (See http://www.fda.gov/cder/guidance/2353fnl.pdf regarding "define.pdf.")

All SAS transport files should use .xpt as the file extension and should not be compressed. The SAS program to open the transport files and an explanation of the format for each SAS variable should be included.

b. You should identify and provide the list of subjects that are included and excluded from each population analysis separately for each product. The variable(s) derived for analysis should include specific data such as treatment per patch, analysis populations (e.g., per protocol (PP) for each of the three analyses), irritation scores, days to patch detachment, days to patch removal, etc. You should also provide the reason(s) for exclusion of subjects from each of the PP and other population(s) used for analysis. These variables could be included in a single SAS transport file.

c. SAS transport file(s) – covering all variables collected in the Case Report Forms (CRFs) per subject: You should provide a summary dataset to include such variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, medical history, compliance and comments, etc.

Primary data sets should consist of two data sets: No Last Observation Carried Forward (No-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).

d. The methods used to derive the variables should be included and explained.

e. The following line listings should be provided for each subject:

- Center/site, subject number
- Race, sex, age
- Adverse events, reason for discontinuation
- Analysis populations for each patch:
    - Test product PP population for irritation analysis (yes/no), reason for exclusion
    - Reference product PP population for irritation analysis (yes/no), reason for exclusion
    - Test product PP population for sensitization analysis (yes/no), reason for exclusion
    - Reference product PP population for sensitization analysis (yes/no), reason for exclusion
    - Test product PP population for adhesion analysis (yes/no), reason for exclusion
    - Reference product PP population for adhesion analysis (yes/no), reason for exclusion

- Patch removed due to strong skin irritation reaction (yes/no)
- Time from first patch application to removal for unacceptable irritation

- Cumulative number of patches removed for unacceptable irritation
- Cumulative number of detached patches
- Reinforced with tape (yes/no)
- Number of days until reinforcement with tape
- New patch application due to detachment (yes/no)
- Date of a new patch application due to detachment
- Time from application to detachment
- Designation of skin sensitization (yes/no)
- Per each visit if data exist
    - Visit number, date of visit, days from baseline
    - Reason for exclusion from each PP population per visit
    - Time from patch application to detachment for both test and reference products
    - Irritation scores for each product
    - Sensitization scores for each product
    - Adhesion scores for each product
    - Identity of the evaluator
    - adverse events
    - reason for discontinuation

31. The OGD is currently evaluating the appropriate statistical tests that should be used to analyze clinically meaningful differences between products with regard to skin irritation, sensitization and adhesion.

32. Please note that the guidance provided in this letter supersedes information provided in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products*, which has been withdrawn and is currently under revision.

33. Please be advised that the information given in this letter is general in nature and represents the current thinking of the Clinical Review Team and the Office of Generic Drugs. The OGD recommends that you submit protocols to the Clinical Review Team for review and comment prior to conducting the studies.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202346 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Lidocaine Patch, 5%

The Division of Clinical Review has completed its review and the data submitted to ANDA 202346 are adequate to demonstrate that the irritation potential of Mylan Technologies, Inc's Lidocaine Patch, 5% is no worse than that of the RLD.

The data also demonstrate minimal potential of Mylan's Lidocaine Patch, 5% to induce sensitization, as also in the case of the reference listed drug (RLD), Lidoderm® Patch.

The data also demonstrate that the adhesive performance of Mylan's Lidocaine Patch, 5% is at least as good as that of the RLD.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. 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,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
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/

NICOLE LEE
05/31/2013

JOHN R PETERS
05/31/2013

DALE P CONNER
05/31/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

CHEMISTRY REVIEWS

Recommendation: Adequate with Post Marketing Commitment

ANDA:

☒ **Approval**

☐ **Information Request – Minor**

(_____days for applicant to response)

☐ **Complete Response - Minor**

☐ **Complete Response – Major**

ANDA 202346

Amendment Review

Drug Name/Dosage Form	Lidocaine Topical Patch 5%
Strength	5%
Reviewer(s)	Robert T. Berendt, Ph.D.
Applicant	Mylan Technologies, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Complete Response Amendment, SD-30	05/06/2015
Quality/Response to IR, SD-31	08/05/2015

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)		Adequate	04/24/2015	Reviewed by C.B. Senanayake; ANDA DS firm's specifications are consistent with the DMF holder's.
14652	Type III	Mylan Technologies	Release Liner	Adequate	11/25/2014	Reviewed by R.Berendt
11404	Type III	Mylan Technologies	Backing film	Adequate with IR	09/23/2014	Reviewed by R.Berendt
(b) (4)	Type III	(b) (4)		Adequate	01/17/2014	Reviewed by R. Berendt
	Type IV			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:
Refer to previous product-quality review, dated 24-APR-2015

FACILITIES:

Overall Recommendation:			
Drug Substance			
Function	**Site Information**	**FEI#**	**Status**
			(b) (4)
Drug Product			
Function	**Site Information**	**FEI #**	**Status**
Drug Product Manufacture, Packaging, Labeling, and Testing Site	Mylan Technologies 110 Lake Street St. Albans, VT 05478	1220747	Approve OPF Re-eval Date: 04/30/2015
			(b) (4)

Following this page, 34 Pages Withheld in Full as (b)(4)

List of Deficiencies To Be Communicated by Information Request or Complete Response:

The firm's submission is **Adequate with Post Marketing Commitment**.

(b) (4)

[redacted]

(b) (4)

.

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier ☐

First Generic – 3 Tier ☐

Other Criteria under "Exceptions List" for Table 1 of SOP – 3 Tier ☒

B. Approvability: – ***No, Major deficiency --*** CMC is inadequate: Major drug-product deficiencies; DS DMF pending amendment review. BE, Labeling, Clinical Bio, and EES are acceptable.

ANDA 202346

Lidocaine Topical Patch, 5%

Mylan Technologies Inc

Review #3

Robert T. Berendt, Ph.D., CR#3
Xihao Li, Ph.D., CR#1, 2
Division of Chemistry I
Office of Generic Drugs

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2. REVIEW: 03 1
3. REVIEW DATE: 03/28/2014; 09/19/2014; 10/20/2014; 11/25/2014; 01/14/2015; 03/16/2015 1
4. REVIEWER: Robert T. Berendt (CR#3), Xihao Li (CR#1,2) 1
5. PREVIOUS DOCUMENTS: 1
6. SUBMISSION(S) BEING REVIEWED: 1
7. NAME & ADDRESS OF APPLICANT: 2
8. DRUG PRODUCT NAME/CODE/TYPE: 2
9. LEGAL BASIS FOR SUBMISSION: 2
10. PHARMACOL. CATEGORY: Local Anesthetic 2
11. DOSAGE FORM: Topical Patch 2
12. STRENGTH/POTENCY: 5% 2
13. ROUTE OF ADMINISTRATION: Topical 2
14. Rx/OTC DISPENSED: _xx__Rx ___OTC 2

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B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:.... **Error! Bookmark not defined.**

Chemistry Review Data Sheet

1. ANDA: 202346

2. REVIEW: 03

3. REVIEW DATE: 03/28/2014; 09/19/2014; 10/20/2014; 11/25/2014; 01/14/2015; 03/16/2015

4. REVIEWER: Robert T. Berendt (CR#3), Xihao Li (CR#1,2)

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date	Location
New ANDA	10/25/2010	SD-1
Quality Information	11/10/2010	SD-2
Quality Stability Information	12/15/2010	SD-3
Patent & Exclusivity/Patent Information	01/27/2011	SD-4
Patent & Exclusivity/Patent Information	02/20/2011	SD-5
Quality Information	03/08/2011	SD-7
Patent & Exclusivity/Patent Information	04/05/2011	SD-8
Quality/Response to Information Request	03/08/2012	SD-11

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Location
Quality/Multiple Categories	06/27/2013	SD-22
Quality/Multiple Categories	10/21/2013	SD-23
Quality/Response to Information Request (DP Samples)	10/28/2013	SD-25
Quality/Response to ECD	11/05/2014	SD-26
Quality/Response to ECD	01/07/2015	SD-27
Quality/Response to Information Request	02/19/2015	SD-28

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies Inc
Address:	110 Lake Street St. Albans, VT 05478
Representative:	Joseph J. Sobecki
Telephone:	(304) 599-2595, extension 6429
Fax:	(304) 285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None

Non-Proprietary Name (USAN): Lidocaine Patch 5%
Code Name/# (ONDC only):
Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

Mylan provides the following with regard to the basis for this ANDA:
1) The name of the Reference Listed Drug is Lidoderm (NDA 020612);
2) The dosage form of the Reference Listed Drug is Topical Patch;
3) The strength of the Reference Listed Drug is 5%.

10. PHARMACOL. CATEGORY: Local Anesthetic

11. DOSAGE FORM: Topical Patch

12. STRENGTH/POTENCY: 5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _xx__Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__xx___Not a SPOTS product

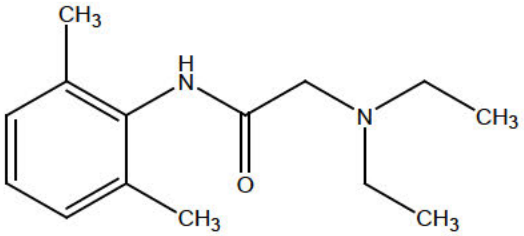
15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__xx____Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Non-proprietary Name (INN):	Lidocaine
Chemical Names:	Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)- 2-(Diethylamino)-2',6'-acetoxylidide
CAS Registry No.:	137-58-6
Empirical Formula:	$C_{14}H_{22}N_2O$
Molecular Structure:	



Molecular Weight:	234.34 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Pending		Pending review of submission dated 02/18/2015 and the response to the filing review request submitted 02/23/2015. Adequate per last review (CR#6) by Shahnaz T. Read (09/22/2014).
14652	III	Mylan Technologies	Release Liner	1	Adequate	11/25/2014	Reviewed by R.Berendt
11404	III	Mylan Technologies	Backing film	3	Adequate with IR	09/23/2014	Reviewed by R.Berendt
(b) (4)	IV	(b) (4)		4			
	III			1	Adequate	01/17/2014	Reviewed by R. Berendt

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Pharmacology/toxicology consult has found the use of polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film in the formulations acceptable. The Pharma/tox review was done by A. Emami 04/22/2011.

Clinical consult found the overall patch design to be adequate with regard to patient perception and safety. The consult was prepared by Trueman W. Sharp, 06/16/2014.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES overall	Acceptable	02/03/2014	
Methods Validation	NA		
Labeling	Acceptable	03/10/2015	B. Turner
Bioequivalence	Adequate	11/24/2014	Yumei Ye
Clinical Bio	Adequate	05/31/2013 05/28/2013	N. Lee (CLINICAL) H. Li (BIOMETRICS)
EA	NA		
Radiopharmaceutical	NA		
Clinical consult	Adequate	06/16/2014	T.W. Sharp
IVPT Method Consult	Inadequate	04/16/2015	S. Raney

Name of Facility	**Functions of the Facility** (manufacturer, testing lab, etc.)	**EES Status** (adequate, pending, to be entered into EES, etc)
Drug Substance		
(b) (4)		

[redacted] (b) (4)		
Drug Product		
Mylan Technologies 110 Lake Street St. Albans, VT 05478 FEI: 1220747	Manufacturing, packaging, labeling, quality control testing of components and finished dosage form	Acceptable (02/03/2014, R. SAFAAIJAZIR)
[redacted] (b) (4)		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _xx___ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 202-346

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to major CMC deficiencies. Labeling, BE, Clinical Bio, and EES are acceptable.

Designation of Major deficiency is based on the firm's [redacted] (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

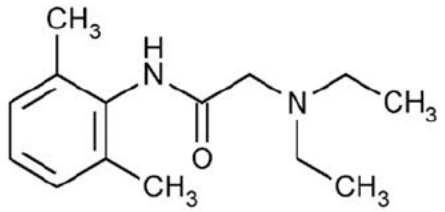
NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DESCRIPTION: Lidocaine patch 5% is comprised of an adhesive material containing 5% lidocaine USP, which is applied to a pigmented polyethylene/polyester backing film printed with brown ink and covered with a silicone coated polyester film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm × 14 cm.

Lidocaine is chemically designated as 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-acetamide, has an octanol: water partition ratio of 43 at pH 7.4, and has the following structure:



Each adhesive patch contains 140 mg of lidocaine, USP (50 mg per gram adhesive) in

a polyisobutylene adhesive matrix.

Two lidocaine 5% topical patch products are approved for the U.S. marketplace: Lidoderm (RLD, NDA 20612, Teikoku Pharma USA) and ANDA 200675 (Watson). (b) (4) [redacted] The difference in the matrix leads to differences in the manufacturing method and solubility of the drug substance within the final product.

(b) (4)

[redacted]

Following this page, 130 Pages Withheld in Full as (b)(4)

A APPENDICES

A.1 Facilities and Equipment (biotech only)

A.2 Adventitious Agents Safety Evaluation

A.3 Novel Excipients

A.4 Nanotechnology Product Information

Office of Pharmaceutical Science MAPP 5015.9 Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____Yes; __X__No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No__X__ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?_____
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____ API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____(Complete 8); No_____ (go to 9).
8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____

9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial?_____ _____

R REGIONAL INFORMATION

R.1 Executed Batch Records

Acceptable

R.2 Comparability Protocols

N/A

R.3 Methods Validation Package

N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

N/A

B. Environmental Assessment Or Claim Of Categorical Exclusion

N/A

III. List Of Deficiencies To Be Communicated

ANDA: 202346
Applicant: Mylan Technologies Inc.
Drug Product: Lidocaine Topical Patch 5%

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ☐ YES ☒ NO

A. Deficiencies

The following deficiencies represent major deficiencies:

(b) (4)

Following this page, 2 Pages Withheld in Full as (b)(4)

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist: Robert T. Berendt/ 03/28/2014; 09/19/2014; 10/20/2014; 11/25/2014; 01/14/2015; 03/21/2015; 04/16/2015
Secondary Reviewer: Dhaval K. Gaglani/09/22/14; Caroline Strasinger
Supervisor: Bhagwant Rege/
Project Manager: Brijet Burton/

TYPE OF LETTER: CR: Major CMC deficiencies

Final Version for DARRTS 2/26/2013
CMC and Bio are deficient. Labeling is AC. Clinical Bio and EES are pending.

Chemist: Xihao Li/2/20/2013
Secondary Reviewer: Bhagwant Rege/ 12/11/2012, 2/22/2013
Deputy Division Director:2/25/2013
Project Manager: Trang Tran2/26/2013

ANDA 202346

Lidocaine Topical Patch, 5%

Mylan Technologies Inc

Review #2

Xihao Li, Ph.D.
Division of Chemistry I
Office of Generic Drugs

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Chemistry Review Data Sheet

1. ANDA: 202346

2. REVIEW: 02

3. REVIEW DATE: 11/20/2012

4. REVIEWER: Xihao Li

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
New ANDA (SD#1)	10/25/2010
Quality Information (SD#2)	11/10/2010
Quality Stability Information (SD#3)	12/15/2010
Patent & Exclusivity/Patent Information (SD#4)	01/27/2011
Patent & Exclusivity/Patent Information (SD#5)	02/20/2011
Quality Information (SD#7)	03/08/2011
Patent & Exclusivity/Patent Information (SD#8)	04/05/2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Quality/Response to Information Request (SD#11)	03/08/2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies Inc
Address:	110 Lake Street St. Albans, VT 05478
Representative:	Wayne Talton
Telephone:	(304) 599-2595, extension 6551
Fax:	(304) 285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None

Non-Proprietary Name (USAN): Lidocaine Patch 5%
Code Name/# (ONDC only):
Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

Mylan provides the following with regard to the basis for this Abbreviated New Drug Application:
1) The name of the Reference Listed Drug is Lidoderm (NDA 020612);
2) The dosage form of the Reference Listed Drug is Topical Patch;
3) The strength of the Reference Listed Drug is 5%.

10. PHARMACOL. CATEGORY:

Local Anesthetic

11. DOSAGE FORM:

Topical Patch

12. STRENGTH/POTENCY:

5%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _xx__Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__xx___Not a SPOTS product

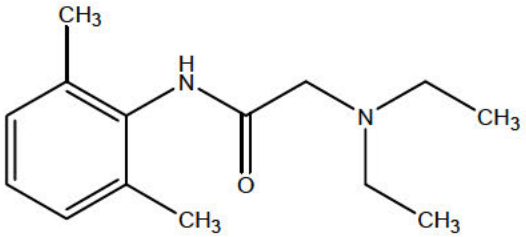
15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__xx___Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Non-proprietary Name (INN):	Lidocaine
Chemical Names:	Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)- 2-(Diethylamino)-2',6'-acetoxylidide
CAS Registry No.:	137-58-6
Empirical Formula:	$C_{14}H_{22}N_2O$
Molecular Structure:	



Molecular Weight:	234.34 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	2/6/2013	Reviewed by A. Langowski
14652	III	Mylan Technologies	Release Liner	1	Adequate	10/12/2011	Reviewed by X. Li
11404	III	Mylan Technologies	Backing film	3	Adequate	04/27/2011	Reviewed by S. Read
(b) (4)	IV	(b) (4)		4			
	III			1	Adequate	10/14/2011	Reviewed by by X. Li

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Pharmacology/toxicology consult has found the use of polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film in the formulations acceptable. The Pharma/tox review was done by A. Emami 04/22/2011.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Acceptable	11/25/2012	B. Turner
Bioequivalence	Deficient	2/25/2013	R. Wang
Clinical Bio	Pending		
EA	NA		
Radiopharmaceutical	NA		

Chemistry Review Data Sheet

Name of Facility	**Functions of the Facility** (manufacturer, testing lab, etc.)	**EES Status** (adequate, pending, to be entered into EES, etc)
Drug Substance		
(b) (4)		
Drug Product		
Mylan Technologies 110 Lake Street St. Albans, VT 05478	Manufacturing, packaging, labeling, quality control testing of components and finished dosage form	OC Recommendations (pending)
(b) (4)		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _xx___ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY ON ORIGINAL

Chemistry Review for ANDA 202-346

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

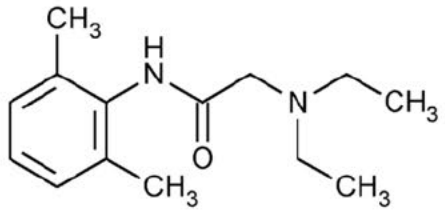
NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DESCRIPTION: Lidocaine patch 5% is comprised of an adhesive material containing 5% lidocaine USP, which is applied to a pigmented polyethylene/polyester backing film printed with brown ink and covered with a silicone coated polyester film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm × 14 cm.

Lidocaine is chemically designated as 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-acetamide, has an octanol: water partition ratio of 43 at pH 7.4, and has the following structure:



Each adhesive patch contains 140 mg of lidocaine, USP (50 mg per gram adhesive) in a polyisobutylene adhesive matrix.

B. Description of How the Drug Product is Intended to be Used

DOSAGE AND ADMINISTRATION: Apply lidocaine patch 5% to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. (See HANDLING AND DISPOSAL) Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides.

When lidocaine patch 5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

HOW SUPPLIED: Lidocaine patch 5% is available as the following:

Carton of 30 patches, packaged into individual child-resistant envelopes.

NDC 0378-9055-93

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

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to minor deficiencies.

A APPENDICES

A.1 Facilities and Equipment (biotech only)

A.2 Adventitious Agents Safety Evaluation

A.3 Novel Excipients

A.4 Nanotechnology Product Information

Office of Pharmaceutical Science MAPP 5015.9 Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____Yes; _____No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No_____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____ API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____(Complete 8); No_____ (go to 9).
8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____

9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial?_____ _____

R REGIONAL INFORMATION

R.1 Executed Batch Records

Acceptable

R.2 Comparability Protocols

N/A

R.3 Methods Validation Package

N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

N/A

B. Environmental Assessment Or Claim Of Categorical Exclusion

N/A

III. List Of Deficiencies To Be Communicated

ANDA: 202346
Applicant: Mylan Technologies Inc.
Drug Product: Lidocaine Topical Patch 5%

The deficiencies presented below are minor deficiencies:

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

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(b) (4)

14.

15.

16.

17.

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20.

21.

22.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters and in-process material attributes
- Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's **Generic Drugs: Information for Industry** webpage:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist: Xihao Li/2/20/2013
Secondary Reviewer: Bhagwant Rege/ 12/11/2012, 2/22/2013
Deputy Division Director:2/25/2013
Project Manager: Trang Tran2/26/2013

TYPE OF LETTER: CMC and Bio are deficient. Labeling is AC. Clinical Bio and EES are pending.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIHAO LI
02/27/2013

TRANG Q TRAN
02/27/2013

BHAGWANT D REGE
02/27/2013

BING CAI
02/27/2013

ANDA 202346

Lidocaine Topical Patch, 5%

Mylan Technologies Inc

Xihao Li, Ph.D.
Division of Chemistry I
Office of Generic Drugs

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7. NAME & ADDRESS OF APPLICANT: 2
8. DRUG PRODUCT NAME/CODE/TYPE: 2
9. LEGAL BASIS FOR SUBMISSION: 2
10. PHARMACOL. CATEGORY: 2
11. DOSAGE FORM: 2
Topical Patch 2
12. STRENGTH/POTENCY: 2
13. ROUTE OF ADMINISTRATION: 2
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Chemistry Review Data Sheet

1. ANDA: 202346

2. REVIEW: 01

3. REVIEW DATE: 10/20/2011

4. REVIEWER: Xihao Li

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
New ANDA (SD#1)	10/25/2010
Quality Information (SD#2)	11/10/2010
Quality Stability Information (SD#3)	12/15/2010
Patent & Exclusivity/Patent Information (SD#4)	01/27/2011
Patent & Exclusivity/Patent Information (SD#5)	02/20/2011
Quality Information (SD#7)	03/08/2011
Patent & Exclusivity/Patent Information (SD#8)	04/05/2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies Inc
Address:	110 Lake Street St. Albans, VT 05478
Representative:	Wayne Talton
Telephone:	(304) 599-2595, extension 6551
Fax:	(304) 285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None

Non-Proprietary Name (USAN): Lidocaine Patch 5%
Code Name/# (ONDC only):
Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

Mylan provides the following with regard to the basis for this Abbreviated New Drug Application:
1) The name of the Reference Listed Drug is Lidoderm (NDA 020612);
2) The dosage form of the Reference Listed Drug is Topical Patch;
3) The strength of the Reference Listed Drug is 5%.

10. PHARMACOL. CATEGORY:

Local Anesthetic

11. DOSAGE FORM:

Topical Patch

12. STRENGTH/POTENCY:

5%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _xx__Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__xx___Not a SPOTS product

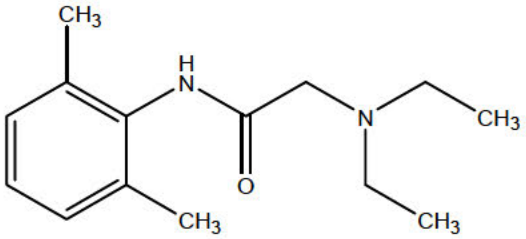
15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__xx___Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Non-proprietary Name (INN):	Lidocaine
Chemical Names:	Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)- 2-(Diethylamino)-2',6'-acetoxylidide
CAS Registry No.:	137-58-6
Empirical Formula:	$C_{14}H_{22}N_2O$
Molecular Structure:	



Molecular Weight:	234.34 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	10/07/2011 by X. Li	
14652	III	Mylan Technologies	Release Liner	1	Adequate	10/12/2011 by X. Li	
11404	III	Mylan Technologies	Backing film	3			
(b) (4)	IV	(b) (4)		4			
	III			1	Adequate	10/14/2011 by X. Li	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Pharmacology/toxicology consult has found the use of polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film in the formulations acceptable. The Pharma/tox review was done by A. Emami 04/22/2011.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	11/2/2011	M. Stock
Methods Validation	NA		
Labeling	Deficient	08/11/2011	T. Vu
Bioequivalence	Deficient	06/02/2011	U. M. Munshi
EA	NA		
Radiopharmaceutical	NA		

Chemistry Review Data Sheet

Name of Facility	**Functions of the Facility** (manufacturer, testing lab, etc.)	**EES Status** (adequate, pending, to be entered into EES, etc)
Drug Substance		
(b) (4) [redacted]		
Drug Product		
Mylan Technologies 110 Lake Street St. Albans, VT 05478	Manufacturing, packaging, labeling, quality control testing of components and finished dosage form	OC Recommendations (AC - 12/29/2010)
(b) (4) [redacted]		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __xx__ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY ON ORIGINAL

Chemistry Review for ANDA 202-346

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

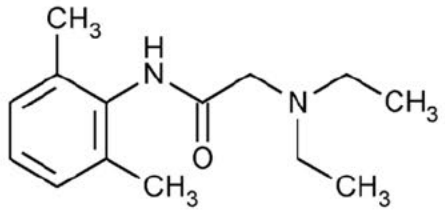
NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DESCRIPTION: Lidocaine patch 5% is comprised of an adhesive material containing 5% lidocaine USP, which is applied to a pigmented polyethylene/polyester backing film printed with brown ink and covered with a silicone coated polyester film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm × 14 cm.

Lidocaine is chemically designated as 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-acetamide, has an octanol: water partition ratio of 43 at pH 7.4, and has the following structure:



Each adhesive patch contains 140 mg of lidocaine, USP (50 mg per gram adhesive) in a polyisobutylene adhesive matrix.

B. Description of How the Drug Product is Intended to be Used

DOSAGE AND ADMINISTRATION: Apply lidocaine patch 5% to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. (See HANDLING AND DISPOSAL) Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides.

When lidocaine patch 5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

HOW SUPPLIED: Lidocaine patch 5% is available as the following:

Carton of 30 patches, packaged into individual child-resistant envelopes.

NDC 0378-9055-93

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

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to minor deficiencies.

A APPENDICES

A.1 Facilities and Equipment (biotech only)

A.2 Adventitious Agents Safety Evaluation

A.3 Novel Excipients

A.4 Nanotechnology Product Information

Office of Pharmaceutical Science MAPP 5015.9 Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____Yes; _____No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No_____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____ API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____(Complete 8); No_____ (go to 9).
8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____

9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial?_____ _____

R REGIONAL INFORMATION

R.1 Executed Batch Records

R.2 Comparability Protocols

R.3 Methods Validation Package

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated

ANDA: 202346
Applicant: Mylan Technologies Inc.
Drug Product: Lidocaine Topical Patch 5%

The deficiencies presented below are minor deficiencies:

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

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B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional long-term stability data that may be available.

2. Please send us your drug product samples and RLD patch samples for evaluation.

3. Your Labeling and Bioequivalence information is pending review. Deficiencies, if any, will be communicated to you separately.

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist: Xihao Li/10/20/2011
Secondary Reviewer: Bhagwant Rege
Project Manager: Esther Chuh / 12/13/11

TYPE OF LETTER: CMC NA Minor

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIHAO LI
12/30/2011

CHRISTINA L KIRBY
12/30/2011

BING CAI
12/30/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

PHARM/TOX REVIEWS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Anesthesia, Analgesia and Addiction Products

CONSULTATION

Application number:	ANDA 202346
Consult number:	2011-0485
Date:	April 4, 2011
To:	Ted C. Palat FDA/CDER/OPS/OGD/DLPS
Through:	Adam Wasserman, Ph.D. Supervisory Pharmacologist, FDA/CDER/OND/ODEII/DAAAP Bob Rappaport, M.D. Division Director FDA/CDER/OND/ODEII/DAAAP
From:	Armaghan Emami, Ph.D. Pharmacology/toxicology reviewer FDA/CDER/OND/ODEII/DAAAP
Subject:	Evaluate acceptability of polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film in Mylan's Lidocaine Patch 5%
Date of submission:	October 25, 2010
Consult date:	January 13, 2011
Date Response Requested:	April 13, 2011

Summary:

Mylan is submitting this ANDA seeking approval of Lidocaine Transdermal Patch 5%. This 5% Patch is a generic version of Lidoderm® (lidocaine) Patch 5%, which was approved on 03/19/1999 for relief of pain associated with post-herpetic neuralgia (NDA 020612). The purpose of this consult from the Office of Generic Drugs (OGD) was to evaluate the safety of several excipients used in the generic patch which exceed levels in Agency-approved topical products. The specific consult request is the following:

The sponsor has submitted pharm/tox data to justify the use of polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film in their formulation. Please review the data and determine if the levels of these ingredients are safe for human use.

Mylan's Lidocaine Patch 5% [redacted] (b) (4) The [redacted] (b) (4) backing [redacted] (b) (4) is a pigmented polyethylene / polyester [redacted] (b) (4) film. The [redacted] (b) (4) is the polyisobutylene adhesive matrix containing the active pharmaceutical ingredient, Lidocaine, USP. The [redacted] (b) (4) is a transparent polyester film coated with silicone release agent. The release liner is removed from the patch and discarded prior to use.

To support the position that the polyisobutylene polymers are acceptable for use, the sponsor states that polyisobutylenes are listed as direct and indirect human food ingredient in accordance with Code of Federal Regulations. The sponsor has also submitted non-clinical data to justify the use of polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film in their formulation.

[redacted] (b) (4) Polyisobutylene [redacted] (b) (4) [redacted] (b) (4) used in Mylan's Lidocaine Patch 5% are outside the IIG limits for the transdermal route of administration. [redacted] (b) (4) [redacted] Polyisobutylenes are inert hydrocarbon polymers and their high-molecular weight [redacted] (b) (4) [redacted]

The Sponsor conducted USP biological reactivity tests (USP <87> and <88>) to address concerns of safety of Polyisobutylenes [redacted] (b) (4) [redacted] (b) (4) These studies lack clinical pathology, histopathology, and toxicokinetic evaluations. According to the Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) the Sponsor should qualify these excipients through conduct of general toxicity studies. It is important that the studies include complete clinical pathology, histopathology, and toxicokinetic analysis. However following reasons reduce the safety concerns and we do not need additional toxicology studies:

1. Polyisobutylenes are inert molecules and are commonly used for Transdermal Delivery Systems (TDS). Since they have high-molecular weight and low solubility in water they have very slow absorption (less likely pass through the skin barrier).
2. The USP biological data showed no *in vitro* and/or *in vivo* biologic reactivity with Polyisobutylenes
3. These chemicals are in FDA-approved products

The backing and release liner component materials used in Mylan's Lidocaine Patch 5% are not listed in the IIG but are present in [redacted] (b) (4) other FDA approved

products. The level of Pigmented Polyethylene is (b) (4) than previously approved product and the level of Silicone Coated Polyester Film is (b) (4) than previously approved product. These excipients are not in direct contact with skin.

The Sponsor conducted (International Organization for Standardization (ISO) compliant biological tests of material biocompatibility to assess the safety of extracts of as well as whole pigmented polyethylene/polyester film and silicone coated polyester material. According to container closure guidance (May 1999), these studies are considered sufficient to provide evidence of acute local safety of the individual chemicals which may migrate into the patch. However these studies provided limited support to evaluate longer term exposures and do not support the absence of genotoxicity of the compounds. Additionally there is a lack of information on identity and potential levels of leachables from this transdermal patch which could potentially be used to address concerns.

In summary, the levels of Polyisobutylenes (adhesive) are acceptable (b) (4) (b) (4)

The levels of Pigmented Polyethylene (contained in the backing film) and Silicone Coated Polyester Film (contained in the release liner) are acceptable since there is no direct skin contact with these ingredients. However there is a lack of information on the identity or potential levels of extractables or leachables from the patch to further confirm acceptability of this generic product. The specific response to OGD can be found at the conclusion of this document.

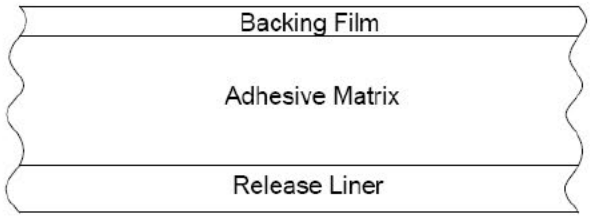
Drug Information

Drug: Lidocaine Patch 5%

Relevant INDs, NDAs, BLAs and DMFs: NDA 020612 and DMF (b) (4)

Drug Formulation: Lidocaine, USP drug substance is manufactured by (b) (4) (b) (4) as described in Drug Master File (DMF (b) (4)). The finished product will be manufactured by Mylan Technologies. Mylan's Lidocaine Patch 5% is a single piece, self-adhering system for topical administration of Lidocaine. The system contains 140 mg of lidocaine in a polyisobutylene (PIB) adhesive matrix. The figure below is a schematic representation of Mylan's Lidocaine Patch 5%, which is designed to be therapeutically equivalent to Teikoku Pharma's (distributed in the U.S. by Endo Pharmaceuticals) LIDODERM® (lidocaine patch 5%).

Schematic Diagram of Mylan's of Lidocaine Patch 5%



Mylan's Lidocaine Patch 5% contains Lidocaine, [redacted] (b) (4) polyisobutylene (PIB) adhesives, a pigmented polyethylene / polyester backing film (PE/PET) and a siliconized polyester (PET) release liner.

Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Lidocaine Patch 5%

Components	Pharmaceutical Function	% w/w	mg per patch
Active Ingredient			
Lidocaine, USP	Active Ingredient	5.00	140.00
Inactive Ingredients			
Polyisobutylene [redacted] (b) (4)	Adhesive	[redacted] (b) (4)	[redacted] (b) (4)
Theoretical Total Matrix		100.00	[redacted] (b) (4)
Components of the Delivery and Packaging System			
Pigmented Polyethylene / Polyester Film (MEDIFLEX® 1501)	Backing	NA	[redacted] (b) (4)
Brown Ink [redacted] (b) (4)	Imprinting Ink	NA	[redacted]
Silicone Coated Polyester Film (MEDIRELEASE® 2249)	Release Liner	NA	[redacted]

The pharmaceutical functions of excipients used in Mylan's product are different with Reference Listed Drug (RLD). See below table provided by the Sponsor.

Comparison of Excipients in Mylan's Lidocaine Patch 5%

Function	Mylan's Lidocaine Patch 5%	LIDODERM®
Adhesive	Polyisobutylene	Polyacrylic acid
[redacted] (b) (4)		

Mylan's hypothesis for the new formulation:

[Verbatim from Sponsor] Mylan recognized LIDODERM® (lidocaine patch 5%) is an extremely complex formulation composed of many inactive ingredients. Due to this complexity and in deference to the LIDODERM® Orange Book patents, [redacted] (b) (4) Rather, Mylan chose to develop a simpler generic formulation using traditional transdermal adhesive technology. [redacted] (b) (4)

(b) (4) [redacted] Therefore, the final design incorporated the simpler drug-in-adhesive design with the same patch size and the same ability to be cut as the RLD, but featuring a thinner, more efficient delivery matrix.

The conditions of use described in the labeling proposed by Mylan for this product have been previously approved for the listed drug, LIDODERM® Patch 5%. The maximum recommended daily dose is up to three patches, only once for up to 12 hours within a 24-hour period. This information is based on a comparison of Mylan's proposed labeling to that currently approved for the reference listed drug. See below table provided by the Sponsor.

	LISTED DRUG	PRODUCT PROVIDED FOR IN THIS APPLICATION
DRUG NAME:	LIDODERM® (lidocaine) Patch 5%	Lidocaine Patch 5%
CONDITIONS OF USE:	Indicated for relief of pain associated with post-herpetic neuralgia	Indicated for relief of pain associated with post-herpetic neuralgia
ACTIVE INGREDIENT(S):	Lidocaine	Lidocaine, USP
DOSAGE FORM(S):	Patch	Patch
ROUTE OF ADMINISTRATION:	Topical	Topical
STRENGTH(S):	5%	5%
BIOEQUIVALENCY DATA:	Mylan has conducted a single-dose fasting *in vivo* bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, LIDODERM® Patch 5%, an adhesion evaluation study and an evaluation of cumulative irritation and sensitization study as detailed in the protocols included in Section 5.3.1.2. The results of these studies are included in this application.	

Comments on Novel Excipients:

1. (b) (4) [redacted] Polyisobutylene (b) (4) [redacted] (b) (4) [redacted] used in Mylan's Lidocaine Patch 5% are outside the IIG limits for the transdermal route of administration. (b) (4) [redacted]

(b) (4) [redacted]

Table below copied from the ANDA submission:

Table Ia: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Adhesive Matrix

Components	Pharmaceutical Function	% w/w	mg/ patch	Maximum Level listed in the FDA *IID*[1] (mg)	Quality Standards
Active Ingredients					
Lidocaine, USP	Active Ingredient	5.00	140.00	NA	DMF (b) (4) and Mylan Specification
Inactive Ingredients					
Polyisobutylene (b) (4)	Adhesive (b) (4)	(b) (4)			(b) (4)
Theoretical Total Matrix		100.00	(b) (4)		

[1]FDA's electronic Inactive Ingredients Database (IID) for Approved Drug Products (last updated July 15, 2010) for transdermal/topical route of administration. All excipient levels are either below the maximum level listed in the IID for this dosage form or a comprehensive review of the safety is provided. 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.

(b) (4)

The investigator's justification of safety of PIBs:

- To support the position that the proposed polymers are acceptable for use, the sponsor has provided a general statement that PIBs are commonly used as an inactive ingredient in pharmaceutical patch formulations that have been approved by the FDA. (b) (4)
- The Sponsor conducted USP Biological Reactivity Tests (USP <87> and <88>) to address concerns of safety of these excipients.

2. The backing and release liner component materials used in Mylan's Lidocaine Patch 5% are not listed in the IIG but are present in Mylan's other FDA approved products. The level of Pigmented Polyethylene is (b) (4) (b) (4) than a previously approved product and the level of Silicone Coated Polyester Film is (b) (4) than a previously approved product.

(b) (4)

[redacted]

Table below copied from the ANDA submission:

Table Ib: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Other Components of Mylan's Lidocaine Patch 5%.

Components	Pharmaceutical Function	mg/ patch	Maximum Level listed in the FDA *IID*[1] (mg)	Quality Standards
Pigmented Polyethylene / Polyester Film (MEDIFLEX® 1501)	Backing	[redacted] (b) (4)		Mylan DMF 11404 and Mylan Specifications
Brown Ink (b) (4)	Imprinting Ink			(b) (4)
Silicone Coated Polyester Film (MEDIRELEASE® 2249)	Release Liner			Mylan DMF 14652 and Mylan Specifications

(b) (4)

[redacted]

Comments on Impurities/Degradants of Concern

There is no request for evaluation of Impurities/degradants and leachable/ extractable for this product from OGD.

Toxicology:

The Sponsor conducted USP biological reactivity tests (USP <87> and <88>) to address concerns of safety of Polyisobutylenes (b) (4) (b) (4) and ISO Biological tests to assess the safety of pigmented polyethylene/polyester film, and silicone coated polyester.

(b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

A complete battery of tests have been performed in accordance with the International Organization for Standardization (ISO) for the biological evaluation of medical devices, ANSI/AAMI/ISO 10993, to assess the safety of the polyethylene/polyester backing film, MEDIFLEX® 1501 as a skin contact surface device with prolonged contact duration of greater than 30 days. This battery was comprised of studying biological effects in standard cytotoxicity assays, irritation as well as delayed-type hypersensitivity (sensitization). In addition, an acute systemic toxicity evaluation was performed in mice in accordance with the requirements of the International Organization for Standardization. All studies were performed in the contract laboratory of North American Science Associates (NAMSA). A brief summary of each study was provided in this IND (not included in this review). Overall, the studies summarized herein demonstrate that MEDIFLEX® 1501 has a low order of acute systemic toxicity, is not cytotoxic, and has negligible potential to cause irritation or delayed-type dermal contact sensitization. Based on these findings, MEDIFLEX® 1501 is considered to be acceptable for human use as a backing film intended for use in transdermal medical products.

- **Silicone coated polyester.**

Copied from the current ANDA submission (Safety Assessment Summary for Use of MEDIRELEASE® 2249 in a Transdermal Patch System).

A series of tests have been performed in accordance with the International Organization for Standardization (ISO) for the biological evaluation of medical devices, ANSI/AAMI/ISO 10993, to assess the safety of the polyester release liner, MEDIRELEASE® 2249 as a potential contact surface device. This battery was comprised of studying biological effects in standard cytotoxicity assays, skin irritation, as well as local tolerance following intracutaneous and intramuscular implantation. In addition, an acute systemic toxicity evaluation was performed in mice accordance with the requirements of the Inter Organization for Standardization. All studies were performed in the contract laboratory of North American Science Associates (NAMSA). A brief summary of each study was provided in this IND (not included in this review). Overall, the studies summarized herein demonstrate that MEDIRELEASE® 2249 has a low order or acute systemic toxicity, is not cytotoxic, and has negligible potential to cause irritation. Based on these findings, MEDIRELEASE® 2249 is considered to be acceptable human use as a release liner intended for use in the final packaging of transdermal medical products.

Evaluation of support:

See Executive Summary for details.

Response to to OGD consult request:

- From the nonclinical pharmacology toxicology perspective, the levels of Polyisobutylenes (adhesive) are acceptable (b) (4)

- The identity and levels of excipients comprising the backing film and release liner are acceptable (b) (4) (b) (4)

- There is a lack of information on the identity and levels of potential leachables to further assess acceptability of this generic product. To support a comprehensive evaluation of safety, the ANDA submission should contain information on potential leachables through conduct of extractable and, if necessary, leachable studies. A toxicological risk assessment of identified substances which determines the safe level of exposure via the dermal route of administration should be provided. The approach for toxicological evaluation of the safety of extractables or leachables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (i.e. chronic or short-term usage).

(b) (4)

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/s/

ARMAGHAN EMAMI
04/22/2011

ADAM M WASSERMAN
04/22/2011

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04/22/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

STATISTICAL REVIEWS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number: 202346

Drug Name: Lidocaine Patch, 5%

Indication(s): Pain associated with post-herpetic neuralgia

Reference Listed Drug: Lidoderm Patch, 5%, Teikoku Pharma USA

Applicant: Mylan Technologies, Inc.

Date(s): Submitted October 26, 2010; July 1, 2011 (amendment); August 9, 2012 (amendment)

Biometrics Division: DB6

Statistical Reviewer: Huaixiang Li, Ph.D.

Concurring Reviewers: Stella Grosser, Ph.D.

Medical Division: Division of Clinical Review (DCR) in OGD

Clinical Team: Nicole Lee, Pharm.D.

Keywords: local analgesic agent, irritation, sensitization, adhesion, non-inferiority, matched pair analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and recommendations

The test patch was found to be non-inferior to the reference patch for irritation, sensitization, and adhesion.

1.2 Brief overview of clinical studies

This application consists of two studies: a two-period irritation and sensitization study #LIDO-1046 and an adhesion study #LIDO-1044.

Study #**LIDO-1046** was an open-label, multiple dose, randomized application site, two-treatment, three-phase study of Mylan's Lidocaine Patch, 5%, versus the RLD, Lidoderm® Patch, 5%. Each subject received one-fourth (1/4)[1] cut patch of the test product and one-fourth (1/4) cut patch of the reference product applied simultaneously to separate sites on the back per every 24 hours and worn for a 12-hour period each day for 21 days. Irritation evaluations occurred 30 to 40 minutes after each application was removed. During the challenge phase, following a 14-day rest period ending on Day 36, subjects who completed the induction phase received one-fourth (1/4) cut patches of each of the two products which were applied to naïve skin sites on the back for 48 hours. Irritation was assessed at 0.5, 24, 48 and 72 hours after removal of the patch, according to the irritation rating scale. This study compared skin irritation and sensitization potential of Mylan's test product with the reference product.

A total of 240 patients was enrolled in the study.

Study **#LIDO-1044** was an open-label, single dose, randomized, one-period, two-treatment study investigating the adhesive properties of Mylan's Lidocaine Topical Patches 5% and Teikoku Pharama Lidoderm® Patches 5% following a single application in 24 healthy adult subjects. On study day 1, one Lidoderm® Patch 5% and one Mylan Lidocaine Topical Patch 5% were each applied to the subject's left back and right back, in a randomized fashion. Each subject wore two patches (one Lidoderm® and one Mylan patch) simultaneously for 12 hours. Adhesion was assessed at 2, 4, 6, 8, 10 and 12 hours during the wear period.

Twenty-four subjects were enrolled into this study to evaluate adhesion only.

1.3 Statistical issues and findings

Irritation and sensitization study #LIDO-1046

Irritation

[1] This is in accord with the guidance to use one-fourth (1/4) cut patch of the test and reference products for the irritation and sensitization study. The guidance says that it needs to be a full patch to correctly determine adhesive property in the adhesion study.

I) The non-inferiority analyses based on the mean cumulative irritation scores showed that the one-sided 95% upper confidence bound (CB) for the adjusted mean difference between test μ_T and reference μ_R (μ_T -1.25μ_R) was less than zero (-0.2383). The non-inferiority test was passed for test patch versus reference patch and the irritation potential of the test patch is considered not worse than that of the reference patch.

II) Analyses based on dichotomized mean cumulative irritation scores:
Analyses were conducted to compare the test and reference with regard to the proportions of subjects who had mean cumulative irritation score greater than or equal to 1 and to 2. Sometimes the proportions P_T for the test product were lower than the proportions P_R for reference (P_T -P_R<0). Based on the 95% upper confidence bound for the difference in proportions, the test might exceed the reference by at most -1.2 (negative) percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 (P_T -P_R= -6.0%). And also, the test might exceed the reference by at most 1.2 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2 (P_T -P_R= -0.4%).

Sensitization

No subject was considered to be potentially sensitized to any of the products tested.

The test patch might exceed the reference patch by at most 2.03 percentage points based on the 95% upper confidence bound for the difference in sensitization rates. The non-inferiority standard such as order of magnitude of the possible range has not yet been specified by OGD to date. If the non-inferiority limit were established as low as 2.1%, the test patch has been shown to be non-inferior to the reference patch.

Adhesion study #LIDO-1044

I) The mean cumulative adhesion scores were analyzed using a mixed linear model. The one-sided 95% upper confidence bound (-0.2834) for the adjusted mean difference μ_T -1.25μ_R was less than zero and the non-inferiority test was passed for test versus reference. Hence, the adhesion potential of the test product is considered non-inferior to that of the reference product.

II) Based on the 95% upper confidence bound for the difference in proportions for mean scores, the test might exceed the reference by at most 6.8 and 1.2 percentage points with regard to the proportion of subjects who had mean scores greater than or equal to 1 (≥10% detached) and to 2 (≥25% detached), respectively.

2 INTRODUCTION

2.1 Overview

Lidocaine Patch, 5% is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin. Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. LIDODERM® (lidocaine patch 5%) is comprised of an

adhesive material containing 5% lidocaine, which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm x 14 cm. Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base.

This review focuses on the studies submitted to ensure that the skin irritation and sensitization potential of this proposed generic topical patch product are no greater than those of the RLD and that the generic product adheres to the skin as well as the RLD over the intended duration of wear.

2.2 Data sources

The data were submitted electronically. The data files are located in the following directories:

Protocol #LIDO-1046: Irritation and Sensitization study
\\cdsesub1\EVSPROD\ANDA202346**0000**\m5**53**-clin-stud-rep**531**-rep-biopharm-stud**5312**-compar-ba-be-stud-rep\lido-cln-**1046**

Protocol #LIDO-1044: Adhesion study
\\cdsesub1\EVSPROD\ANDA202346**0008**\m5**53**-clin-stud-rep**531**-rep-biopharm-stud**5312**-compar-ba-be-stud-rep\lido-**1044**-sas

Remark

The original submission was received on October 26, 2010 and two amendments were received on July 1, 2011 and August 9, 2012.

On August 9, 2012, Sponsor submitted their responses based on the OGD request for information: "*Please submit a justification as to why the skin irritation and sensitization study was conducted with patches worn for 12 hours per 24 hours instead of the full 24 hours as recommended in the FDA Bioequivalence Draft Guidance.*" The clinical reviewer comments that in the sponsor's response,

> *"[t]he firm states that to be reflective of normal wear and to be consistent with the currently approved labeling for the reference listed drug, they chose the 12 hours per 24 hours of wear instead of the full 24 hours. They note that the FDA Draft Guidance for Lidocaine Patch allows for up to 24 hours detachment in any one of the sequential patch application periods. They state this provision suggests that intermittent application is acceptable for determination of comparable irritation or sensitization potential. The firm conducted 2 pilot clinical cumulative irritation studies which included testing of Lidoderm based on a continuous patch wear design, with application every 24 hrs and included testing of Lidoderm based on intermittent patch wear, aligned with the approved RLD label, both for 21 days. The data showed that a range of scores are achieved following either study design. According to the sponsor, the results illustrate that the intermittent wear study design is at least as provocative as (and trending to be more provocative than) the continuous wear study design."*

OGD Reviewer's comments: *"Based on the pilot cumulative irritation studies conducted by the firm, it was shown that both continuous and intermittent wear produced similar irritation results. Thus, this reviewer agrees that the study design for the cumulative irritation is acceptable."*

In this report, all tables, unless otherwise specified, are taken from FDA clinical reviewer's and/or the sponsor's report. Analysis results and tables calculated by FDA statistical reviewer are noted in the text and/or the title of the tables.

3 STATISTICAL EVALUATION

3.1 Statistical methodologies

Each subject received two patches simultaneously in both studies: test and reference patches in the skin irritation and sensitization study (#LIDO-1046) and in the adhesion study (#LIDO-1044). As a result, observations taken from the same subject might be correlated. For the analysis of continuous data, linear mixed models were used; the random effects in the mixed model structure assessed and reflected the correlation of observations. Also for matched pair dichotomous data, the McNemar, Clopper-Pearson, and, Schuirmann tests were used to compare the test and the reference in the difference between proportions.

3.1.1 Continuous data

<Mixed Model>

The statistical reviewer used a mixed model with treatment (TRT) as a fixed effect and SUBJECT as a random effect to analyze the mean cumulative irritation score and adhesion score (primary endpoint in study #1046 and 1044, respectively).

The statistical method for continuous data uses the estimate of the adjusted mean difference μ_T - $1.25\mu_R$, to test the hypotheses

H_0: $\mu_T - 1.25\mu_R > 0$ vs H_1: $\mu_T - 1.25\mu_R \leq 0$

where μ_T is the mean response for the test and μ_R is the mean response for the reference. One-sided 95% confidence intervals (CIs) were obtained based on the estimated means. If the upper limit of the CI is less than or equal to 0, the null hypothesis is rejected and the test may be considered non-inferior to the reference. Otherwise it is concluded that the test may be worse than the reference.

The SAS® (Version 9.2) PROC MIXED statements for the relevant analysis are

```
Proc Mixed Data = <dataset name>;
Class Subject TRT;
Model X = TRT/DDFM = SATTERTH;
Repeated TRT / sub = Subject type = fa0(2) r;
Estimate 'Test – 1.25*Reference' int -0.25 TRT 1 -1.25/cl alpha = 0.1;
LSMEANS TRT;
```

Run;

3.1.2 Binary data

<Matched pairs dichotomized analysis>

Additional (secondary) endpoints considered were the dichotomized mean cumulative irritation score and irritation score per evaluation time and rate of sensitization (study 1046); and dichotomized mean cumulative adhesion score and adhesion score per evaluation time (study 1044). Methods based on the work of McNemar, Clopper-Pearson, and Schuirmann were used to compare the test and reference with regard to the binary endpoints (proportions). The McNemar test is a common method for matched pair dichotomized analysis. The Clopper-Pearson method is considered as an "exact" test specifically for small proportions. Schuirmann (2008) examined another method and showed it better preserves type I error for small proportions. The testing procedure was as follows.

For each method used to assess the non-inferiority of the test versus reference, a 95% upper confidence bound for the difference of the proportions between test and reference was calculated.

Let
p_T = rate of the test, p_R = rate of the reference (p_T and p_R might be irritation rates, sensitization rate, or adhesion rates, depending on the analysis);
n = total number of subjects;
b = number of subjects with a negative outcome (irritation, sensitization or detachment) using the test but not the reference;
and c = number of subjects with a negative outcome (irritation, sensitization or detachment) using the reference but not the test.
Hypotheses: H_0: $p_T - p_R > \delta$ vs H_1: $p_T - p_R \leq \delta$, where δ *is* a given non-inferiority bound.

Data on two outcomes from matched pairs

		Reference	
		Score≥crit	Score<crit
Test	Score≥crit	a	b
	Score<crit	c	d
Total n=a+b+c+d			

*: Critical value (crit) was used to dichotomize the score.

The difference of $p_T - p_R$ may be estimated by the quantity (b – c)/n.

Based on McNemar's test, the 95% upper confidence bound (U) for the quantity $p_T - p_R$ was calculated as

$$U = \frac{(b-c)}{n} + \frac{1}{n} + 1.645\frac{\sqrt{(b+c) - \frac{(b-c)^2}{n}}}{n}$$

This formula for the upper confidence bound is algebraically the same as that given by Fleiss (1981, p117).

Based on the Clopper-Pearson test (1934), the 95% upper confidence bound (U) for the quantity p_T - p_R was calculated as:

$$U = \left[1+\frac{n-x}{(x+1)F_{2(x+1),2(n-x),\alpha/2}}\right]^{-1} \qquad \text{if } b \geq c$$

or,

$$U = -\left[1+\frac{n-x+1}{xF_{2x,2(n-x+1),1-\alpha/2}}\right]^{-1} \qquad \text{if } b < c$$

where x = | b-c | and α=0.10. $F_{2(x+1),\,2(n-x),\,\alpha/2}$ denotes the (1-α/2) quantile from the F distribution with degrees of freedom 2(x+1) and 2(n-x). $F_{2x,\,2(n-x+1),\,1-\alpha/2}$ denotes the α/2 quantile from the F distribution with degrees of freedom 2x and 2(n-x+1).

Based on the Schuirmann (2008) test, the 95% upper confidence bound (U) for the quantity p_T - p_R was calculated as follows.

Let $$Z = \frac{\hat{\delta}+CC-U}{\sqrt{\frac{\xi^*-U^2}{n}}},$$

Here, $$\hat{\delta}=\frac{b-c}{n}, CC=\frac{1}{n}, \xi^*=\max\left(\frac{b+c}{n}, |U|\right).$$

The value of U is the 95% upper confidence bound for the quantity p_T - p_R when Z is equal to $Z_{\alpha/2}$ = -1.645, α=0.10.

For any given non-inferiority bound δ, the null hypothesis H_0 may be rejected if this 95% upper confidence bound U for the quantity p_T - p_R is less than or equal to δ, that is: U ≤ δ. Rejection of the null hypothesis H_0 supports the conclusion of non-inferiority of the test to the reference. The non-inferiority standard δ is yet to be decided by OGD.

3.2 Protocol LIDO-1046: Evaluation of irritation and sensitization

3.2.1 Study design and endpoints

Objectives

The objective of this study was to evaluate the cumulative dermal irritation and contact sensitization potential of Mylan's lidocaine transdermal patch and Lidoderm® patch manufactured by Teikoku following daily applications worn for 12 hours of each treatment (cut to ¼ size) simultaneously for three weeks.

Study design

Study #LIDO-1046 was an open-label, multiple dose, randomized application site, two-treatment, three-phase study of Mylan's Lidocaine Patch, 5%, versus the RLD, Lidoderm® Patch, 5%. Each subject received one-fourth (1/4) cut patch of the test product and one-fourth (1/4) cut patch of the reference product which applied simultaneously to separate sites in clean, dry areas on the back according to the randomization scheme of the protocol. Each patch was worn for a 12-hour period each day (over every 24 hours) for 21 days. Irritation evaluations occurred 30 to 40 minutes after each application was removed. Any evaluations made less than 30 minutes or greater than 40 minutes were documented as protocol deviations. The twenty-one (21) applications (per patch) performed during this three-week phase were designated applications 1 through 21, respectively. If a subject developed an edematous reaction or a reaction of 3 or greater, according to the Irritation Rating Scale, the subject did not have any further patches applied to the same application site during the Induction phase of the study. In this case, any re-applications for Induction were made at a designated alternate site and appropriately documented and diagrammed.

Following the 14-day Rest Phase, a Challenge application of ¼ of a lidocaine patch (Mylan) and ¼ of a Lidoderm® patch simultaneously applied to a clean, dry area of the skin on the back (naïve site) according to the randomization scheme of the protocol. If the presence of residual reactions from the Induction sites made the Challenge application inadvisable, an alternative naïve site was used and documented on the subject's case report form. Patches were removed at 48 hours (±2 hours) after application. Irritation was assessed at 0.5, 24, 48 and 72 hours after removal of the patch, according to the irritation rating scale.

This study compared skin irritation and sensitization potential of Mylan's test product with the reference product.

Irritation study: Induction period (Study Days 1 to 22)	Rest period (Study Days 23 to 35)	Sensitization study: Challenge period (Study Days 36 to 41)

Treatments

Article	Description
Test	One-fourth (1/4) Lidocaine Topical Patch, 5%, Lot No. R6B0017, Mylan
Reference	One-fourth (1/4) Lidoderm® Patch, 5%, Lot No. 97278, expired 08/2010, Teikoku

Outcome variables

The following scales were used by the sponsor for evaluating both irritation and sensitization:

Scoring Scale for Evaluation of Induction and Challenge Phase Applications:
Dermal Response**:**

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; 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 site

Other Effects:

A	(0) Slight glazed appearance
B	(1) Marked glazing
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 total score was derived by adding the Dermal Response score and Other Effects score (treated numerically).

Endpoints

Irritation study

Primary endpoint:

Mean cumulative irritation scores for each test article per subject were obtained by averaging all irritation scores over the induction period (total scores from visit day 1 to 21 dividing by the number of observations, 21).

Secondary endpoints:

- Proportion of subjects who had mean cumulative irritation scores ≥ 1
- Proportion of subjects who had mean cumulative irritation scores ≥ 2

- Proportion of subjects who had irritation scores ≥ 1 on Day 7, 14, and 21.
  Proportion of subjects who had irritation scores ≥ 2 on Day 7, 14, and 21.

Sensitization study

Endpoint: Based on the FDA clinical reviewer's comments: "*Please evaluate sensitization as a test vs. reference difference in the proportion of patches producing a potential sensitization reaction, defined as a score of 2 or greater at 48 and/or 72 hours after challenge patch removal. If the subject had scores in the induction period that were at least as high as the scores in the challenge period, then the reaction should be considered irritation instead of sensitization. Mean scores are not useful in evaluating sensitization potential.*"

3.2.2 Subject disposition

The FDA's Irritation Per Protocol population (IRRFPP) and Sensitization Per Protocol population (SENFPP) were same as the sponsor's IRRPP and SENPP populations.

Irritation study

Irritation Study population

A total of two hundred and forty (240) healthy adult subjects were enrolled in this study. Each subject received two study treatments simultaneously during the study.

Two hundred and thirty-two (232) subjects were included in the IRRFPP population. Eight (8) subjects were not included in the IRRFPP due to having fewer than 16 irritation scores recorded.

Demographics

Table 1 shows the distribution of age, gender, and race for the IRRFPP population.

Table 1: Demographic characteristics (IRRFPP)

	Total (N=232)
Age (years)	
Mean (Range)	32.4 (18-68)
Gender	
Female	157 (67.7%)
Male	75 (32.3%)
Race	
White	208 (89.7%)
Black/African American	12 (5.2%)
Other	12 (5.2%)

Sensitization study

Sensitization study population

Two hundred and eighteen (218) subjects were included in the SNSFPP population. Twenty-two (22) subjects were not included in the SNSFPP population due to following reasons: exclusion

from IRRFPP (8), dropped by investigator due to AE (1) or non-compliance (7), subject withdrew due to family emergency (1) or schedule conflict (5).

Demographics

Table 2 shows the distributions of age, gender, and race for the SNSFPP population.

Table 2: Demographic characteristics (SNSFPP)

	Total (N=218)
Age (years)	
Mean (Range)	32.5 (18-68)
Gender	
Female Male	149 (68.4%) 69 (31.7%)
Race	
White Black/African American Other	194 (89.0%) 12 (5.5%) 12 (5.5%)

3.2.3 Results and conclusions

3.2.3.1 Sponsor's analysis results

The sponsor summarized their results and conclusion as below.

Irritation study (per sponsor)

Cumulative Irritation Results (per sponsor)

Least-Squares Mean Cumulative Irritation		*μ_1-1.25μ_2*[1]	*90% Confidence Interval*[2]	*μ_1-μ_2*[3]	*90% Confidence Interval*[4]
Treatment A Mylan	*Treatment B Lidoderm®*				
0.654	*0.741*	*-0.272*	*-0.305 – -0.239*	*-0.087*	*-0.116 –-0.06*

[1] *Estimated as Mylan least-squares mean – 1.25 x Lidoderm® least-squares mean.*
[2] *Upper 90% confidence interval < 0 indicates Mylan is non-inferior to Lidoderm®.*
[3] *Estimated as Mylan least-squares mean – Lidoderm® least-squares mean.*
[4] *Upper 90% confidence interval ≤0.25 indicates Mylan is non-inferior to Lidoderm®*

Sensitization study (per sponsor)

"No evidence of sensitization reactions were observed after the 24 hour challenge phase since neither treatment produced an irritation score greater than 2 in the challenge phase of the study. Therefore, no subjects were identified as potentially sensitized."

3.2.3.2 Reviewer's results

A) Irritation study

Primary endpoint: Mean Cumulative Irritation scores

Table 3 presents the frequency of irritation scores for each treatment. Frequencies of maximum and mean cumulative irritation scores per each patch per subject are shown in Table 4 and Table 5.

Table 3: Frequency of irritation scores (IRRFPP)

Visit Day	Treatment	score				
		0	1	2	3	5
Day 7	Test	67	154	10	1	
	Reference	44	176	11	1	
Day 14	Test	71	155	4	1	1
	Reference	48	177	4	2	1
Day 21	Test	73	153	4	1	1
	Reference	68	159	2	2	1

Table 4: Frequency of maximum irritation scores per each patch per subject (IRRFPP)

	0	1	2	3	5
Test	14	176	40	1	1
Reference	11	169	49	2	1

Table 5: Frequency of mean cumulative irritation scores (S) per each patch per subject (IRRFPP)

	S=0	0<S<1	1≤S≤ 2	2≤S≤ 3	3≤S≤ 4
Test	14	191	25	1	1
Reference	11	180	38	2	1

Statistical analysis was carried out as described in Section 3.1.1, with the primary endpoint treated as a continuous variable.

Table 6: Analysis for the mean cumulative irritation scores using mixed model (IRRFPP)

Test (Mean μ_T)	Reference (Mean μ_R)	Upper limit one-sided 95% CB (μ_T -1.25μ_R)	Pass the Non-inferiority test
0.6541	0.7410	-0.2383	Yes

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was less than zero and the non-inferiority test was passed for test patch versus reference patch. Therefore, the irritation potential of the test patch is not worse than that of the reference patch.

Secondary endpoints: dichotomized variables

Secondary endpoints examined the dichotomized mean cumulative irritation scores and irritation scores at visit day 7, 14, and 21. Analyses of these endpoints, following section 3.1.2 for binary data, are below.

Dichotomized Mean Cumulative Irritation Scores

In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and reference with regard to the proportion of subjects who had mean cumulative irritation score greater than or equal to 1 and 2. Sometimes, the proportions for test are lower than the proportions for reference (P_T -P_R<0). Based on the 95% upper confidence bound for the difference in proportions, the test might exceed the reference by at most -1.2 (negative) percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 (P_T -P_R= -6.0%). Also, the test might exceed the reference by at most 1.2 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2 (P_T -P_R= -0.4%).

Table 7: Analysis of the dichotomized mean cumulative irritation scores (IRRFPP)

Critical value (crit)	Score ≥ crit for Test & not for Reference	Score ≥ crit for Reference & not for Test	P_T -P_R*	95% Upper CB# for P_T -P_R		
				McNemar	Clopper	Schuirmann
1	12	26	-.060	-.013	-.037	**-0.012**
2	0	1	-.004	0.007	-.000	**0.012**

*: p_T=P (mean cumulative irritation score greater than/equal to crit for test), and p_R=P (mean cumulative irritation score greater than/equal to crit for reference).
#: The highest upper bound is marked in bold.

Dichotomized Irritation Scores at visit day 7, 14, and 21

Based on the 95% upper confidence bound for the difference in proportions, the test might exceed the reference by at most 4.2 percentage points (at Day 21) with regard to the proportion of subjects who had irritation scores greater than or equal to 1. Also, the test might exceed the reference by at most 2.6 percentage points (at Day 21) with regard to the proportion of subjects who had irritation scores greater than or equal to 2.

Table 8: Analysis of the dichotomized irritation scores for each study day (IRRFPP)

Visit Critical value (crit)	Score ≥crit for Test & not for Reference	Score≥crit for Reference & not for Test	P_T -P_R*	95% Upper CB# for P_T -P_R		
				McNemar	Clopper	Schuirmann
Crit=1						
Day 7	14	37	-0.099	-0.045	-0.069	**-0.044**
Day 14	18	41	-0.099	-0.041	-0.069	**-0.041**
Day 21	32	37	-0.022	**0.042**	-0.009	0.042
Crit=2						
Day 7	4	5	-0.004	**0.021**	-0.000	0.021
Day 14	2	3	-0.004	**0.016**	-0.000	0.016
Day 21	3	2	0.004	0.024	0.020	**0.026**

*: p_T=P (mean cumulative irritation score greater than or equal to crit for test), and p_R=P (mean cumulative irritation score greater than or equal to crit for reference).
#: The highest upper bound is marked in bold (in some cases the difference is only in the 4th decimal place).

Patch moving in the induction period

When a strong irritation reaction occurred, the patch was moved to another site in the induction phase of the study. If the patch was moved or completely removed due to a strong irritation reaction, the total irritation score before moving was carried forward for statistical analysis (LOCF).

Three patients had patches moved to a second or third site due to strong irritation reached at the site. Patient (b) (6) moved once and patient (b) (6) moved twice for both test and reference patches. Patient (b) (6) moved once for reference patch only.

B) Sensitization study

Table 9 presents the frequency of irritation scores for the challenge period for the Sensitization Per-Protocol population (SNSFPP).

Table 9: Frequency of irritation scores for the challenge period (SNSFPP)

Evaluation Day	Treatment	Irritation score			
		0	1	2	5
30 min	Test	115	98	5	
	Reference	130	86	2	
24 hours	Test	143	72	3	
	Reference	141	74	2	1*
48 hours	Test	194	22	2	
	Reference	203	13	2	
72 hours	Test	214	3	1	
	Reference	216	1	1	

FDA medical reviewer's comments (*): "*One subject, subject* (b) (6) *had an irritation score of 5 at the 24 hour of the challenge phase. The score resolved to 2 at the 48 and 72 hour challenge phase measurements. In addition, the induction scores reached a 5 at patch number 10 out of 21. This would suggest that the scores seen in the challenge phase are due to irritation, not sensitization.*"

No evidence of sensitization reactions were observed after the 24 hour challenge phase since neither treatment produced an irritation score greater than 2 at the 48 and 72 hour in the challenge phase of the study. Therefore, no subjects were identified as potentially sensitized.

Table 10 presents the 95% upper confidence bounds for the difference in proportions of potentially sensitized patients for the test versus reference, based on the Sensitization Per-Protocol population. Based on the 95% upper confidence bound for the difference in proportions, the test might exceed the reference by at most 2.03 percentage points with regard to the proportion of subjects who had sensitization.

Table 10: Analysis of the potentially sensitized scores (SNSFPP)

Test potentially sensitized and reference not potentially sensitized (P_T)	Test not potentially sensitized and reference potentially sensitized (P_R)	Total N	P_T -P_R*	95% Upper CB# for P_T -P_R		
				McNemar	Clopper	Schuirmann
0	0	218	0	0.0046	0.0136	**0.0203**

*: p_T=P (Test potentially sensitized and reference not potentially sensitized), and p_R=P (Test not potentially sensitized and reference potentially sensitized).
#: The highest upper bound is marked in bold.

3.3 Protocol LIDO-1044: Evaluation of adhesion

3.3.1 Study design and endpoints

<u>Study Objective</u>

This study was designed to evaluate adhesion only. The primary objective of this study was to evaluate the adhesive properties of Mylan's lidocaine transdermal patch and Lidoderm® patch manufactured by Teikoku following a 12-hour single-dose application in 24 healthy volunteers. A secondary objective was to assess acute dermal irritation after patch removal.

Study design

This was an open-label, single dose, randomized, one-period, two-treatment study investigating the adhesive properties of Mylan's Lidocaine Topical Patches 5% and Teikoku's Lidoderm® Lidocaine Patches 5% following a single application in 24 healthy adult subjects. At day 1, one Lidoderm® Patch 5% and one Mylan Lidocaine Topical Patch 5% were applied to the subject's left back and right back, in a randomized fashion. Adhesion was assessed at 2, 4, 6, 8, 10 and 12 hours during the wear period.

Treatments

Article	Description
Test	Lidocaine Topical Patch, 5%, Lot No. R6B0017, Mylan
Reference	Lidoderm® Patch, 5%, Lot No. 97278, expired 08/2010, Teikoku

Adhesion evaluations

0	90% or more adhered (essentially no lift off of 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	<50% adhered but not detached (more than half the system lifting off of the skin but not detached
4	0% adhered-Patch detached (patch completely off the skin)

Clinical endpoints

Primary endpoint: Mean Cumulative Adhesion Scores

The mean cumulative adhesion scores per subject were obtained by adding the scores at 2, 4, 6, 8, 10 and 12 hours of the application period and dividing by the number of observations (6).

Secondary endpoints: The clinical reviewer requested to compare the difference between test and reference with regard to the proportion of patch applications with meaningful detachment. Two dichotomized endpoints, defined as more than or equal to a score of 1 (≥10% detached) and more than or equal to a score of 2 (≥25% detached), were analyzed for the mean cumulative adhesion scores and adhesion scores at 2, 4, 6, 8, 10 and 12 hours.

3.3.2 Subject disposition

A total of 24 healthy adult subjects entered into this study and were included in the sponsor's Per Protocol (PP) for adhesion analysis. The FDA's Adhesion PP population (ADHFPP) was same

as the sponsor's PP population.[2]

3.3.3 Results and conclusions

3.3.3.1 Sponsor's analysis results

Based on the mean adhesive cumulative scores, the sponsor concluded that the test product (mean = 0.55) demonstrated better adhesive characteristics compared to the reference product (mean = 0.92), over a single application period of 12 hrs.

Frequency Distribution of Adhesion Scores at Hour 12 (per sponsor)

	Adhesion Score				
	0	1	2	3	4
Test	12 (50%)	10 (42%)	1 (4%)	1 (4%)	0
Reference	4 (17%)	9 (38%)	6 (25%)	1 (4%)	4 (17%)

Based on this data, the sponsor concluded the adhesiveness of the test product was determined to be not inferior to that of Lidoderm®.

3.3.3.2 Reviewer's results

The analysis is based on FDA's Per Protocol population (ADHFPP).

The frequency of cumulative adhesion scores per each patch at each evaluation day is shown in Table 11.

Table 11: Frequency of adhesion scores (ADHFPP)

Evaluation hours	Treatment	Adhesion score				
		0	1	2	3	4
2	Test	16	8			
	Reference	23	1			
4	Test	11	12	1		
	Reference	19	4		1	
6	Test	9	12	3		
	Reference	9	11	2		2
8	Test	15	7	2		
	Reference	10	6	4	2	2
10	Test	14	7	3		
	Reference	7	8	5	1	3
12	Test	12	10	1	1	
	Reference	4	9	6	1	4

Primary endpoint: Mean cumulative adhesion score

[2] Demographic information (gender, race, and age) could not be found in the electronic dataset.

The frequency of mean cumulative adhesion scores per each patch per subject is shown in Table 12. The mean cumulative adhesion scores were analyzed using a mixed model and are presented in Table 13.

Table 12: Frequency of mean cumulative adhesion scores (ADHFPP)

Mean	0	0.167	0.333	0.5	0.667	0.833	1	1.167	1.333	1.5	2	2.167	2.667	3.167
Test	4	4	4	3	2	1	1	2	2	1				
Reference	3	4	1	2	5			2	1	2	1	1	1	1

Table 13: Analysis for the mean cumulative adhesion scores using mixed model (ADHFPP)

Test (Mean)	Reference (Mean)	Upper limit one-sided 95% CB (μ_T -1.25μ_R)	Pass the Non-inferiority test
0.5486	0.9167	-0.2834	Yes

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was less than zero and the non-inferiority test was passed for test versus reference patch. Therefore, the adhesion potential of the test is non-inferior to that of the reference.

Secondary endpoint: Dichotomized adhesion scores

Table 14: Analysis of the dichotomized adhesion score (ADHFPP)

Evaluation	Score ≥crit for Test & not for Reference	Score ≥crit for Reference & not for Test	$P_T - P_R$*	95% Upper CB# for $P_T - P_R$		
	Crit=1			McNemar	Clopper	Schuirmann
2 hrs	7	0	0.292	0.486	0.479	**0.501**
4 hrs	9	1	0.333	**0.561**	0.521	0.542
6 hrs	4	4	0.000	**0.236**	0.117	0.221
8 hrs	1	6	-0.208	0.001	-0.079	**0.015**
10 hrs	0	7	-0.292	-0.097	-0.127	**-0.070**
12 hrs	1	9	-0.333	-0.106	-0.151	**-0.076**
Mean	1	4	-0.125	0.064	-0.034	**0.068**
	Crit=2					
2 hrs	0	0	0.000	0.042	0.117	**0.167**
4 hrs	1	1	0.000	0.139	0.117	**0.167**
6 hrs	2	3	-0.042	**0.153**	-0.002	0.145
8 hrs	1	7	-0.250	-0.034	-0.103	**-0.015**
10 hrs	0	6	-0.250	-0.063	-0.103	**-0.041**
12 hrs	0	9	-0.375	-0.171	-0.175	**-0.133**
Mean	0	4	-0.167	0.000	-0.056	**0.012**

*: p_T=P (adhesion score greater than or equal crit for test), and p_R=P (adhesion score greater than or equal crit for reference).
#: The highest upper bound is marked in bold.

In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and references with regard to the proportion of subjects who had mean and visit adhesion score greater than or equal to 1 and to 2.

The test might exceed the reference by at most 6.8 percentage points for mean scores greater than or equal to 1 and 1.2 percentage points for mean scores greater than or equal to 2.

Over all the visit hours, the test might exceed the reference by at most 56.1 percentage points for visit scores greater than or equal to 1 and at most 16.7 percentage points for visit scores greater than or equal to 2.

Table 14, above, gives more details.

Additional sensitivity analysis

The adhesion scores usually change from low to high at early visit to late visit. However there were some different cases in this study. Eleven (11) subjects had adhesion scores equal to 1 at an early visit and reduced to 0 at a late visit. Three subjects (3) had adhesion scores equal to 2 at an early visit and reduced to 0 or 1 at a late visit. FDA clinical reviewer inquired about those cases. The sponsor's explanation was those patients might turn around in their sleep to make the patch re-attached. Here, the additional sensitivity analysis was carried out using the highest adhesion scores carried forward (HOCF) for the FDA's per protocol population (ADHFPP).

The frequency of cumulative adhesion scores per each patch at each evaluation day is shown in Table 15.

Table 15: Frequency of adhesion scores (HOCF)

Evaluation hours	Treatment	Adhesion score*				
		0	1	2	3	4
2	Test	16	8			
	Reference	23	1			
4	Test	*10*	*13*	1		
	Reference	19	4		1	
6	Test	*7*	*14*	*3*		
	Reference	9	11	2		2
8	Test	*6*	*14*	*4*		
	Reference	*8*	*8*	4	2	2
10	Test	*6*	*13*	*5*		
	Reference	*6*	*9*	5	1	3
12	Test	*4*	*15*	*4*	1	
	Reference	*3*	*10*	6	1	4

*: The numbers in italic differ from those without HOCF in Table 11.

Primary endpoint: Mean cumulative adhesion score

The frequency of mean cumulative adhesion scores using imputed data as described above per each patch per subject is shown in Table 16. The mean cumulative adhesion scores were analyzed using a mixed model and are presented in Table 17.

Table 16: Frequency of mean cumulative adhesion scores (HOCF)

Mean	0	0.167	0.333	0.5	0.667	0.833	1	1.167	1.333	1.5	1.667	1.833	2	2.167	2.667	3.167
Test	4	2	0	1	3	5	4		1	1	2	1				
Reference	3	3	2	1	4	2		2	1	2			1	1	1	1

Table 17: Analysis for the mean cumulative adhesion scores using mixed model (HOCF)

Test (Mean)	Reference (Mean)	Upper limit one-sided 95% CB (test-1.25ref)	Pass the Non-inferiority test
0.7917	0.9444	-0.07253	Yes

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was less than zero and the non-inferiority test was passed for test versus reference patch. Therefore, the adhesion potential of the test is non-inferior to that of the reference.

Secondary endpoint: Dichotomized adhesion scores

Table 18: Analysis of the dichotomized adhesion score (HOCF)

Evaluation	Score≥crit for Test & not for Reference	Score ≥crit for Reference & not for Test	P_T -P_R*	95% Upper CB# for P_T -P_R		
	Crit=1			McNemar	Clopper	Schuirmann
2 hr	7	0	0.292	0.486	0.479	**0.501**
4 hr	9	0	0.375	0.579	0.563	**0.582**
6 hr	5	3	0.083	**0.317**	0.240	0.293
8 hr	4	2	0.083	**0.291**	0.240	0.275
10 hr	3	3	0.000	**0.210**	0.117	0.196
12 hr	0	1	-0.042	0.067	-0.002	**0.101**
Mean	3	3	0.000	**0.210**	0.117	0.196
	Crit=2					
2 hr	0	0	0.000	0.042	0.117	**0.167**
4 hr	1	1	0.000	0.139	0.117	**0.167**
6 hr	2	3	-0.042	**0.153**	-0.002	0.145
8 hr	1	5	-0.167	0.033	-0.056	**0.042**
10 hr	0	4	-0.167	0.000	-0.056	**0.012**
12 hr	0	6	-0.250	-0.063	-0.103	**-0.041**
Mean	0	4	-0.167	0.000	-0.056	**0.012**

*: p_T=P (mean cumulative/daily adhesion score greater than or equal crit for test), and p_R=P (mean cumulative/daily adhesion score greater than or equal crit for reference).
#: The highest upper bound is marked in bold.

In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and references with regard to the proportion of subjects who had mean and visit adhesion score greater than or equal to 1 and 2.

The test might exceed the reference by at most 21.0 percentage points for mean scores greater than or equal to 1 and 1.2 percentage points for mean scores greater than or equal to 2.

The test might exceed the reference by at most 58.2 percentage points for visit scores greater than or equal to 1 and at most 16.7 percentage points for visit scores greater than or equal to 2.

The test patch was found to be non-inferior to the reference patch for adhesion based on this additional sensitivity analysis.

4 SUMMMARY AND CONCLUSIONS

4.1 Statistical Issues and Findings

<u>Irritation and sensitization study #LIDO-1046</u>

Irritation

Primary endpoint: Mean cumulative irritation scores were analyzed. Mean cumulative irritation scores were 0.6541 for test patch and 0.7410 for reference patch. The non-inferiority criterion

was satisfied for test patch versus reference patch, implying that we can conclude that the population mean of the mean cumulative irritation for the test patch does not exceed that of the reference patch by more than 25% (i.e., $\mu_T / \mu_R \leq 1.25$).

Secondary endpoints: Dichotomized endpoints for mean cumulative irritation scores were considered for the secondary analyses. Sometimes, the proportions for test are lower than the proportions for reference ($P_T - P_R < 0$). Based on the 95% upper confidence bound for the difference in proportions, the test might exceed the reference by at most -1.2 (negative) percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 ($P_T - P_R = -6.0\%$)). Also, the test might exceed the reference by at most 1.2 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2 ($P_T - P_R = -0.4\%$).

The test and reference patches were compared with regard to the proportion of product applications with irritation scores greater than or equal to 1 or 2 at visit day 7, 14, and 21. The test might exceed the reference by at most 4.2 percentage points based on scores greater than or equal to 1. And also the test might exceed the reference by at most 2.6 percentage points based on scores greater than or equal to 2.

Sensitization

No subject was identified to be potentially sensitized to test or reference patches.

The test patch might exceed the reference patch by at most 2.03 percentage points based on the 95% upper confidence bound for the difference in sensitization rates.

<u>Adhesion study #LIDO-1044</u>

The mean cumulative adhesion scores were analyzed using a mixed linear model. Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was less than zero (-0.2834) and thus the non-inferiority test was passed for test versus reference patch.

Based on the 95% upper confidence bound for the difference in proportions of subjects who had mean and visit adhesion score greater than or equal to 1 and 2, the test might exceed the reference by at most 6.8 and 1.2 percentage points for mean scores greater than or equal to 1 and to 2. Over all the visit hours, the test might exceed the reference by at most 56.1 percentage points for visit scores greater than or equal to 1 and at most 16.7 percentage points for visit scores greater than or equal to 2

<u>Main difference between sponsor's results and our results:</u>

Where the sponsor's results differ from our own results, mainly it is due to the following reasons.

a) For the non-inferiority analyses based on the mean cumulative irritation scores, the sponsor and FDA presented the same one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$). However, the sponsor also presented the one-sided 95% upper CB for the mean difference ($\mu_T - \mu_R$) and noted that Upper 90% confidence interval $\leq$0.25 indicates Mylan is

non-inferior to Lidoderm®. Their method has not been accepted by FDA clinical and statistical reviewers.

b) The sponsor did not carry out a statistical analysis for sensitization study since no subject demonstrated evidence of a sensitization reaction.

c) The sponsor provided the frequency table for adhesion score at each evaluation hour and the adhesion mean scores for test and reference. The sponsor concluded that the adhesiveness of the test product was determined to be not inferior to that of Lidoderm® with no further statistical analysis.

4.2 Conclusions

The test patch was found to be non-inferior to the reference patch for irritation, sensitization, and adhesion.

_____	_____
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_____
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/s/

NITIN K PATEL on behalf of HUAIXIANG LI
05/28/2013

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05/28/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202346
Drug Product Name	Lidocaine Patch
Strength(s)	5%
Applicant Name	Mylan Technologies Inc.
Applicant Address	110 Lake St. St. Albans, VT 05478
Applicant's Point of Contact	S. Wayne Talton Vice President, Regulatory Affairs 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Contact's Telephone Number	304-599-2595 ext. 6551
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Original Submission Date(s)	10/26/2010
Submission Date(s) of Amendment(s) Under Review	06/26/2013
First Generic (Yes or No)	No
Reviewer	Yumei Ye, Ph.D.

Study Number (s)	**LIDO-1037**	LIDO-09255	LIDO-1044	LIDO-1046	**LIDO-09254**
Study Type (s)	**Fasting (Pivotal)**	Adhesion (Pilot)	Adhesion	Cumulative Irritation and Sensitization	**Fasting (Pilot)**
Strength (s)	**5%**	5%	5%	5%	**5%**
Clinical Site	Cetero Research				Cetero Research
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104				625 Demers Avenue East Grand Forks, MN 56721
Analytical Site	Mylan Pharmaceuticals, Inc. Bioanalytical Department				
Analytical Site Address	3711 Collins Ferry Road Morgantown, WV 26505				

OSI Status	**ADEQUATE (Clinical and Analytical Sites)**
REVIEW RESULT	**ADEQUATE**
WAIVER REQUEST RESULT	**N/A**

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 6, 22	FASTING STUDY	5%	ADEQUATE
1, 6, 22	FASTING STUDY	5%	ADEQUATE
1, 6	DISSOLUTION	5%	ADEQUATE

1 EXECUTIVE SUMMARY

This is an amendment review.

Mylan Technologies Inc. has submitted ANDA No. 202346 for its test product, Lidocaine Patch, 5%. This ANDA references NDA No. 020612, Teikoku Pharma USA's, Lidoderm® (lidocaine) Patch, 5%.

Consistent with the Bioequivalence Drug Specific Product Guidance,[1] the firm's original application submitted on 10/26/2010 contains the results of three studies, (1) a pivotal fasting bioequivalence (BE) study with PK endpoints (LIDO-1037), comparing the test product Mylan's Lidocaine Patch, 5% to the corresponding reference product Teikoku Pharma USA's, Lidoderm® (lidocaine) Patch, 5%; (2) Adhesion study (Study LIDO-1044); and (3) Sensitization/Irritation study (Study LIDO-1046). The pivotal fasting BE study (LIDO-1037) was reviewed by the Division of Bioequivalence I (DBI). Per the original full BE review dated 02/25/2013, the application was inadequate pending a satisfactory response from the firm to the deficiencies related to "apparent dose" and adhesion assessment in the pivotal BE study and the impact of the OSI findings at the analytical site.[2] The Adhesion Study (LIDO-1044) and Sensitization/Irritation Study (LIDO-1046) were reviewed by the Division of Clinical Review (DCR).

In the current amendment dated 06/26/2013, the firm satisfactorily addressed all bioanalytical and clinical deficiencies related to the pivotal fasting BE study. Therefore, the pivotal fasting BE study (LIDO-1037) is **adequate.**

The firm's dissolution testing is **adequate**[2]**.**

No OSI inspection of the clinical or analytical sites is necessary at this time[2].

The application is now **acceptable** with no deficiencies.

---

[1] Draft Guidance on Lidocaine (Recommended Dec 2006; Revised May 2007, July 2014); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf

[2] DARRTS: ANDA 202346 REV-BIOEQ-21(Primary Review) (Final Date: 02/25/2013)

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2 REVIEW OF SUBMISSION

2.1 Review of the Amendment Dated June 26, 2013

Deficiency #1

For the bioequivalence (BE) study LIDO-1037, you reported the "apparent dose" delivered. However, the validity of your reported data for the "apparent dose" delivered cannot be confirmed as the study report did not include the complete analytical report, validation report, and the detailed experimental procedures. Please provide this information. Please provide your analysis to show that the "apparent dose" delivered for your test product was comparable to the reference product.

FIRM'S (MYLAN) RESPONSE 1

When reviewing the residual analysis data, one must take into account that one is measuring what remains in the patch along with the amount left on the skin at the time of patch removal (captured by the alcohol wipes). A reflection of the starting total drug content within the patch is obtained from an average of three (3) control patches from each treatment (these patches were never applied to a subject) collected at the completion of each period and processed in the same manner as a patch being removed from a subject. A subject's average "apparent dose" in a period is then simply a subtraction of the average total drug content of a formulation from that period's control samples and the average observed residual analysis data from the applied patches in that period.

In the LIDO-1037 study, since two patches of a formulation were worn in a period, the average of those observed residual analyses were reported for each subject. In this study, the depletion (or roughly the amount absorbed or "apparent dose") of Mylan's Lidocaine Patch 5% was 14.72 mg ± 5.68 mg (38.6%CV), while the depletion from Lidoderm® was 19.92 mg ± 14.96 mg (75.1%CV). This data demonstrates the similarity in the amount released between the two products and represents approximately 10.5% and 2.8% depletion of total drug load for Mylan patch and Lidoderm respectively. The LIDO-1037 also established that Mylan's Lidocaine Patch 5% was bioequivalent to Lidoderm®, thus confirming the similar rate and extent of absorption of the two products.

Mylan tested the remaining drug in the patches and wipes used for LIDO-1037 BE study using the following methods.

- Mylan Lidocaine Patches – STM-0793
  - The method and method validation report were provided in our original ANDA submission in Section 3.2.P.5.2 and 3.2.P.5.3.
- Lidoderm Patches – STM-0610
  - The standard test method (STM-0610) and method verification report have been provided in Section 2.7.1 and Section 2.7.5, respectively.

- Method extraction volume increased from 25 mL to 350 mL since entire patch (140 cm^2) is being extracted for this analysis (method is written to assay a 10 cm^2 diecut)

- Wipes – Samples are analyzed on an isocratic, reverse phase HPLC method with UV detection (method is consistent with one employed to analyze for residual drug after equipment cleaning)

Reviewer's Comments:

The firm's response to above deficiency comment (#1) is **adequate** due to the following reasons:

- It is noted that currently the OGD only recommends reporting the "apparent dose" delivered as indicated below[1]:

  In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. Analyze and include in the calculation the amount of adhesive residue from each patch left on the skin.

- Per the original BE review on current application, the Lidocaine Patches worn during the study were saved and analyzed for their residual lidocaine levels. These values, along with the residual lidocaine levels on the alcohol wipes used to clean the skin area after transdermal system removal, were subtracted from control patch levels (described in the firm's response above) to arrive at an apparent dose, which is in accordance with the BE guidance for Lidocaine Patch as mentioned above.

- In the current amendment, the firm provided the detailed experimental procedures (STM-0793 for the test product and STM-0610 for the RLD product) and their validation reports, which were used to determine the residual amount of the patches used in the fasting study. The reviewer compared these two SOPs and noted that the sample extraction procedures and assay conditions were different between these two SOPs. However, these two assay methods were both validated in terms of the validation parameters submitted in the validation reports.

- The table below is the statistic summary table submitted by the firm for the results of residual patch analysis.

Overall Summary of Lidocaine Depletion from Topical System, mg

Treatment A

	Period 1	Period 2	Combined
Average	11.98	17.65	14.72
Standard Deviation	5.14	4.82	5.68
RSD, %	42.9	27.3	38.6
Median	12.20	19.30	14.30
Range	0.40 - 23.8	5.6 - 23.3	0.40 - 23.8
number of subjects	15	14	29

Treatment B

	Period 1	Period 2	Combined
Average	13.96	25.49	19.92
Standard Deviation	15.60	12.36	14.96
RSD, %	111.7	48.5	75.1
Median	16.00	28.90	22.80
Range	-13.5 - 34.4	3.4 - 47.2	-13.5 - 47.2
number of subjects	14	15	29

- The reviewer conducted a t-test to compare the lidocaine dose absorbed per patch for the test and RLD products and obtained a p value as 0.08. It should be noted that currently the OGD only recommends reporting the "apparent dose" delivered in addition to pharmacokinetic data. Also, the 90% confidence intervals of AUC0-t, AUC∞ and Cmax of lidocaine met the acceptance criteria of 80.00-125.00% for the test product (Please see table below).

Lidocaine Patch 5% Dose (2 patches, each containing 5% w/w lidocaine in adhesive matrix) N=29 (M=15, F=14) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study (Study Code: LIDO-1037) Analyte: lidocaine					
Parameter (units)	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	936.83	1002.70	0.93	86.01	101.49
AUC∞ (hr *ng/ml)	958.91	1022.89	0.94	86.67	101.40
Cmax (ng/ml)	67.92	71.70	0.95	85.12	105.40

Deficiency #2

2. We note that a number of subjects in the study LIDO-1037 were evaluated with adhesion score as 1 or 2 at some time points during the study. According to the protocol, score 1 means >=75% to <90% adhered (some edges only lifting off the skin) and score 2 means >=50% to 75% adhered (less than half the system lifting off the skin). You submitted the adhesion scores at 3 time points (4, 8 and 12 hours (± 10 minutes) after patch application) for each patch applied for all the subjects. However, you did not provide statistical summary data of the adhesion scores for the test and reference patches (Mean, SD, Minimum, Median, Maximum, confidence interval etc.) and the acceptance criterion for comparable adhesion of the test and reference products. Please provide this information.

MYLAN RESPONSE 2

The primary objective of LIDO-1037 study was a cross-over study for assessment of pharmacokinetic bioequivalence between Mylan's Lidocaine Patch 5% and Lidoderm® following a single 12-hour application of two patches. Acute dermal irritation assessment (based on single applications) was a secondary objective. The comparison of adhesive qualities of the two products was not an objective of this study for the following reasons:

1. Pivotal adhesion comparison assessments were performed in the LIDO-1044 study.
2. In LIDO-1037, hypoallergenic tape was applied to the short edges of the patches at the time of application, thus making inherent adhesion comparisons not appropriate.

Performing the definitive adhesion assessment in a separate study (ie. outside of the scope of the PK study and cumulative irritation/sensitization study) is considered an acceptable practice as noted in FDA's Draft Guidance on Lidocaine Topical Patch, issued May 2007 (italicization added for emphasis).

> 17. Cutting patches to a smaller size is likely to change the shape as well as the size of the patch and may change adhesive performance of the patch. Therefore, adhesion data from your skin irritation and sensitization study may not be adequate to demonstrate that your to-be-marketed patch adheres at least as well as the RLD. Therefore, you should consider collecting adhesion data during your PK bioequivalence study, using an acceptable 5-point (0 to 4) scale. Reinforcement of the patches should therefore not be allowed in the PK study if it is also being used to demonstrate adequate adhesion, and you may need to increase the size of that study to allow for detached patches. *Alternately, you may conduct a separate paired single-application adhesion study to demonstrate that your product adheres at least as well as the RLD.*

For the reviewer's ready reference, a summary of the results from the LIDO-1044 adhesion study is provided in the tables below.

Hour (hr)	Arithmetic Mean (%CV) A = Mylan	Arithmetic Mean (%CV) B = Lidoderm®
2	0.33 (144.5)	0.04 (489.9)
4	0.58 (100.0)	0.29 (236.7)
6	0.75 (90.1)	0.96 (117.1)
8	0.46 (143.6)	1.17 (112.1)
10	0.54 (133.1)	1.38 (95.5)
12	0.63 (123.1)	1.67 (78.5)
Cumulative Mean	0.55 (86.6)	0.92 (95.5)

Results from the LIDO-1044 Adhesion Study:

Least-Squares Mean		$\mu_1 - 1.25\ \mu_2$[1]	90% Confidence Interval
Treatment A Mylan	**Treatment B Lidoderm®**		
0.549	0.917	-0.597	-0.879 – -0.315

[1] Estimated as Mylan least-squares mean – 1 25 x Lidoderm® least-squares mean.
[2] Upper 90% confidence interval ≤ 0 indicates Mylan is non-inferior to Lidoderm®.

Adhesion Frequency Tables from LIDO-1044, where Treatment A is Mylan's Lidocaine Patch 5% product and Treatment B is Lidoderm®

Frequency

Table 1 of HOUR by SCORE						
Controlling for TREAT=A						
	SCORE					
HOUR	0	1	2	3	4	Total
2	16	8	0	0	0	24
4	11	12	1	0	0	24
6	9	12	3	0	0	24
8	15	7	2	0	0	24
10	14	7	3	0	0	24
12	12	10	1	1	0	24
Total	77	56	10	1	0	144

Frequency

Table 2 of HOUR by SCORE						
Controlling for TREAT=B						
	SCORE					
HOUR	0	1	2	3	4	Total
2	23	1	0	0	0	24
4	19	4	0	1	0	24
6	9	11	2	0	2	24
8	10	6	4	2	2	24
10	7	8	5	1	3	24
12	4	9	6	1	4	24
Total	72	39	17	5	11	144

The LIDO-1044 study results demonstrate that Mylan's Lidocaine Topical 5% Patch is non-inferior to Lidoderm® in regards to patch adhesion following a single 12-hour application.

For the reasons discussed, adhesion recorded in LIDO-1037 was not considered as pivotal data, but was monitored to verify adhesion was maintained by use of adhesion aid (tape on edges). Files containing the Adhesion Raw Data Listing, Adhesion Data Listing with Summary Statistics, and Adhesion Frequency Tables are provided in Section 5.4.

Reviewer's Comments:

The firm's response to the above deficiency comment (#2) in the current amendment is **acceptable** due to the following reasons:

- Per the Clinical review dated 05/31/2013, adhesion data from study #LIDO-1044 demonstrated that the adhesive performance of Mylan's Lidocaine Patch, 5% is at least as good as that of the RLD product.[3]

- The firm provided the requested statistical summary data of the adhesion scores for the test and reference patches (Mean, SD, Minimum, Median, Maximum, confidence interval etc.) as indicated below.

- The firm's data suggested that none patch was scaled at 3 or 4 after 12's worn, and no severe detachment was observed.

[3] DARRTS: ANDA 202346 REV-CLINICAL-21(Primary Review)(Final Date: 05/31/2013)

Lidocaine 5% Dermal Patches [LIDO-1037]
Single Dose, Fasting Bioequivalence, 2 patches worn for 12 hours
Patch Adhesion Analysis

08/03/2010

The FREQ Procedure

Frequency

Table 1 of hour by score				
Controlling for treat=A				
	score			
hour	0	1	2	Total
4	52	6	0	58
8	48	8	2	58
12	33	16	9	58
Total	133	30	11	174

Frequency

Table 2 of hour by score				
Controlling for treat=B				
	score			
hour	0	1	2	Total
4	55	5	0	60
8	56	4	0	60
12	35	19	6	60
Total	146	28	6	180

Lidocaine 5% Dermal Patches [LIDO-1037]
Single Dose, Fasting Bioequivalence, 2 patches worn for 12 hours
Patch Adhesion Analysis
Adhesion Data Listing with Summary Statistics

08/03/2010

treat=A

			Hour			
Subject	Period	Site	4	8	12	Cumulative Mean
1	1	R1			(b) (4)	0.00
		R2				0.00
2	2	L1				0.00
		L2				0.33
3	1	R1				0.67
		R2				0.33
4	2	L1				0.33
		L2				0.33
5	2	L1				0.00
		L2				0.33
6	1	R1				0.00
		R2				0.00
7	1	R1				0.33
		R2				1.00
8	2	L1				0.33
		L2				0.67
9	2	L1				0.33
		L2				0.00
10	1	R1				0.00
		R2				0.33
11	2	L1				0.00
		L2				0.00
12	1	R1				0.67
		R2				1.67
13	2	L1				0.00
		L2				0.00
14	1	R1				0.33
		R2				0.33
15	2	L1				0.00
		L2				0.00
16	1	R1				0.00
		R2				0.00
17	1	R1				0.67
		R2				1.33
18	2	L1				0.00
		L2				0.67
19	1	R1				0.00
		R2				0.33
20	2	L1				0.00
		L2				0.00

Treatment A: Lidocaine Topical Patch, 5%, Dose:2 patches for 12 hours, Mylan
Treatment B: Lidoderm Topical Patch, 5%, Dose: 2 patches for 12 hours, Endo

treat=A

			Hour			
Subject	Period	Site	4	8	12	Cumulative Mean
21	2	L1			(b) (4)	0.67
		L2				0.67
22	1	R1				0.00
		R2				0.00
23	2	L1				0.33
		L2				0.00
24	1	R1				0.00
		R2				1.67
25	1	R1				0.00
		R2				0.00
26	2	L1				0.33
		L2				0.67
28	1	R1				0.00
		R2				0.67
29	1	R1				1.00
		R2				0.00
30	2	L1				0.00
		L2				0.00
N			58	58	58	58.00
Mean			0.10	0.21	0.59	0.30
STD			0.307	0.487	0.750	0.41
CV			297.0	235.4	128.0	138.10
Max					(b) (4)	1.67
Median			0	0	0	0.00
Min					(b) (4)	0.00

Adhesion Evaluation Scoring System

Score 0, >= 90% adhered (essentially no lift off from the skin)
Score 1, >= 75% to < 90% adhered (some edges only lifting off the skin)
Score 2, >= 50% to < 75% adhered (less than half of the system lifting off the skin)
Score 3, < 50% adhered but not detached (more than half lifting off the skin)
Score 4, patch detached (patch completely off the skin)

treat=B

			Hour			
Subject	Period	Site	4	8	12	Cumulative Mean
1	2	L1			(b) (4)	1.00
		L2				0.00
2	1	R1				0.00
		R2				0.33
3	2	L1				0.33
		L2				0.00
4	1	R1				1.33
		R2				0.00
5	1	R1				0.00
		R2				0.33
6	2	L1				0.33
		L2				0.33
7	2	L1				0.33
		L2				1.00
8	1	R1				0.00
		R2				0.00
9	1	R1				0.00
		R2				0.33
10	2	L1				0.00
		L2				0.00
11	1	R1				0.33
		R2				0.00
12	2	L1				0.33
		L2				1.00
13	1	R1				0.00
		R2				0.00
14	2	L1				0.00
		L2				0.00
15	1	R1				0.33
		R2				0.33
16	2	L1				0.00
		L2				0.00
17	2	L1				0.00
		L2				0.00
18	1	R1				0.00
		R2				0.33
19	2	L1				0.33
		L2				0.00
20	1	R1				0.00
		R2				0.00

Treatment A: Lidocaine Topical Patch, 5%, Dose:2 patches for 12 hours, Mylan
Treatment B: Lidoderm Topical Patch, 5%, Dose: 2 patches for 12 hours, Endo

08/03/2010

treat=B

			Hour			
Subject	Period	Site	4	8	12	Cumulative Mean
21	1	R1			(b) (4)	0.00
		R2				0.00
22	2	L1				0.00
		L2				0.00
23	1	R1				0.00
		R2				0.00
24	2	L1				0.00
		L2				0.33
25	2	L1				0.00
		L2				0.00
26	1	R1				0.00
		R2				0.67
28	2	L1				0.67
		L2				0.33
29	2	L1				1.33
		L2				0.33
30	1	R1				0.00
		R2				0.33
N			58	58	58	58.00
Mean			0.09	0.07	0.50	0.22
STD			0.283	0.256	0.682	0.34
CV			328.4	370.6	136.4	155.42
Max					(b) (4)	1.33
Median			0	0	0	0.00
Min					(b) (4)	0.00

Adhesion Evaluation Scoring System

Score 0, >= 90% adhered (essentially no lift off from the skin)
Score 1, >= 75% to < 90% adhered (some edges only lifting off the skin)
Score 2, >= 50% to < 75% adhered (less than half of the system lifting off the skin)
Score 3, < 50% adhered but not detached (more than half lifting off the skin)
Score 4, patch detached (patch completely off the skin)

Deficiency #3

3. The FDA's Office of Scientific Investigations (OSI) previously conducted an inspection at the analytical site, Mylan Pharmaceutical Inc. (3711 Collins Ferry Rd, Morgantown, WV 26505), for a different application. This analytical site is the same as that used for the BE study LIDO-1037 in your application. The FDA Form 483 issued to the analytical site at the end of the inspection noted the following:

1) Stability of processed samples was determined with only mid level QCs during pre-study validation for the audited studies. Processed stability was not evaluated with low and high QC concentrations.
2) Failure to document all aspects of study conduct.
No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes during the audited studies.

MYLAN RESPONSE 3

Processed Sample Stability

Processed sample stability was demonstrated for 121 hours at the low and high quality control (QC) concentrations in Lidocaine Validation Addendum 1. This time exceeded the original interval of 98 hours and was sufficient to cover all runs in the LIDO-1037 study. Thus there was no impact of this finding on the current ANDA. Please refer to Lidocaine Validation Addendum 1 Report which was submitted in a Gratuitous Bioequivalence Amendment (Sequence 0005) in Section 5.3.1.4.

Reviewer's Comments:

- The firm's response to the above OSI finding #1 at the analytical site is **acceptable** due to the following reason:
    - Per Lidocaine Validation Addendum 1 Report, stability of processed samples was determined with low (3 ng/mL) and high (120 ng/mL) QC levels of lidocaine (121.25 hours at room temperature) during pre-study validation. And the data suggested that the processed samples were stable for up to 121.25 hours at room temperature. Therefore, the OSI finding that "*processed stability was not evaluated with low and high QC concentrations*" would not impact the outcome of the BE studies for the current application.

MYLAN RESPONSE 3

Balance Documentation

As detailed in our 08-Sep-2010 483 response, to ensure the ID of the balance was captured, Laboratory Procedure (LP) LP-013 ("Maintenance, Qualification and Use of Handheld Pipettes") was revised to include a prompt on the data worksheet for the analyst to record the balance ID at the time that pipette qualification is performed. The revised LP was made effective on 03-Sep-2010. The bioanalytical phase of the LIDO-1037 study ran from 01-Jun-2010 (pre-study method qualification run) through 09-Jun-2010, and thus was conducted under the previous version of LP-013.

As summarized in Table 3-1, 4 pipettes were used in the LIDO-1037 study. The then-current (at the time of use) qualification dates[4] for these pipettes are also provided in Table 3-1.

Table 3-1: Pipettes used during the LIDO-1037 study and their qualification dates

Pipette ID	Qualification Dates[a]
5100	01-Feb-2010; 24-May-2010
5169	01-Mar-2010
5191	26-Feb-2010; 03-Jun-2010
5196	17-Mar-2010

[a] The qualification interval for pipettes in the Laboratory is quarterly and expires on the last day of the month in which the due date falls (e.g. a

pipette qualified on 17-Mar may be used until 30-Jun without re-qualification). The qualification dates shown for each pipette are those covering the period from the start of method validation (07-May-2010) through the end of the LIDO-1037 study (09-Jun-2010).

For each of these pipettes, a similar impact assessment as detailed in our 08-Sep-2010 483 response was performed.

With regard to the identity of the balances used for the pipette qualifications, as noted in the 2010 response, analysts in the laboratory typically use a specific Mettler-Toledo SAG285 analytical balance (PLE 8622), located in the laboratory's balance room, for pipette qualification. This balance is interfaced to a PC that runs a validated spreadsheet application that processes the pipette qualification data. This system was viewed by one of the DSI inspectors during the 2010 inspection. We recognize, however, that this does not provide conclusive evidence that balance 8622 was used for the qualification of pipettes used in the lidocaine project. However as discussed below, we have established that all Bioanalytical Laboratory balances were in a qualified state and were therefore valid to use during this time period.

All Bioanalytical Laboratory balances are tracked, maintained, and qualified from receipt until retirement. The top-loading balances (Mylan IDs 8612 and 8633) read to a maximum of 3 decimal places. The weights recorded during the pipette qualifications contain 5 decimal place readings, precluding the possibility of using a precision balance. The requisite precision for the pipette qualification could have been provided only by the analytical or micro balances. Five such balances were in service in February through June 2010.

- Analytical Balance ID 8492
- Analytical Balance ID 8507
- Analytical Balance ID 8622
- Micro Balance ID 8600
- Micro Balance ID 8611

[4] The balance qualification reviews extended back to February 2010 in order to encompass the time period of reagent and system suitability sample preparation performed in May 2010 just prior to the analytical phase of the study.

The then-current (as of Feb - June 2010) quarterly balance qualification records for these 5 balances were reviewed. These records show that each in-service balance was in a qualified state during the qualifications of pipettes 5100, 5169, 5191, and 5196, and as such each would have been acceptable to use for pipette qualification.

The Pipette Qualification Worksheets relevant to the lidocaine project (listed in Table 3-1) for pipettes 5100, 5169, 5191, and 5196, as well as the then-current Balance Qualification documents are provided in Section 5.4 for the reviewer's reference.

Based on the above, there was no impact of this finding on the current ANDA.

Reviewer's Comments:

The firm's response to the above OSI findings #2 at the analytical site is **acceptable** due to the following reasons:

- Although the identity of the balances used for the pipette qualifications was not documented in the qualification worksheets for the 4 pipettes used in the BE studies for the current application, the firm indicated that analysts in the laboratory typically use a specific analytical balance (PLE 8622) for pipette qualification. This balance is interfaced to a PC that runs a validated spreadsheet application that processes the pipette qualification data.

- Per the current amendment, the firm reviewed the quarterly balance qualification records for the 5 balances (including the balance # 8622), used during the BE studies conducted in 01-Jun-2010 (pre-study method qualification run) through 09-Jun-2010 for current application. The documents for the balances show that each in-service balance (including the balance # 8622) was in a qualified state during the qualification of the pipettes used for the current BE studies. The qualification worksheets for the 4 pipettes also show that the results of the qualification test for each pipette passed the firm's acceptance criteria.

- In addition, the firm has revised its laboratory procedure worksheet requiring the analyst to record the balance ID used for pipette calibration.

Deficiency #4

You approved the bioanalytical method validation report on June 15, 2010, after the completion date of the sample analysis on June 9, 2010 for the study LIDO-1037. The analytical method is considered validated only after the method validation report is approved by signatory authority. For future submission, please ensure a validated analytical method is used for study sample analysis.

MYLAN RESPONSE 4

We acknowledge the Agency's comment and would like to note that a preliminary method validation report was approved on 02-Jun-2010, the date on which study sample analysis began. The preliminary report consisted of tabular summaries of the data from each validation experiment and was reviewed and approved by Scientific and Management staff in the Laboratory, including the validation Principal Investigator, the Method Development scientist, and a Laboratory Director. The Lidocaine Preliminary Validation Report is provided in Section 5.4 for the reviewer's reference.

Reviewer's Comments:

The reviewer verified that preliminary method validation report approved on 02-Jun-2010 (the date on which study sample analysis began) contains tabular summaries of the data from each validation experiment and was reviewed and approved by Scientific and Management staff in the Laboratory. The reviewer spot checked that the data presented in tabular summaries of this primary report are the same as that in the bioanalytical method validation report on June 15, 2010. Therefore, the firm's response to the above deficiency comment (#4) in the current amendment is **acceptable.**

Deficiency #5

For better understanding for your formulation and dissolution method development and optimization, please provide individual concentration and pharmacokinetic data of pilot study LIDO-09254 and the dissolution testing data for all formulations used in this study, if available.

MYLAN RESPONSE 5

Mylan is providing the SAS Transport Files for the LIDO-09254 study as requested by the Agency. Listed below are the file names associated with this pilot study:

- 09254lido-cc.xpt
- 09254lido-define.pdf
- 09254lido-pk.xpt

Regarding the requested dissolution testing data, the submitted Drug Release method, STM-0824, had not yet been developed at the time this pilot clinical study was performed, so the requested data is not available. At that time, the Drug Release media contained a very high concentration of organic solvent based on a desire to achieve greater than 80% of the dose delivered over the course of dissolution run, and development work that showed a high concentration of organic solvent ((b) (4) (b) (4) was needed to achieve that target.

Reviewer's Comments:

The firm's response to above deficiency comment (#5) in the current amendment is **acceptable** due to the following reasons:

- The firm provided the requested individual concentration and pharmacokinetic data of pilot study LIDO-09254 in SAS Transport format.

  The firm did not provide the requested dissolution data, which is not available as indicated by the firm's response above.

- Per the original BE review of the current application, LIDO-09254 was a single-dose, pilot-scale, 4-treatment, pharmacokinetic study on 20 subjects with two patches worn for twelve hours. The primary purpose of the study was to evaluate the BE of three formulations of Mylan's Lidocaine Patch 5% to the RLD product, Lidoderm® patch 5%. Total 19 subjects completed the study and were included in the statistical analysis. The 90% confidence intervals of AUC0-t and Cmax for lidocaine met the acceptance criteria of 80.00-125.00% for all three formulations. Formulation A was selected and modified slightly into the formulation used in the pivotal study. The firm has provided the summary tables for this pilot study. Please see the original review for details.

- As the objective of the pilot study (LIDO-09254) was to optimize the formulation and the test formulation adopted in the pivotal study (LIDO-1037) was different from the formulations used in the pilot study, the outcome of the pilot study does not have impact on the outcome of the pivotal study. In addition, the information for the pilot study was requested for information purpose only.

3 DEFICIENCY COMMENTS

None.

4 RECOMMENDATIONS

1. The Division of Bioequivalence finds the fasting BE study (LIDO-1037) conducted by Mylan Technologies Inc. on its Lidocaine Patch, 5% (Lot # R6B0017) comparing it to Teikoku Pharma USA' s Lidoderm (lidocaine) Patch, 5% (Lot #97278), to be **adequate**.

2. The firm's in vitro dissolution testing is **acceptable**. The DB acknowledges that the firm will use the following in vitro drug release method and specifications for its product:

Apparatus:	V (Paddle over Disk)
Speed:	50 rpm
Medium:	10 mM Sodium Acetate Buffer, pH 4.0
Temperature:	32°C
Volume:	500 mL
Specifications:	1.5 h: (b) (4)%
	6 h: (b) (4)%
	12 h: (b) (4)%
	24 h: (b) (4)%

5 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
N/A	

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	202346
APPLICANT:	Mylan Technologies Inc.
DRUG PRODUCT:	Lidocaine Patch, 5%

The Division of Bioequivalence I (DBI) 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,

{See appended electronic signature page}

Archived copy does not contain a signature page

Wayne DeHaven, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202346			
Drug Product Name	Lidocaine Patch			
Strength(s)	5%			
Applicant Name	Mylan Technologies Inc			
Applicant Address	110 Lake St. St. Albans, VT 05478			
US Agent Name and the mailing address	S. Wayne Talton Vice President, Regulatory Affairs 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310			
US agent's Telephone Number	304-599-2595 ext. 6551			
US Agent's Fax Number	304-285-6407			
Original Submission Date(s)	10/26/2010			
Submission Date(s) of Amendment(s) Under Review	2/8/2011 (Bioequivalence/Long term stability)			
First Generic (Yes or No)	No			
Reviewer	Rong Wang, Pharm.D., Ph.D.			
Study Number (s)	**LIDO-1037**	LIDO-09255	LIDO-1044	LIDO-1046
Study Type (s)	**Fasting (Pivotal)**	Adhesion (Pilot)	Adhesion	Cumulative Irritation and Sensitization
Strength (s)	**5%**	5%	5%	5%
Clinical Site	Cetero Research			
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104			
Analytical Site	Mylan Pharmaceuticals, Inc. Bioanalytical Department			
Analytical Site Address	3711 Collins Ferry Road Morgantown, WV 26505			
Study Number (s)	**LIDO-09254**			
Study Type (s)	**Fasting (Pilot)**			
Strength (s)	**5%**			
Clinical Site	Cetero Research			
Clinical Site Address	625 Demers Avenue East Grand Forks, MN 56721			
Analytical Site	Mylan Pharmaceuticals, Inc. Bioanalytical Department			
Analytical Site Address	3711 Collins Ferry Road Morgantown, WV 26505			

OSI Status	**ADEQUATE (Clinical and Analytical Sites)**		
Nature of OSI Findings	**SYSTEMIC (Clinical Site)**		
OVERALL REVIEW RESULT	**INADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 6	**Fasting Study**	**5%**	**INADEQUATE**
1	**Dissolution**	**5%**	**ADEQUATE**

REVIEW OF BIOEQUIVALENCE SUBMISSION AND OSI INSPECTION REPORT

1 EXECUTIVE SUMMARY

This application contains the results of three studies, (1) a fasting bioequivalence (BE) study with PK endpoint, comparing the test product Mylan's Lidocaine Patch, 5% to the corresponding reference product Teikoku Pharma USA's, Lidoderm® (lidocaine) Patch, 5%; (2) Adhesion study (Study LIDO-1044); and (3) Sensitization/Irritation study (Study LIDO-1046). The division of bioequivalence will review the bioequivalence study, and the Division of Clinical Review will review the Adhesion Study and Sensitization/Irritation Study. The fasting BE study was designed as a single-dose, two-way crossover study in healthy male and female subjects, in which acute dermal irritation, adhesion of the patches and residue in the patches were also assessed. The firm's fasting BE study is incomplete pending a satisfactory response from the firm to the deficiencies related to "apparent dose" and adhesion assessment in the BE study and the impact of the OSI findings at the analytical site. The results are summarized in the table below.

Lidocaine Patch 5% Dose (2 patches, each containing 5% w/w lidocaine in adhesive matrix) N=29 (M=15, F=14) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study (Study Code: LIDO-1037) Analyte: lidocaine					
Parameter (units)	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	936.83	1002.70	0.93	86.01	101.49
AUC∞ (hr *ng/ml)	958.91	1022.89	0.94	86.67	101.40
Cmax (ng/ml)	67.92	71.70	0.95	85.12	105.40

Additionally, the firm submitted the results of a pilot fasting BE study (LIDO-09254). The purpose of the pilot study was to evaluate the bioequivalence of three formulations of Mylan's Lidocaine Patch 5%, differing in the composition of the adhesive matrix, to the RLD product, Lidoderm® patch 5%. The pilot study was designed as a single-dose, four-way crossover study, in which 20 healthy male subjects were enrolled. Nineteen subjects completed the study and were included in the statistical analysis. The 90% confidence interval of AUC0-t and Cmax of lidocaine met the acceptance criteria of 80-125% for all 3 formulations.

The firm has conducted acceptable comparative drug release testing on Lidocaine Patch 5% using the FDA-recommended method as follows: (DARRTS: ANDA 202346; Munshi, Utpal M; 6/02/2011;REV-BIOEQ-02 (Dissolution Review); Original-1; Archive)

Apparatus: V (Paddle over Disk)

Speed: 50 rpm
Medium: 10 mM Sodium Acetate Buffer, pH 4.0
Temperature: 32°C
Volume: 500 mL

The DB also accepted the firm proposed specification:
1.5 h: (b) (4) %
6 h: (b) (4) %
12 h: (b) (4) %
24 h: (b) (4) %

The last inspection at the clinical site, Cetero Research (4801 Amber Valley Pkwy, Fargo, ND 58104), conducted by the Office of Scientific Investigations (OSI) was a routine inspection requested for NDA202834. The inspection was completed on August 29, 2012, and the outcome was No Action Indicated (NAI).

RECOMMENDATION RELATED TO OSI INSPECTION REPORT REVIEW

An inspection of the clinical site was also requested on 2/11/2012 for the current ANDA 202346 for the Cumulative Irritation and Sensitization Study (LIDO-1046) and Adhesion Study (LIDO-1044). The inspection was completed on February 3, 2012 and the outcome was Voluntary Action Indicated (VAI). No Form FDA 483 was issued but two observations were communicated to the management of the clinical site. The reviewer considers that the following finding is systemic and may affect other dermatological studies conducted at this clinical site.

1. ***Record review of computer generated pharmacy Drug Inventory control records for Study LIDO-1044 reveals the pharmacy's record of the randomization codes for placement of the patches on subjects has been "over" written manually and changed by pharmacy staff to reflect the correct placement as set in the protocol. The firm's SOPs and computer program, called "Study Monitor Program" are incomplete, in that; there is no current computer program that will print in and for pharmacy the protocol placement of the patches; and the SOPs fail to provide guidance for randomization documentation of dermatological studies. In addition, pharmacy has no applicable guidelines for the dermatology studies to follow.***

The Project Manager should assign all related ANDAs for **transdermal patch products only**, for review to determine the acceptability of other dermatological studies conducted at the same clinical facility. For the current application, since the OSI did not indicate concerns for data integrity because of this practice, the firm will not be asked for further evaluation of the impact of this observation.

☐ **Isolated** ☒ **Systemic**

The last inspection of the analytical site, Mylan Pharmaceuticals Inc. (3711 Collins Ferry Rd, Morgantown, WV 26505), was a routine inspection requested for ANDA200462. The OSI inspection was completed on 9/15/2010 and the outcome was VAI. A form FDA-483 was issued to the analytical site with the following findings:

1. ***For ropinirole (study #s ROPI-08204 and ROPI-08205) studies, only 5% of samples were repeated for incurred sample reanalysis (ISR). The firm's SOP L-324-01 for ISR effective date March 10, 2009, requires a fixed percentage (5%) of the total samples to be reanalyzed, irrespective of sample size.***

2. ***Stability of processed samples was determined with only mid level QCs during pre-study validation for ropinirole (study#s ROPI08204 AND ROPI08205) studies. Processed stability was not evaluated with low and high QC concentrations.***

3. ***Failure to document all aspects of study conduct.***

   No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes (including PLE#s: 5176, 5187, 5032, 5168, 5081, 5199, 5069, 5177, 5138, and 5172) during ropinirole (study #s ROPI08204 and ROPI08205) studies.

The parent ANDA reviewer from DB II reviewed the OSI inspection report for the analytical site but did not evaluate whether those findings are systemic or specific to the audited studies. Currently, the DB does not have an official policy on the number of samples to be used for conducting ISR. Therefore, the firm will not be asked to address finding # 1. The firm will be asked to evaluate the impact of findings # 2and 3 on the current application.

The application is **inadequate** due to the deficiencies identified in Section 3.13 of this review.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[1]

Test Product	Lidocaine Patch, 5%*
Reference Product	Lidoderm® (lidocaine) Patch, 5%*
RLD Manufacturer	Teikoku Pharma USA
NDA No.	NDA 020612
RLD Approval Date	March 19, 1999
Indication[2]	LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin.

* The total amounts of lidocaine per patch in the test and RLD products are140 mg and 700 mg respectively. However, the w/w of lidocaine per patch (50 mg per gram adhesive) is 5% for both the test and RLD products. It is also noted that per the Orange Book, the strength of Lidoderm® is 5%.

3.2 PK/PD Information[2]

Bioavailability	The amount of lidocaine systemically absorbed from LIDODERM is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three LIDODERM patches were applied over an area of 420 cm2 of intact skin on the back of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The dose absorbed was 64 ± 32 mg, Cmax was 0.13 ± 0.06 µg/mL and Tmax was 11 hours. When LIDODERM is used according to the recommended dosing instructions, **only 3 ± 2% of the dose applied is expected to be absorbed.** At least 95% (665 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 µg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for three days, indicated that the lidocaine concentration does not increase with daily use.
Food Effect	The RLD label does not mention food effect.
Tmax	11 hours
Distribution	When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.6 SD, n = 15). At concentrations produced by application of LIDODERM, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 µg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.

[1] The Orange Book, Search Term: Lidocaine; Last Access: 11/25/2012
[2] Drugs@FDA: Search Term: Lidoderm; Last Access: 11/25/2012.

Metabolism	It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM (lidocaine patch 5%). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.
Excretion	Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 SD, n = 15).
Half-life	81-149 minutes (mean 107 ± 22 SD, n=15)
Dosage and Administration	Apply LIDODERM to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination. If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides. When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.
Maximum Daily Dose	Three patches simultaneously for 12 hours
Drug Specific Issues (if any)	**HANDLING AND DISPOSAL** Hands should be washed after the handling of LIDODERM, and eye contact with LIDODERM should be avoided. Do not store patch outside the sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that, the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them. LIDODERM should be kept out of the reach of children. **WARNINGS** **Accidental Exposure in Children** Even a used LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important for patients to **store and dispose of LIDODERM out of the reach of children, pets and others.** **Excessive Dosing** Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects. Lidocaine toxicity could be expected at lidocaine blood

	concentrations above 5µg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of LIDODERM, the average peak blood concentration is about 0.13 µg/mL, but concentrations higher than 0.25 µg/mL have been observed in some individuals.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2

1.	**Type of study:**	Fasting
	Design:	Single-dose, in-vivo, using three topical patches
	Strength:	5%; 700 mg/ patch[3]
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	• Apply three topical patches (2100 mg total dose) simultaneously over a 12-hour period. • You may use a smaller number of patches provided the plasma concentrations of lidocaine are measurable to adequately characterize the pharmacokinetic profile of lidocaine for bioequivalence assessment based on the 90% confidence interval criteria. • Please include a 24-hour post-dose sampling time in the bioequivalence study. • In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. The amount of adhesive residue from each patch left on the skin should be analyzed and included in the calculation.

Analytes to measure (in plasma):	Lidocaine in plasma. Please utilize a validated analytical method such as LC-MS/MS to reliably measure plasma lidocaine concentrations. A lower limit of quantitation (LLOQ) of 0.20 ng/ mL is recommended to adequately characterize the pharmacokinetics at the 2100 mg study dose.
Bioequivalence based on:	90% CI of lidocaine

2.	**Type of study:**	Skin irritation/sensitization study
	Design:	Single-dose, in-vivo (preceded by an induction phase and a rest period)
	Strength:	5%; 700 mg/patch
	Subjects:	Normal healthy males and females, general population

[3] Note: Although the current draft guidance for the drug product states the strength as "5%; 700 mg/patch", the Orange Book currently states the strength as "5%" only.

	Additional Comments:	See Draft Guidance on Lidocaine (Recommended Dec 2006; May 2007) for specific recommendation regarding this study

APPEARS THIS WAY ON ORIGINAL

General Recommendations	• Please note that the name of RLD is designated as lidocaine topical patch, 5%. This designation is based on the concentration of lidocaine in the adhesive, which is 5%. Please formulate your product to contain 5% of lidocaine in the adhesive, to have the same surface area and the same total amount of lidocaine in the patch as the RLD. • You may submit a full bioequivalence study protocol for review prior to initiating the study.

Waiver Request of in vivo testing:	Not Applicable
Source of most recent recommendations:	Draft Guidance on Lidocaine (Recommended Dec 2006; May 2007); http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf
Summary of OGD or DB History (for details, see Appendix Error! Reference source not found.**):**	According to the Orange Book, there is one approved generic product for Lidocaine Patch, 5% (ANDA# 200675; Submitted by Watson Laboratories Inc; Approved on 11/25//2012). According to DARRTS as of 11/25/2012, the OGD has received (b) (4) ANDAs for Lidocaine Patch, 5%: **ANDA#** / **Firm** / **Status** 200675 / Watson Laboratories Inc / Approved (b) (4) 202346 / Mylan Technologies Inc / Pending (b) (4) Numerous Controlled Correspondences have been submitted to the OGD for Lidocaine Patch. The OGD has received the following protocols related to Lidocaine Patch, 5%: **Protocol No.** / **Firm** / **Review Status** 05-030 / Mylan Pharm / Closed 09-006 / (b) (4) / Closed 09-039 / / Closed 09-046 / / Closed 10-005 / / Closed

Note: The following is the OGD's interactions with Mylan regarding Lidocaine Patch, 5%[4]

[4] \\Cdsnas\ogds11\FIRMSAM\MYLAN\CONTROLS\090618C1109.memo.doc

Protocol P05-030

On June 20, 2005, Mylan requested that the OGD provide comments on a proposed Lidocaine Patch 5% PK bioequivalence study protocol LIDO-05108 (OGD P05-030). On May 19, 2006 via an 8-page fax, the OGD Clinical Review Team: 1) notified Mylan that their proposal to conduct a single dose pharmacokinetic study to establish bioequivalence between their generic lidocaine patch, 5% and Lidoderm® was acceptable, a clinical endpoint study was not being requested by the Agency, and recommendations regarding the PK study and dissolution testing were deferred to the Division of Bioequivalence, and 2) provided recommendations on the skin irritation, sensitization and adhesion studies.

Control 06-1542 and Duplicate Control 06-1594

Mylan requested written recommendations from the Division of Bioequivalence as soon as possible for demonstrating bioequivalence for the Lidocaine Patch 5%. On October 27, 2006, the OGD provided the requested comments to Mylan (re: Protocol 05-030, Control 06-1542 and Control 06-1594) in a 10-page regulatory letter. In December 2006, an individual drug product Draft Guidance on Lidocaine (patch/topical) was posted. In May 2007, the posted Draft Guidance on Lidocaine (patch/topical) was revised.

Control 09-0618

On November 17, 2009, Mylan submitted a meeting request to discuss their proposed clinical development plan for a generic to Lidoderm® (lidocaine patch 5%). Their submission was assigned Controlled Correspondence No. 09-0618 and it contained the following 3 questions:

1) *If equivalence is demonstrated in the proposed clinical studies, Mylan proposes that our patch containing less total lidocaine than the reference listed drug (RLD) can be considered therapeutically equivalent and approved as an AB rated generic. Does the Agency agree?*
2) *Does the Agency agree that skin irritation and skin sensitization can be evaluated in separate clinical studies?*
3) *Mylan proposes to assess irritation according to the protocol outlined in Appendix A. Does the Agency agree with Mylan's proposal to conduct the cumulative irritation study using an intermittent application of the patch, following the directions in the product labeling, for a total of 21 days?*

No action on this meeting request was taken by the OGD due to the pending Citizen Petition FDA-2006-P-0346 submitted December 18, 2006 by Endo Pharmaceuticals for this drug product, with amendments to that petition dated August 29, 2007 and March 12,

2012. The Agency issued their response to this CP on August 22, 2012 and the OGD is now able to respond to the Controlled Correspondences and Protocols for this drug product.

In the meantime, Mylan submitted ANDA 202346 for the Lidocaine Patch on October 26, 2010.and it has been received as of that same date. Thus, there is no longer any need to discuss with Mylan their proposed clinical development plan for a generic to Lidoderm® (lidocaine patch 5%).

On September 6, 2012, Mylan was called at 304-599-2595 Ext. 6551 and this reviewer was informed that Mr. Talton is currently not available due to being away at an off-site meeting all week. A telephone message was left for Mr. Talton that his meeting request dated November 17, 2009 was assigned Controlled Correspondence No. 09-0618 and it has been closed due to the submission by Mylan of ANDA 202346 for the Lidocaine Patch. The message was left that because of Mylan's submission of an ANDA for this drug product (and the receiving of this ANDA by the OGD), there is no longer any need for the OGD to discuss with Mylan their proposed clinical development plan for a generic to Lidoderm® (lidocaine patch 5%). The phone number of this reviewer was left on the message, in case Mr. Talton has any questions.

Reviewer's Comments:
Although the RLD product, Lidoderm® contains 700 mg lidocaine per patch, the strength of Lidoderm® is 5% as per the Orange Book. Therefore, "700 mg/patch" noted as the strength in the BE guidance for Lidocaine Patch is not the same strength stated for the drug product in the Orange Book, i.e., 5% only.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1 (pivotal); 1 (pilot)
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	Yes	1
Waiver requests	No	-
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-

Amendments	No	-

APPEARS THIS WAY ON ORIGINAL

3.5 Pre-Study Bioanalytical Method Validation

Parameters	Data
Bioanalytical method validation report location	Lidocaine Bioanalytical Method Validation Report, Sections 5.3.1.4. See Lidocaine Validation Table 1
Analyte	Lidocaine (LIDO)
Internal standard (IS)	Lidocaine-d10 (DLID)
Method description	Liquid-liquid; LC/MS/MS - ESI
Limit of quantitation (ng/ml)	1
Average recovery of drug (%)	HQC (40 ng/mL): 77.99% MQC (6.67 ng/mL): 75.30% LQC (1 ng/mL): 74.32%
Average recovery of IS (%)	75.86%
Standard curve concentrations (ng/ml)	1, 2, 3, 5, 15, 30, 60, 90, 135, 150
QC concentrations (ng/ml)	3, 20, 60, 120
QC Intraday precision range (CV %)	HQC: 1.24-1.66% MQC: 0.90-2.81% M1-QC: 1.41-1.78% LQC: 1.74-3.74% LLOQQC: 1.63-6.08%%
QC Intraday accuracy range (%)	HQC: 97.58-99.25% MQC: 97.12-98.52% M1-QC: 97.05-99.5% LQC: 96.27-99.33% LLOQQC: 91.2-98.2%
QC Interday precision range (CV %)	HQC: 1.51% MQC: 1.88% M1QC: 1.79% LQC: 2.92% LLOQ QC: 4.76%
QC Interday accuracy range (%)	HQC: 98.5% MQC: 97.82% M1QC: 98.45% LQC: 98.30% LLOQ QC: 95%
Bench-top stability (hrs)	24.25 hours @ Room Temperature
Solution stability	LIDO Stock Solution 29 days @ Room Temperature LIDO Working Solution 29 days @ Room Temperature DLID Stock Solution 29 days @ Room Temperature DLID Working Solution 30 days @ Room Temperature
Processed stability (hrs)	98 hours @ Room Temperature
Freeze-thaw stability (cycles)	4 cycles below -70 ^{o}C
Long-term storage stability (days) (Accuracy%, CV %)*	185 days at -70 ^{o}C in plasma HQC (98.75%, 1.64%) LQC (94.60%, 1.15%) 185 days at -15 ^{o}C in plasma HQC (98.29%, 1.71%) LQC (93.87%, 3.26%)
Dilution integrity (Accuracy%, CV %)	600.0 ng/mL (in plasma): 5 fold dilution (101.73%,

	1.44%)
Selectivity	No interfering peaks noted in 6 lots of blank plasma samples

* The long term storage stability data was reported in validation report addendum 1 (section 5.3.1.4; submission date: 2/8/2011).

SOPs submitted	Yes L-301-05: Bioanalytical Methods Validation; effective date: 10/09/2007
Was the % recovery consistent across QC concentrations?	Yes
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes (K2EDTA)
If not, was cross validation study conducted?	
Was the dilution factor adequate for the current study sample analysis?	Yes
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	Yes (plasma)
Does the duration of the each of the stability parameters support the sample preparation and assay dates?	Yes (for long term stability). Information not available for other stabilities
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	Yes

Comments on the Pre-Study Method Validation:

1. It was noted that the report of bioanalytical method validation was approved (June 15, 2010) after the completion date (June 9, 2010) of the study sample analysis. The analytical method is considered validated only after the method validation report is approved by signatory authority. For future submission, the firm should ensure a validated analytical method is used for study sample analysis.

2. K2EDTA is used as an anticoagulant in the pre-study bioanalytical validation, which is the same anticoagulant used in the clinical studies. The spiked calibration standards and quality control samples were prepared with human plasma containing K2EDTA during method validation and study.

3. The storage time for the long term stability samples in plasma at -70 ºC and -15 ºC (185 days) is sufficient to cover the maximum storage period of the study samples from the fasted study (a maximum 31 days at -70 ºC±15 ºC, from May 9, 2010 to June 09, 2010).

4. According to the BE guidance for Lidocaine Patch, a lower limit of quantitation (LLOQ) of 0.20 ng/mL is recommended to adequately characterize the pharmacokinetics at the 2100 mg study dose. The firm conducted the fasting BE study with 2 Lidocaine Patches per subject per period, which suggests 1400 mg of RLD product and 280 mg of test product were used in the study. The reviewer checked the plasma concentrations of

study samples and noted that a total of 72 out of 1062 samples (12.3%) were below LOQ, in which there are 54 samples at first time point (1 hour), 12 samples at second time point (2 hours), and 6 samples at the last time point (36 hours). The median Tmax is between 10-11 hours and there are at least 5 additional blood draws between 2 hours and 10 hours. The reviewer considers the sensitivity of the bioanalytical method is sufficient to adequately characterize the pharmacokinetic profiles for the subjects in the fasting BE study.

The pre-study method validation is complete.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Fasting Study (Pivotal)

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})	
					Lidocaine						
LIDO-1037	Single-Dose Fasting Bioequivalence Study of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers	Open-label, Single-dose, Randomized, Two-period, Two-treatment Crossover	A=Lidocaine Patch 5%, 2 patches for 12 hours topical route, Lot#R6B0017	30 Dosed 29 Completed and Analyzed Healthy Subjects Mean Age: 40 (Range: 18 to 68)	70.58 ± 20.94	10.00 (8-16)	973.1 ± 291.3	994.0 ± 288.7	4.196 ± 0.557	0.1678 ± 0.0208	Section 5.3.1.2
			B= Lidoderm® Patch 5%, 2 patches for 12 hours topical route Lot #97278 exp. 08/2010		77.01 ± 31.78	11.05 (9-14)	1054 ± 350.9	1074 ± 353.1	4.706 ± 0.699	0.1504 ± 0.0223	

Fasting Study (Pilot) (Informational)

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})	
					Lidocaine						
LIDO-09254	Single-Dose Fasting Bioequivalence Pilot Study of Three Formulations of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers	Open-label, Single-dose, Randomized, Four-period, Four-treatment Crossover	A=Lidocaine Patch 5%, Ext. (b) (4) 140 mg lidocaine topical route, Lot# R6A0041	20 Dosed 19 Completed 19 Analyzed Healthy Subjects Mean Age: 50 (Range: 18 to 70)	77.49 ± 20.67	10.00 (7-16)	1036 ± 268.1	1050 ± 269.5	4.442 ± 0.565	0.1587 ± 0.0220	Section 5.3.1.2
			B=Lidocaine Patch 5%, (b) (4) (b) (4) lidocaine topical route, Lot# R6A0042		77.79 ± 21.08	10.00 (4-16)	1058 ± 262.3	1078 ± 261.9	4.489 ± 0.814	0.1591 ± 0.0282	
			C=Lidocaine Patch 5%, (b) (4) 140 mg lidocaine topical route, Lot# R6A0043		79.19 ± 22.11	10.00 (4-16)	1083 ± 307.3	1104 ± 305.2	4.647 ± 0.811	0.1534 ± 0.0265	
			D= Lidoderm® Patch 5% 700 mg lidocaine topical route, Lot #97278 exp. 08/2010		83.39 ± 49.45	10.00 (8-16)	1094 ± 529.2	1127 ± 515.1	5.788 ± 2.993	0.1350 ± 0.0354	

[1]In accordance with FDA's Final Rule published in the Federal register on January 16, 2009 and the Draft Guidance for Industry *Submission Summary of Bioequivalence data for ANDAs* (April 2009), all bioequivalence (BE) studies conducted on the same drug product formulation subject of this ANDA have been included within this submission. This summary table is therefore provided for informational purposes only.

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Lidocaine Patch 5% Dose (2 patches, each containing 5% w/w lidocaine in adhesive matrix) N=29 (M=15, F=14) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study (Study Code: LIDO-1037) Analyte: lidocaine					
Parameter (units)	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	936.83	1002.70	0.93	86.01	101.49
AUC∞ (hr *ng/ml)	958.91	1022.89	0.94	86.67	101.40
Cmax (ng/ml)	67.92	71.70	0.95	85.12	105.40

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE? Yes

Table 3. Reanalysis of Study Samples

LIDO-1037 – BE Study Repeat Analysis Results for Lidocaine								
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	0	0	0	0	0
Reason A	1	1	0.10	0.10	1	1	0.10	0.10
Reason B	0	1	0	0.10	0	1	0	0.10
Reason C	1	0	0.10	0	1	0	0.10	0
Total	2	2	0.19	0.19	2	2	0.19	0.19

Reason A: Abnormal Internal Standard (IS) Response
Reason B: Sample Outside of Curve Range (ALQ)
Reason C: Confirmation of Original Value

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
D-400-10	02/24/2010	Reassay or Reinjection of Clinical Samples

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria**: analytical and pharmacokinetic**	Yes
If not, list the criteria that you don't agree and provide additional comment below	
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	
Did reviewer reanalyze study results?	Yes
Was the study outcome changed based on reviewer reanalysis?	No

Did the firm provide a comprehensive table of repeat samples in the format recommended by the DB?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes

Comments from the Reviewer:

1. According to SOP D-400-10 (Title: Reassay or Reinjection of Clinical Samples), *a clinical sample having an internal standard peak area (or height) <50% or 150% of the mean internal standard peak area (or height) of all samples spiked with internal standard (i.e. single blanks, calibrators, QCs and study samples) will be reassayed due to abnormal internal standard response.* The reviewer verified from the raw numerical data that the IS area response was (b) (4) for sample sub (b) (6) (b) (6) which was <50% of the mean IS area response for the corresponding run (b) (4). The IS area response for sample sub (b) (6) was 1681689, which was also <50% of the mean IS area response for the corresponding run (b) (4) Please note that both samples were analyzed in run 6 and that the reviewer calculated the mean IS area according to the SOP D-400-10. The reanalysis of these two samples is justified.

2. Sample Sub (b) (6) was reanalyzed due to sample concentration above the limit of quantitation. The reviewer verified from the raw data of the original run (run 14) that the instrument response (b) (4) of this sample exceeds that (3.288574) of the upper limit of quantitation (ULOQ). The firm reanalyzed this sample with 2 fold dilution. In addition, the diluted sample was accompanied by 4 high QC samples that were also diluted by 2 fold according to the SOP D-400-10. The reanalysis of sample Sub (b) (6) is justified. The reassayed value was approximately 15% higher than the ULOQ.

3. Sample Sub (b) (6) was reanalyzed for reason of confirmation of original value (BLOQ). The reviewer verified from the raw data of the original run (run 15) that no instrument response was generated for this sample. The sample was reanalyzed in triplicate and the mean (86.41 ng/mL) of the three repeat results was reported as per the SOP. Further, the reviewer verified from the plasma concentration table of study samples, the concentration of the study sample was 78.28 ng/mL at the 11 hour time point and 81.62 ng/mL at 13 hour time point. The reviewer considers it is less likely that the plasma concentration at 12 hour time point can decrease to the level of BLOQ. The reanalysis of sample Sub (b) (6) is justified.

3.7 Summary of Adhesion and Irritation Assessment of the Lidocaine Patch in the PK Study

In addition to conducting separate skin irritation and sensitization study (#Lido-1046) and adhesion study (#Lido-1044), the firm also assessed adhesion and irritation for the pivotal BE study. Since the OGD's Division of Clinical Review (DCR) evaluates the skin irritation/sensitization and adhesion studies, the DCR should evaluate the irritation/sensitization and adhesion results from the fasting bioequivalence study (Lido-1037), as well. The information for the skin irritation and adhesion from the BE study as provided by the firm is included here for information purpose only.

Summary of Adhesion Assessment: Transdermal adhesion of the lidocaine patch was assessed at 4, 8 and 12 hours (± 10 minutes) after patch application to ensure good contact with skin for drug delivery. The following rating scale was used to assess adhesion:

Score	Definition
0	>= 90% Adhered (essentially no lift off from the skin)
1	>= 75% to <90% Adhered (some edges only lifting off the skin)
2	>= 50% to <75% Adhered (less than half the system lifting off the skin)
3	>0% to <50% Adhered but not detached (more than half lifting off the skin)
4	Patch detached (patch completely off the skin)

According to the PK report synopsis, all patches maintained good skin contact throughout the wear period. Patch adhesion was ≥ 50% for both treatments for 12 hours. The firm submitted the adhesion scores at the above mentioned 3 time points for each patch applied in all the subjects. However, the firm did not provide statistical summary data of the adhesion scores for the test and reference patches (Mean, SD, Minimum, Median, Maximum, confidence interval etc.) and the acceptance criterion for comparable adhesion of the test and reference products. The firm will be asked to provide this information.

Summary of Irritation Assessment

Skin irritation was evaluated at 30 to 35 minutes after removal using the following rating scales:

<u>Dermal Response:</u>
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 erythema
5 : Erythema, edema, and papules
6 : Vesicular eruption
7 : Strong reaction spreading beyond test site

Other Effects:
A(0): Slight glazed appearance
B(1): Marked glazing 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 scorabs

After 30 minutes, the mean (± SD) cumulative irritation score was 0.45 ± 0.67 and 0.69 ± 0.66 for Mylan's lidocaine patch 5% and Lidoderm® Patch 5%, respectively. Therefore, barely perceptible erythema (on average) was seen with both treatments half hour after patch removal. Below is summary statistics of the irritation scores:

Treatment	N	Mean	SD	CV	Max	Median	Min
Test	29	0.45	0.67	150	2.00	0	0
RLD	29	0.69	0.66	95.7	2.00	1.00	0

The firm also submitted the frequency table of irritation score at 0.5 hour after Patch removal:

Table of treat by score					
treat	score				Total
	0	1	2	3	
A	39	14	3	2	58
B	25	26	7	0	58
Total	64	40	10	2	116

* A: Test product-Mylan's Lidocaine Topical Patch, 5%; Dose: 2 patches for 12 hours.
* B: RLD product-Endo's Lidoderm Topical Patch, 5%; Dose: 2 patches for 12 hours.

Reviewer's Note: The firm did not state if the scores were the combined scores of dermal response score plus other effects score or not.

3.8 Summary of Residual Patch Analysis in the PK Study

In accordance with the BE guidance for Lidocaine Patch, the firm determined the amount of adhesive residue from each patch left on the skin in the residual patch assay. The transdermal systems worn during the study were saved and were analyzed for their residual lidocaine levels. These values, along with the residual lidocaine levels on the alcohol wipes used to clean the skin area after transdermal system removal, were subtracted from control patch levels to arrive at an apparent dose. Residual assay results indicated the average theoretical dose absorbed (i.e. "apparent dose" delivered) was 14.72 mg for the test product Lidocaine Patch 5% and was 19.92 mg for the RLD, Lidoderm Patch 5% following a single 12-hour application of one Lidocaine Patch. Below is the summary table for the results of residual patch analysis.

	Mylan's Lidocaine Patch, 5% (mean±SD)	**Teikoku's Lidoderm (lidocaine)Patch, 5%(mean±SD)**
Lidocaine Dose Absorbed per Patch (mg)	14.72±5.68	19.92±14.96
Fraction of the original dose absorbed	11.3±4.3%	3.0±2.2%

According to the RLD labeling, only 3±2% of 700 mg lidocaine contained in the patch is expected to be absorbed. At least 95% (665 mg) of lidocaine will remain in a used patch. The RLD labeling also indicated that a dose of 64 ± 32 mg was absorbed for three patch wear, which means about 21±11 mg was absorbed for one patch. It is noted that the lidocaine dose absorbed per patch and its fraction to the original dose for the RLD product observed in study LIDO-1037 are also consistent with the RLD labeling claim.

The data show that a dose of 14.72 ± 5.68 mg was absorbed per patch for the test product compared to 19.92 ± 14.96 mg absorbed for the reference product, i.e. the absorbed dose is approximately 26% lower for the test product compared to the reference product. The validity of the data for the residual patch assay cannot be confirmed as the study report did not include the complete analytical report or the detailed experiment procedures and the validation report. The firm did not conduct any statistical analysis to evaluate if the dose adsorbed per patch from the test product was comparable to the reference product. The firm will be asked to provide this information. It is noted that currently the OGD only recommends reporting the "apparent dose" delivered.

3.9 Formulation

Location in appendix	Section 4.1.2, Page 52
If a tablet, is the RLD scored?	No
If a tablet, is the test product biostudy/exhibit batch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.10 In Vitro Dissolution

Location of DB Dissolution Review	DARRTS: ANDA 202346; Munshi, Utpal M; 6/02/2011;REV-BIOEQ-02 (Dissolution Review); Original-1; Archive
Submitted Method (USP, FDA, or Firm)	FDA
Recommended Method (details below) for the current ANDA	FDA
Medium*	10 mM Sodium Acetate Buffer, pH 4.0
Temperature	32ºC
Volume (mL)	500 mL
USP Apparatus type	V (Paddle over Disk)
Rotation (rpm)	50 rpm
Recommended Sampling Time (min)	10, 20, 30, 60, 120 and 180 minutes
Specifications	**FDA recommended:** NLT (b) (4) per patch at 30 minutes; **The firm proposed (accepted by the DB I)** 1.5 h: (b) (4)%; 6 h: (b) (4)%; 12h: (b) (4)%; 24h: (b) (4)%
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	N/A
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	N/A
If no, reason why F2 not calculated	
Is method acceptable?	**Acceptable**
If not then why?	

* The FDA-recommended method in the external and internal database does not indicate the molarity of the dissolution medium. The firm used 10mM sodium acetate buffer, pH 4.0

3.11 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	Yes
Waivers granted?	**N/A**
If not then why?	N/A

3.12 Deficiency Comments

Deficiency related to OSI inspection

1. The last inspection of the analytical site was a routine inspection requested for ANDA200462. The OSI inspection was completed on 9/15/2010 and the outcome was VAI. A form FDA-483 was issued to the analytical site with the following findings:

1. ***For ropinirole (study #s ROPI-08204 and ROPI-08205) studies, only 5% of samples were repeated for incurred sample reanalysis (ISR). The firm's SOP L-324-01 for ISR effective date March 10, 2009, requires a fixed percentage (5%) of the total samples to be reanalyzed, irrespective of sample size.***

2. ***Stability of processed samples was determined with only mid level QCs during pre-study validation for ropinirole (study#s ROPI08204 AND ROPI08205) studies. Processed stability was not evaluated with low and high QC concentrations.***

3. ***Failure to document all aspects of study conduct.***

   No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes (including PLE#s: 5176, 5187, 5032, 5168, 5081, 5199, 5069, 5177, 5138, and 5172) during ropinirole (study #s ROPI08204 and ROPI08205) studies.

The parent ANDA reviewer from DB II reviewed the OSI inspection report for the analytical site but did not evaluate whether those findings are systemic or specific to the audited studies. Currently, the DB does not have an official policy on the number of samples to be used for conducting ISR. Therefore, the firm will not be asked to address finding # 1. The firm will be asked to evaluate the impact of findings # 2 and 3 on the current application.

Deficiency related to the BE study

2. It was noted that a number of subjects were evaluated with adhesion score as 1 or 2 at some time points during the study. According to the protocol, score 1 means >=75% to <90% adhered (some edges only lifting off the skin) and score 2 means >=50% to 75% adhered (less than half the system lifting off the skin). The firm did not provide statistical summary data of the adhesion scores for the test and reference patches (Mean, SD, Minimum, Median, Maximum, confidence interval etc.) and the acceptance criterion for comparable adhesion of the test and reference products. The firm will be asked to provide this information.

3. The firm reported the "apparent dose" delivered. However, the validity of the data for the "apparent dose" delivered cannot be confirmed as the study report did not include the

complete analytical report, validation report or the detailed experimental procedures. The firm did not conduct any statistical analysis to evaluate if the dose absorbed per patch from the test product was comparable to the reference product. The firm will be asked to provide this information.

3.13 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (LIDO-1037) **incomplete** due to the deficiencies mentioned above. Mylan Technologies Inc conducted the fasting BE study on its Lidocaine Patch, 5% (Lot # R6B0017) comparing it to Teikoku Pharma USA' s Lidoderm (lidocaine) Patch, 5% (Lot #97278).

2. The firm's in vitro dissolution testing is **acceptable.** The DB acknowledges that the firm will use the following in vitro drug release method and specifications for its product:

Apparatus:	V (Paddle over Disk)
Speed:	50 rpm
Medium:	10 mM Sodium Acetate Buffer, pH 4.0
Temperature:	32°C
Volume:	500 mL
Specifications:	1.5 h: (b) (4) %
	6 h: (b) (4) %
	12 h: (b) (4) %
	24 h: (b) (4) %

3.14 Comments for Other OGD Disciplines

Discipline	Comment
NA	NA

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	LIDO-1037
Study Title	Single-Dose Fasting Bioequivalence Study of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers
Clinical Site (Name & Address)	Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104, USA 701-239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 09-May-2010 Period II: 16-May-2010
Analytical Site (Name & Address)	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505, USA 304-598-5430
Analysis Dates	Jun 02, 2010 – Jun 09, 2010
Analytical Investigator	Patrick Vallano, Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	31 days at -70ºC ± 15ºC [Date of 1st sample collection – 09-May-2010; Date of last sample extraction – 09-Jun-2010]

Table 6. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	Lidocaine Patch 5%	Lidoderm®
Manufacturer	Mylan Technologies Inc.	Teikoku Seiyaku Co., Ltd. for Endo Pharmaceuticals Inc
Batch/Lot No.	R6B0017	97278
Manufacture Date	03/31/2010	N/A
Expiration Date	N/A	08/2010
Strength	5%	5%
Dosage Form	Topical Patch	Topical Patch
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	101.0%	100.6%
Content Uniformity (range, %CV)	94.3% - 105.4% (3.3%)	Not available
Dose Administered	2 patches for 12 hours (BE study)	2 patches for 12 hours (BE study)

Route of Administration	Topical	Topical

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	N/A
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	N/A

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled: 30 subjects** **Dosed:30 subjects** **Completed: 29 subjects (subject 27 was dropped prior to period II dosing due to a positive breathalyzer test)** **Samples Analyzed: 29 subjects** **Data Analyzed: 29 subjects**
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	**RT:** 2, 4, 5, 8, 9, 11, 13, 15, 18, 20, 21, 23, 26, 27, 30 **TR:** 1, 3, 6, 7, 10, 12, 14, 16, 17, 19, 22, 24, 25, 28, 29
Blood Sampling Times	Blood samples were collected at pre-dose and at 1, 2, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 24 and 36 hours post dose.
Blood Volume Collected/Sample	6 mL/sample; 36 samples per subject.
Anticoagulant	K2EDTA
Blood Sample Processing & Storage (include storage temperature)	Blood samples were collected in K2EDTA tubes via direct venipuncture. The tubes were inverted 5-10 times immediately after collection, and immediately placed in an ice bath. The samples were centrifuged within 30 minutes of collection at 3000rpm for 10 minutes at 4ºC to separate plasma. The separated plasma was transferred to polypropylene tubes in two equal aliquots. The plasma samples were then stored upright in a freezer at a temperature -70ºC±15ºC within 60 minutes. The plasma samples were transferred to analytical site after the completion of clinical phase.
IRB Approval	3/10/2010
Informed Consent	3/10/2010
Length of Fasting	At least 10 hours of overnight fasting prior to dose and 4 hours postdose.
Length of Confinement	The subjects were housed in the clinical facility from the evening prior to dosing and remained at the clinical site until 24 hours after dosing.

Safety Monitoring	Medical examination, vital signs and clinical laboratory tests were performed at times specified in the protocol. Adverse events were monitored throughout the study.

Was the study design used for the fasting BE study acceptable?	YES

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 8A. Demographics Profile of Subjects Completing the Bioequivalence Study

FASTING BIOEQUIVALENCE STUDY MYLAN STUDY NUMBER – LIDO-1037			
		TREATMENT GROUPS	
		Test Product N=29[1]	Reference Product N=29[1]
Age (years)	Mean ± SD	36.0 ± 15.6	36.0 ± 15.6
	Range	18 - 68	18 - 68
Age Groups	< 18	-	-
	18 – 39	17 (58.6%)	17 (58.6%)
	40 – 64	11 (37.9%)	11 (37.9%)
	65 – 75	1 (3.4%)	1 (3.4%)
	> 75	-	-
Sex	Male	15 (51.7%)	15 (51.7%)
	Female	14 (48.3%)	14 (48.3%)
Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	-	-
Not Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	-	-
	I	-	-
	IA	1 (3.4%)	1 (3.4%)
	W	27 (93.1%)	27 (93.1%)
	WB	1 (3.4%)	1 (3.4%)
BMI	Mean ± SD	25.6 ± 3.0	25.6 ± 3.0
	Range	19.3 - 29.9	19.3 - 29.9
Other Factors		n/a	n/a

[1]Subjects completing clinical study and whose samples were analyzed

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 8B. Demographics Profile of Individual Subjects Completing the Bioequivalence Study

Number	Initial	Age	Weight (Kg)	Height (cm)	BMI Frame	Gender	Ethnicity	Race
	(b) (6)	40	77.9	179.10	24.3	Male	X	W
		22	81.9	166.93	29.4	Female	X	W
		68	64.9	157.35	26.2	Male	X	W
		23	78.8	171.58	26.8	Female	X	W
		33	75.8	172.39	25.5	Female	X	W
		40	63.1	171.27	21.5	Female	X	W
		23	90.3	176.28	29.1	Female	X	WB
		54	58.1	157.18	23.5	Female	X	W
		40	86.5	180.87	26.4	Male	X	W
		59	91.5	175.29	29.8	Female	X	W
		55	78.5	172.80	26.3	Male	X	W
		20	85.8	177.34	27.3	Male	X	IA
		21	67.0	171.58	22.7	Male	X	W
		64	78.1	174.93	25.5	Male	X	W
		24	81.9	177.60	26.0	Male	X	W
		54	69.2	157.38	28.0	Female	X	W
		19	66.1	182.07	19.9	Male	X	W
		39	88.3	171.88	29.9	Female	X	W
		50	64.2	161.34	24.7	Female	X	W
		20	91.3	190.91	25.0	Male	X	W
		24	78.8	186.13	22.7	Male	X	W
		46	67.2	156.67	27.4	Female	X	W
		23	93.1	179.88	28.8	Male	X	W
		25	74.7	183.87	22.1	Male	X	W
		24	67.4	176.28	21.7	Female	X	W
		54	88.1	174.24	29.0	Male	X	W
		20	73.1	171.40	24.9	Male	X	W
		39	74.7	164.06	27.7	Female	X	W
		22	81.3	173.36	27.0	Male	X	W
		18	49.9	160.83	19.3	Female	X	W

Ethnicity:
Hispanic or Latino H; Not Hispanic or Latino X

Race:
American INdian or Alaskan Native: N
Asian: A
Black or African American: B
Native Hawaiian or Other Pacific Islander: I
White: W

Table 9. Dropout Information, Fasting Bioequivalence Study

Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with

(b) (6)	Subject was dropped prior to Period II due to a positive breathalyzer test.	II	No	N/Ap

Table 10. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event [1]	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Mylan Study Number - LIDO-1037	
	Test N=30[2]	Reference N=29[2]
	n (%)[3]	n (%)[3]
General disorders and administration site conditions		
Application site erythema	11 (36.67%)	18 (62.07%)
Application site pain	1 (3.33%)	-
Application site pruritus	1 (3.33%)	1 (3.45%)
Feeling hot	1 (3.33%)	-
Injury, poisoning and procedural complications		
Sunburn	-	1 (3.45%)
Nervous system disorders		
Headache	1 (3.33%)	-
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	-	1 (3.45%)
Total Subjects Reporting at Least One Adverse Event	**13 (43.33%)**	**18 (62.07%)**

[1] MedDRA Version 12.1
[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)%)

Subjects Experiencing Emesis
None

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?
None

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*? N/A

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.
Yes

Are there any safety concerns based on the adverse event profile?
No

Table 11. Protocol Deviations, Fasting Bioequivalence Study

PK sample Collection Deviations

	Subject No.	Scheduled (hr:min)	Actual (hr:min)	+ / -
Period I	(b) (6)	1:00	1:03	+0:03
		12:00	12:03	+0:03
		16:00	16:04	+0:04
		20:00	20:06	+0:06
		36:00	Schedule Conflict/No Sample	
Period II		ALL	Dropped/No Sample	
		1:00	1:06	+0:06
		4:00	4:04	+0:04
		6:00	6:04	+0:04
		7:00	7:03	+0:03
		7:00	7:03	+0:03
		11:00	11:05	+0:05
		11:00	11:04	+0:04
		11:00	11:04	+0:04
		11:00	11:05	+0:05
		11:00	11:03	+0:03
		12:00	12:03	+0:03
		13:00	13:03	+0:03
		18:00	18:04	+0:04
		24:00	24:04	+0:04
		36:00	35:22	-0:38

All other Protocol deviations

Mylan FASTING Study Number – LIDO-1037		
Type	Subject #'s (Test)	Subject #'s (Ref.)
Period I, study hour 2.00 vital signs repeated 22 minutes after initial collection	(b) (6)	
Period I, study hour 2.00 vital signs repeated 19 minutes after initial collection		
Period I, study hour 8.00 out of range vital signs approved by manager instead of investigator		
Period I, study hour 16.00 out of range vitals repeated 25 minutes after initial collection		
Period I, study hour 12.00 adhesion evaluation done 12		

Mylan FASTING Study Number – LIDO-1037		
Type	Subject #'s (Test)	Subject #'s (Ref.)
hrs. 11 minutes. post application	(b) (6)	
Period I, study hour 12.50 irritation evaluation done between 25-28 minutes post removal		
Period I subject transdermal patch systems placed in freezer between 83-90 minutes post removal (Subject 11 lower right patch)		
Period I subject transdermal patch systems placed in freezer between 61-66 minutes post removal (Subject 11 upper right patch)		
Period I alcohol wipes placed in freezer between 61-69 minutes after subject swabbing		
Period I, study hour 10.25: subject consumed <75% of meal		
Period I, study hour 36.00 return: no query, vital signs, or sample collected due to subject schedule conflict		
Period II, study hour 12.00 out of range vital signs repeated 27 minutes after initial collection		
Period II, study hour 16.00 out of range vital signs repeated 32 minutes after initial collection		

Did dropouts/adverse events/protocol deviations affect the study outcome? Please see comment below.

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. A total of 30 subjects were enrolled in the study and 30 subjects were dosed. 29 subjects completed the study. Subject (b) (6) was withdrawn from the study prior to period II dosing due to a positive breathalyzer test. The reviewer verified the information for subject (b) (6) in the case report forms and considers the withdrawal acceptable.
2. A total of 63 adverse events for the test and reference products were reported by 22 subjects in the study. All the adverse events were mild to moderate in nature. All adverse events were resolved. No death or serious adverse events were observed during the study. The adverse event profile observed during the fasting bioequivalence study was comparable for the test and reference product.
3. A number of subjects had blood sampling time deviation. The time deviations ranged from 3 minutes to 38 minutes. The reviewer checked that the maximum % deviation from the scheduled time was 6.67% (6 minutes deviation from 1 hour sampling time point). According to the study protocol (LIDO-1037), *Blood*

samples between 1-24 hours, which are collected within 2 minutes of scheduling, and blood samples collected at 36 hours, which collected within 10 minutes of scheduling, will not be considered protocol deviations. The reviewer verified that all those sampling time deviations were documented following the description in the protocol. The deviation did not have an impact on the outcome of the study as the actual time of sample collection was used for those samples during pharmacokinetic analysis by the firm and the reviewer.

4. Subjects (b) (6) had protocol deviation related to vital sign measurements. The reviewer considers this protocol deviation would not have any impact to the outcome of the study.
5. For Subjects (b) (6) adhesion evaluation was performed 12 hours 11 minutes after application in period I. The time deviation from the scheduled time for adhesion evaluation was only 1.53%. The reviewer considers the protocol deviation would have any impact to the outcome of the study.
6. In period I, the irritation evaluation was performed on all the subjects between 25 to 28 minutes post removal. According to the protocol (LIDO-1037), *irritation evaluation will occur 30 to 35 minutes after each application is removed*. The reviewer does not consider the time deviation in irritation evaluation would have impact on the outcome of the PK study.
7. For subject (b) (6) the blood sample was not collected at 36 hour time point. As the sample concentration at 36 hours post-dose was considered as missing data in the pharmacokinetic analysis, the reviewer considers this deviation will not have impact on the outcome of the study.
8. Other protocol deviations are related to the retention of removed patches and alcohol wipes and meal consumption. The reviewer considers these deviations will not have impact on the outcome of the study.

4.1.1.3 Bioanalytical Results

Table 12. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study

Bioequivalence Study LIDO-1037 LIDOCAINE										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	1.000	2.000	3.000	5.000	15.00	30.00	60.00	90.00	135.0	150.0
Inter day Precision (%CV)	1.13	2.04	1.61	1.48	1.00	1.03	1.10	1.34	1.18	1.47
Inter day Accuracy (%Actual)	104.6	92.25	99.2	98.6	97.73	98.2	101.62	102.58	103.33	102.0
Linearity	0.9968-0.9993									
Linearity Range (ng/mL)	1.000-150.0									
Sensitivity/LOQ (ng/mL)	1.000									

Bioequivalence Study LIDO-1037 LIDOCAINE					
Parameter	**Quality Control Samples**				
	LQC	**MQC**	**M1QC**	**HQC**	**HQC (DILUTED)**
Concentration (ng/ml)	3.000	20.00	60.00	120.0	120.0 (diluted)
Inter day Precision (%CV)	1.79	2.29	7.88	1.99	2.69
Inter day Accuracy (%Actual)	102.90	101.65	99.70	101.83	100.33
Number of Acceptable Runs	18				
Number of Rejected Runs (Run ID, volume/page location)	1; Run 7, please see section 5.3.1.4.3 Study Report Body; Table 1 Analytical Run Summary Study LIDO1037				
If sample and QC diluted during study, specify all dilution factors	2				
Was 100% of raw numerical data submitted?	Yes				

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (30 x 20%=6)
Were chromatograms serially or randomly selected?	Serially (1, 2,3, 4,5,6)
Were the chromatograms submitted by the firm acceptable?	Yes

Table 136. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
D-400-10	02/24/2010	Reassay or Reinjection of Clinical Samples
D-416-06	03/11/2009	Reassay of Whole Subjects

Table 147. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	

Were Calibration and Quality Control for the Sample Analysis acceptable?
Yes.

Summary/Conclusions, Study Assays:

1. The firm conducted incurred sample reanalysis (ISR) on 56 samples (5.4% of 1043 samples). All the incurred sample concentrations are within 20% of the mean of original and the ISR concentration for samples (100%) analyzed for lidocaine. The acceptance criteria set by the firm is at least 67% of the incurred reanalysis results shall be within 20% of the mean of original and ISR concentrations. The ISR data are acceptable per the firm's criterion.

The study assay is acceptable.

4.1.1.4 Pharmacokinetic Results

Table 15. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Figure 1

Fasting Bioequivalence Study, Study No. LIDO-1037									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	973.105	29.94	608.32	1839.37	1054.391	33.28	511.18	1939.51	0.92
AUC∞ (hr *ng/ml)	993.537	29.05	647.26	1847.60	1074.135	32.87	528.37	1989.21	0.92
Cmax (ng/ml)	70.578	29.67	39.42	130.20	77.010	41.27	34.03	175.20	0.92
Tmax* (hr)	10.000	.	8.00	16.00	11.050	.	9.00	14.00	0.90
Kel (hr^{-1})	0.170	12.30	0.13	0.22	0.151	14.91	0.11	0.19	1.13
T1/2 (hr)	4.128	12.65	3.15	5.45	4.691	14.98	3.57	6.25	0.88

* Tmax values are presented as median, range

Table 16. Geometric Means and 90% Confidence Intervals - Firm Calculated

Lidocaine Patch 5% Dose (2 x 5%) N=29 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Study Code: LIDO-1037) Analyte: lidocaine				
Parameter	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	936.8	1003	0.93	86%-101%
AUC∞ (hr *ng/ml)	959.3	1023	0.94	87%-101%
Cmax (ng/ml)	67.92	71.70	0.95	85%-105%

Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Lidocaine Patch 5% Dose (2 patches, each containing 5% w/w lidocaine in adhesive matrix) N=29 (M=15, F=14) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasted Bioequivalence Study (Study Code: LIDO-1037) Analyte: lidocaine							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	936.83	29	1002.70	29	0.93	86.01	101.49
AUC∞ (hr *ng/ml)	958.91	29	1022.89	29	0.94	86.67	101.40
Cmax (ng/ml)	67.92	29	71.70	29	0.95	85.12	105.40

Reviewer's Note:
According to the Orange Book, the first generic Lidocaine Patch, 5% was approved under ANDA 200675 on 8/23/2012. The reviewer compared the PK parameters from LIDO-1037 in the current application with those in ANDA 200675[5] and found that the PK parameters (ACUt, AUCi and Cmax) in the current application were approximately 2 times as those in ANDA 200675. It should be noted that only one patch was applied to each subject in the BE study in ANDA 200675 while two patches were used for each subject in study LIDO-1037 in the current application.

Table 18. Additional Study Information, Fasting Study No. LIDO-1037

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	The firm did not indicate in the report the time points used to calculate Ke. The reviewer selected the Ke_first and Ke_last time points in the calculation.	
Root mean square error, AUC0-t*	0.1850	
Root mean square error, AUC∞*	0.1754	
Root mean square error, Cmax*	0.2387	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	29	29
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	yes	yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as Cmax	None	None
Cmax at the first time point	None	None
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞[6]				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	29	0.98	0.93	1.00
Reference	29	0.98	0.96	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	n/a			

[5] DARRTS: ANDA 200675; MITCHELL, DEANAH L 11/30/2011 N/A 11/30/2011 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive
[6] See individual test to reference ratios of PK Parameters in SAS Output.

Was the fasting bioequivalence study acceptable? Inadequate due to the deficiencies.

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

1. The firm did not provide the sampling time-points used in its Kel calculations. However, the reviewer checked the individual semi-log plasma concentration vs. time graphs for each subject and verified that each subject had a linear elimination phase. The reviewer used SAS code, CALCKE, for statistical analysis of the data. This particular SAS code allows the reviewer to select the time points to calculate the elimination rate constant, Kel, along with other PK parameters. The reviewer used the actual sampling times to calculate the 90% CIs.

2. The 90% confidence intervals for lnAUC0-t, lnAUCi and lnCmax calculated by both the reviewer and the firm meet the acceptable criteria of 80-125%.

3. It was noted that a number of subjects were evaluated with adhesion score as 1 or 2. According to the protocol, score 1 means >=75% to <90% adhered (some edges only lifting off the skin) and score 2 means >=50% to 75% adhered (less than half the system lifting off the skin). <u>The reviewer will ask the firm to submit statistical summary data of the adhesion scores for the test and reference patches from all the subjects (Mean, SD, Minimum, Median, Maximum, confidence interval etc.) and the acceptance criterion for comparable adhesion of the test and reference products. The reviewer will then evaluate whether the variable adhesion indicated by different scores would affect the outcome of the study.</u>

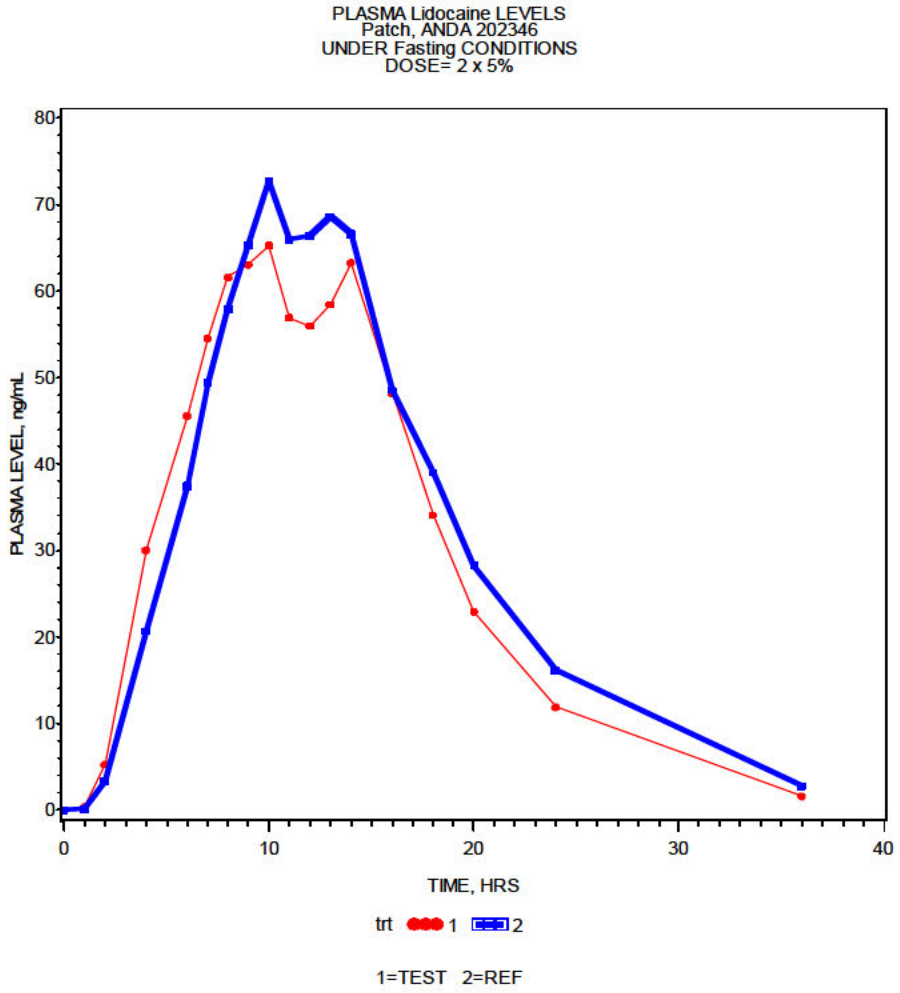
Table 19. Mean Plasma Concentrations (Actual Sampling Times), Single-Dose Fasting Bioequivalence Study

	Test (n=29)		Reference (n=29)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	0.35	310.63	0.04	519.62	8.32
1.05	.	.	0.00	.	.
1.10	.	.	1.56	.	.
2.00	5.25	122.03	3.30	107.49	1.59
4.00	30.03	68.51	20.08	66.12	1.50
4.07	.	.	38.20	.	.
6.00	45.57	46.28	37.75	52.41	1.21
6.07	.	.	31.34	.	.
7.00	54.78	40.85	49.04	49.19	1.12
7.05	47.99	.	61.25	.	0.78
8.00	61.59	37.35	57.86	44.43	1.06
9.00	63.10	31.99	65.32	43.15	0.97
10.00	65.27	29.99	72.77	44.88	0.90
11.00	57.07	27.01	67.08	41.33	0.85
11.05	.	.	81.07	.	.
11.07	52.58	.	37.03	.	1.42
11.08	57.25	.	51.67	.	1.11
12.00	55.96	28.13	64.11	36.97	0.87
12.05	.	.	97.54	28.07	.
13.00	57.82	30.18	68.63	34.50	0.84
13.05	76.71	.	.	.	.
14.00	63.28	29.95	66.61	33.70	0.95
16.00	48.24	24.59	48.28	27.83	1.00
16.07	.	.	56.02	.	.
18.00	33.36	22.94	39.00	29.53	0.86
18.07	54.40	.	.	.	.
20.00	23.04	24.60	28.28	29.77	0.81
20.10	20.08	.	.	.	.
24.00	11.88	31.41	16.13	35.33	0.74
24.07	.	.	16.06	.	.
35.37	.	.	3.09	.	.
36.00	1.58	73.74	2.76	50.30	0.57

Table20. Mean Plasma Concentrations (Scheduled Sampling Times), Single-Dose Fasting Bioequivalence Study

	Test (n=29)		Reference (n=29)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	0.35	310.63	0.09	378.88	3.76
2.00	5.25	122.03	3.30	107.49	1.59
4.00	30.03	68.51	20.71	65.03	1.45
6.00	45.57	46.28	37.53	51.87	1.21
7.00	54.55	40.35	49.46	48.11	1.10
8.00	61.59	37.35	57.86	44.43	1.06
9.00	63.10	31.99	65.32	43.15	0.97
10.00	65.27	29.99	72.77	44.88	0.90
11.00	56.92	26.13	66.00	41.02	0.86
12.00	55.96	28.13	66.41	37.57	0.84
13.00	58.47	29.91	68.63	34.50	0.85
14.00	63.28	29.95	66.61	33.70	0.95
16.00	48.24	24.59	48.54	27.34	0.99
18.00	34.09	24.85	39.00	29.53	0.87
20.00	22.94	24.38	28.28	29.77	0.81
24.00	11.88	31.41	16.13	34.70	0.74
36.00	1.58	73.74	2.77	49.23	0.57

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Pilot Fasting Bioequivalence Study

Please note that the following summary tables as provided by the firm are listed here for information purpose only. The reviewer did not perform statistical analysis for the firm's pilot study since the firm did not submit the datasets for SAS analysis

4.1.2.1 Study Design

Table 19 Study Information

Study Number	LIDO-09254
Study Title	Single-Dose Fasting Bioequivalence Pilot Study of Three Formulations of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers
Clinical Site (Name, Address, Phone #)	Cetero Research 625 Demers Avenue East Grand Forks, MN 56721, USA 218-773-5560
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 08-Dec-2009 Period II: 11-Dec-2009 Period III: 14-Dec-2009 Period IV: 18-Dec-2009
Analytical Sites (Name, Address, Phone #)	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505, USA 304-598-5430
Analysis Dates	19-Jan-2010 – 26-Jan-2010
Analytical Director	Patrick Vallano, Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	49 days at a minimum of -70ºC ± 15ºC [Date of 1st sample collection – 08-Dec-2009; Date of last sample extraction – 26-Jan-2010]

Table 20 Product Information

Product	**Test**	**Test**	**Test**	**Reference**
Treatment ID	Treatment A	Treatment B	Treatment C	Treatment D
Product Name	Lidocaine Patch 5%	Lidocaine Patch 5%	Lidocaine Patch 5%	Lidoderm®
Manufacturer	Mylan Technologies Inc.	Mylan Technologies Inc.	Mylan Technologies Inc.	Teikoku Seiyaku Co., Ltd. for Endo Pharmaceuticals Inc.
Batch/Lot No.	R6A0041	R6A0042	R6A0043	97278
Manufacture Date	11/06/2009	10/1/2009	10/1/2009	N/A
Expiration Date	N/A	N/A	N/A	08/2010
Strength	5%	5%	5%	5%
Dosage Form	Topical Patch	Topical Patch	Topical Patch	Topical Patch
Bio-batch Size	(b) (4)			N/A
Production Batch Size	N/A	N/A	N/A	N/A

Potency	96.7%	107.3%	102.4%	97.1%
Content Uniformity (range, %CV)	92.8%-101.5%, 3.0%	106.4%-107.7%, 0.4%	101.2%-104.1%, 1.1%	Not tested
Dose Administered	2 patches worn for 12 hours	2 patches worn for 12 hours	2 patches worn for 12 hours	2 patches worn for 12 hours
Route of Administration	topical	topical	topical	topical

4.1.2.2 Clinical Results

Table 22 Demographic Profile of Subjects Completing the Bioequivalence Study

FASTING BIOEQUIVALENCE STUDY MYLAN STUDY NUMBER – LIDO-09254 – PILOT			
		TREATMENT GROUPS	
		Test Product N=19[1]	**Reference Product N=19[1]**
Age (years)	Mean ± SD	49.6 ± 14.4	49.6 ± 14.4
	Range	18 – 70	18 – 70
Age Groups	< 18	-	-
	18 – 39	4 (21.1%)	4 (21.1%)
	40 – 64	14 (73.7%)	14 (73.7%)
	65 – 75	1 (5.3%)	1 (5.3%)
	> 75	-	-
Sex	Male	11 (57.9%)	11 (57.9%)
	Female	8 (42.1%)	8 (42.1%)
Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	2 (10.5%)	2 (10.5%)
Not Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	15 (78.9%)	15 (78.9%)
BMI	Mean ± SD	25.9 ± 3.0	25.9 ± 3.0
	Range	20.1 – 30.3	20.1 – 30.3
Other Factors		n/a	n/a

[1]Subjects completing clinical study and whose samples were analyzed

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 23 Study Adverse Events, Pilot Single-dose Fasting Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups Fasting Bioequivalence Study Mylan Study Number – LIDO-09254			
	Treatment A N=19[2]	Treatment B N=20[2]	Treatment C N-19[2]	Treatment D N=20[2]
	n (%)[3]	n (%)[3]	n (%)[3]	n (%)[3]
Eye disorders				
Eye swelling	-	-	1 (5.26%)	-
General disorders and administration site conditions				
Application site erythema	7 (36.84%)	4 (20.00%)	6 (31.58%)	8 (40.00%)
Application site irritation	1 (5.26%)	1 (5.00%)	1 (5.26%)	1 (5.00%)
Pyrexia	-	-	-	1 (5.00%)
Vessel puncture site reaction	-	-	-	1 (5.00%)
Nervous system disorders				
Dysgeusia	-	-	1 (5.26%)	-
Headache	-	1 (5.00%)	-	1 (5.00%)
Paraesthesia	-	-	1 (5.26%)	-
Respiratory, thoracic and mediastinal disorders				
Dry throat	-	-	1 (5.26%)	-
Epistaxis	-	-	1 (5.26%)	-
Hiccups	-	-	1 (5.26%)	-
Total Subjects Reporting at Least One Adverse Event	8 (42.11%)	5 (25.00%)	9 (47.37%)	8 (40.00%)

[1] MedDRA Version 12.1
[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)%)

Table 24 Dropout Information

FASTING BIOEQUIVALENCE STUDY MYLAN STUDY NUMBER – LIDO-09254 - PILOT				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Subject was dropped by Investigator prior to Period III check-in due to adverse event (pyrexia); per influenza response plan.	II	n/a	n/a

Table 25 Protocol Deviation

Fasting Bioequivalence Study Mylan Study Number – LIDO-09254 - PILOT				
Type	Subject #s (Treatment A)	Subject #s (Treatment B)	Subject #s (Treatment C)	Subject #s (Treatment D)
Concomitant medications	(b) (6)			
Blood sample collection time deviations				
Missed blood sample collections				
Period II, Mylan PK/DM Department not contacted prior to concomitant drug administration				
All periods, study hour 4, 8, and 12, adhesion scoring was not completed at scheduled times due to concurrent blood sample collection timing				
All periods, study hour 12, patch removal was not completed at scheduled time due to concurrent blood sample collection timing				
Period II, patch application sites 3 and 4 wiped with alcohol prior to irritation scoring				
Period III, caffeine-containing food consumed during washout period prior to patch application				
Period I, study hour 4, vital signs not collected 20 minutes prior to blood sample collection				
Period I, study hour 8, vital signs not collected 20 minutes prior to blood sample collection				
Period I, study hour 36, vital signs not collected 20 minutes prior to blood sample collection				
Period II, study hour 2, vital signs not collected 20 minutes prior to blood sample collection				

Fasting Bioequivalence Study Mylan Study Number – LIDO-09254 - PILOT				
Type	Subject #s (Treatment A)	Subject #s (Treatment B)	Subject #s (Treatment C)	Subject #s (Treatment D)
Period II, study hour 4, vital signs not collected 20 minutes prior to blood sample collection				(b) (6)
Period III, study hour 4, vital signs not collected 20 minutes prior to blood sample collection				
Period III, study hour 8, vital signs not collected 20 minutes prior to blood sample collection				
Period III, study hour 12, vital signs not collected 20 minutes prior to blood sample collection				
Period III, study hour 16, vital signs not collected 20 minutes prior to blood sample collection				
Period IV, study hour 24, vital signs not collected 20 minutes prior to blood sample collection				
Period I, study hour -13, less than 75% of meal was consumed (Subject (b) (6)				
Period I, study hour 10.25, less than 75% of meal was consumed				
Period II, study hour -13, less than 75% of meal was consumed				
Period III, study hour -13, less than 75% of meal was consumed				
Period III, study hour 4.25, less than 75% of meal was consumed				
Period IV, study hour -13, less than 75% of meal was consumed				
Period IV, study hour 4.25, less than 75% of meal was consumed				

4.1.2.3 Bioanalytical Results

Table 26 Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses

Bioequivalence Study LIDO-09254 LIDOCAINE										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	1.000	1.500	3.000	5.000	10.00	20.00	40.00	60.00	80.00	100.0
Inter day Precision (%CV)	1.57	2.43	2.41	1.48	1.25	1.64	1.60	1.54	1.74	1.15
Inter day Accuracy (%Actual)	101.60	98.73	98.70	99.28	97.89	100.10	100.35	102.18	101.74	99.46
Linearity	0.9982 – 0.9997									
Linearity Range (ng/mL)	1.000 – 100.0									
Sensitivity/LOQ (ng/mL)	1.000									

Bioequivalence Study LIDO-09254 LIDOCAINE				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	3.000	10.00	75.00	75.00 (diluted)
Inter day Precision (%CV)	2.36	1.76	2.05	3.17
Inter day Accuracy (%Actual)	98.93	95.55	95.68	93.88

Table 27 Reanalysis of Study Samples

LIDO-09254 – BE Study Repeat Analysis Results for Lidocaine Additional Information is Available Upon Request																
Reason why assay was repeated[2]	**Number of samples reanalyzed**								**Number of recalculated values used after reanalysis**							
	Actual Number				**% of total assays**				**Actual Number**				**% of total assays**			
	T1	**T2**	**T3**	**R**	**T1**	**T2**	**T3**	**R**	**T1**	**T2**	**T3**	**R**	**T1**	**T2**	**T3**	**R**
Pharmacokinetic	0	0	0	0	0%	0%	0%	0%	0	0	0	0	0%	0%	0%	0%
Reason A	4	8	8	45	0.29%	0.59%	0.59%	3.30%	4	8	8	45	0.29%	0.59%	0.59%	3.30%
Reason B	3	2	5	3	0.22%	0.15%	0.37%	0.22%	3	2	5	3	0.22%	0.15%	0.37%	0.22%
Reason C	0	0	2	0	0%	0%	0.15%	0%	0	0	2	0	0%	0%	0.15%	0%
Total	7	10	15	48	0.51%	0.73%	1.10%	3.52%	7	10	15	48	0.51%	0.73%	1.10%	3.52%

[2]Reason A = Sample Outside Limits of Curve Range (ALQ)
Reason B = Abnormal Internal Standard (IS) Response

Reason C = Measurable Concentration in Subject Zero Sample

4.1.2.4 Pharmacokinetic Results (Firm's calculation)

Table 28 Summary of Bioequivalence Study of Lidocaine

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})	
					Lidocaine						
LIDO-09254	Single-Dose Fasting Bioequivalence Pilot Study of Three Formulations of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers	Open-label, Single-dose, Randomized, Four-period, Four-treatment Crossover	A=Lidocaine Patch 5%, Ext. (b) (4) 140 mg lidocaine topical route, Lot# R6A0041	20 Dosed 19 Completed 19 Analyzed Healthy Subjects Mean Age: 50 (Range: 18 to 70)	77.49 ± 20.67	10.00 (7-16)	1036 ± 268.1	1050 ± 269.5	4.442 ± 0.565	0.1587 ± 0.0220	Section 5.3.1.2
			B=Lidocaine Patch 5%, (b) (4) (b) (4) lidocaine topical route, Lot# R6A0042		77.79 ± 21.08	10.00 (4-16)	1058 ± 262.3	1078 ± 261.9	4.489 ± 0.814	0.1591 ± 0.0282	
			C=Lidocaine Patch 5%, (b) (4), 140 mg lidocaine topical route, Lot# R6A0043		79.19 ± 22.11	10.00 (4-16)	1083 ± 307.3	1104 ± 305.2	4.647 ± 0.811	0.1534 ± 0.0265	
			D= Lidoderm® Patch 5% 700 mg lidocaine topical route, Lot #97278 exp. 08/2010		83.39 ± 49.45	10.00 (8-16)	1094 ± 529.2	1127 ± 515.1	5.788 ± 2.993	0.1350 ± 0.0354	

Table 29 Statistical Summary of the Bioequivalence Data

LIDOCAINE PATCH 5% Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals										
LIDO-09254 lidocaine										
	Geometric Means				Ratio*			90% C.I.**		
Parameter	Test (A)	Test (B)	Test (C)	Reference (D)	A/D	B/D	C/D	A	B	C
AUC0-t	1005	1019	1040	963.9	1.04	1.06	1.08	96% – 114%	97% – 115%	99% – 117%
AUC∞	1019	1040	1062	1010	1.01	1.03	1.05	94% – 109%	96% – 111%	98% – 113%
C_{max}	74.80	74.18	76.13	68.62	1.09	1.08	1.11	98% – 121%	97% – 120%	100% – 124%

Reviewer's Comments:

1. LIDO-09254 was a single-dose, pilot-scale, 4-treatment, pharmacokinetic study with two patches worn for twelve hours. Total 20 subjects were enrolled into the four period cross-over pilot study. The primary purpose of the study was to evaluate the bioequivalence of three formulations of Mylan's Lidocaine Patch 5% to the RLD product, Lidoderm® patch 5%. 19 subjects completed the study and were included in the statistical analysis.
2. The 90% confidence interval of AUC0-t and Cmax for lidocaine met the acceptance criteria of 80-125%. This study demonstrate that all three formulations of Mylan's Lidocaine Patch, 5% are bioequivalent to the RLD product, Lidoderm® Patch, 5% following application of two patches worn simultaneously for 12 hours.
3. Formulation A was selected and modified slightly into the formulation used in the pivotal study. The table below listed the 3 formulations tested in the pilot study LIDO-09254.

Component	Mylan Lot #					
	Formulation A		Formulation B		Formulation C	
	R6A0041		R6A0042		R6A0043	
	(b) (4)					
	Target		Target		Target	
	% w/w	g/m^2	% w/w	g/m^2	% w/w	g/m^2
Lidocaine USP	5%	(b) (4)	5%	(b) (4)	5%	(b) (4)
(b) (4)	(b) (4)		(b) (4)		(b) (4)	
Total	100%		100%		100%	

4.2 Formulation Data of the test product

Ingredient	Amount (mg/Patch)	Amount (% w/w)
Components of the Adhesive Matrix		
Lidocaine, USP	140.00	5.00
Polyisobutylene (PIB) (b) (4)	(b) (4) (b) (4)	
Total (Theoretical Matrix Weight)	(b) (4)	**100.00**
Other Components		
Pigmented Polyethylene/ Polyester Film (MEDIFLEX® 1501)	(b) (4)	N/A
Brown Ink (b) (4)		N/A
Silicone Coated Polyester Film (MEDIRELEASE® 2249)		N/A

Excipients				
Strengths	**Excipient**	**Amount/unit (mg)**	**Maximum Intake/day based on MDD (mg)**	**IIG Limit (mg) for Transdermal Patch (mg)**
5%	Polyisobutylene (PIB) (b) (4)	(b) (4)		119
	(b) (4)			
	Pigmented Polyethylene/ Polyester Film (MEDIFLEX® 1501)	(b) (4)	See comment below	N/A
	Brown Ink (b) (4)		Trace	N/A
	Silicone Coated Polyester Film (MEDIRELEASE® 2249)		See comment below	873
MDD used for calculation	Three Patches simultaneously for 12 hours.			

Reviewer's Note: The test product, Lidocaine Patch, 5%, (b) (4). The (b) (4) backing (b) (4) is a pigmented polyethylene / polyester laminate film. The (b) (4) is the polyisobutylene adhesive matrix containing the active pharmaceutical

ingredient, Lidocaine, USP. The (b) (4) is a transparent polyester film coated with silicone release agent. The release liner is removed from the patch and discarded prior to (b) (4).

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Formulation of the RLD product (Lidoderm®)[7]

Ingredient Name	Potency	Type
LIDOCAINE	5%	ACTIVE
GELATIN	(b) (4)	INACTIVE
POLYVINYL ALCOHOL		INACTIVE
(b) (4)		INACTIVE
EDETATE DISODIUM		INACTIVE
SORBITOL (b) (4)		INACTIVE
KAOLIN		INACTIVE
SODIUM POLYACRYLATE (b) (4)		INACTIVE
CARBOXYMETHYLCELLULOSE SODIUM		INACTIVE
GLYCERIN		INACTIVE
TARTARIC ACID		INACTIVE
(b) (4)		INACTIVE
PROPYLENE GLYCOL		INACTIVE
METHYLPARABEN		INACTIVE
PROPYLPARABEN		INACTIVE
DIHYDROXYALUMINUM AMINOACETATE		INACTIVE

Reviewer's Comment:
1. It was noted that on the first page of the checklist review[8] of ANDA 202346, the dosage form was indicated as Patch, 5% (**700 mg**/24 hours), which is **incorrect.**

2. The RLD label indicates that 700 mg of lidocaine is contained within the 140 cm2 (10 cm x 14 cm) patch. This is in contrast to the 140 mg of lidocaine contained in each 140 cm2 (10 cm x 14 cm) patch of the test product. Although the total amount of lidocaine per patch is different between the test and RLD product (140 mg/patch vs 700 mg/patch), the w/w% of lidocaine per patch (50 mg per gram adhesive) is 5% for both the test and RLD products. Please also note that the size (surface area) of the patch is the same between the test and RLD products while the thickness of the adhesive layer which contains the lidocaine is different between the test (approximately 0.2 mm) and RLD products (approximately 1mm).

[7] DPFR: NDA 020612; last access: 11/27/2012
[8] DARRTS: ANDA 202346; MANDULA, HARITHA 11/22/2010 N/A 11/22/2010 REV-BIOEQ-07(Filing Review) Original-1 Archive

3. The labeling reviewer noted the difference in the loading dose in the labeling between the test and RLD products and questioned the firm about the efficiency of drug delivery. The labeling reviewer provided the firm the following deficiency comments[9]:
1). Please explain why your pouch and carton label states "Lidocaine, USP 140 mg (50 mg per gram adhesive)..." while the reference listed drug (RLD), Lidoderm states "Lidocaine 700 (50 mg per gram adhesive)..." Why does your patch deliver 140 mg per patch while the RLD delivers 700 mg of lidocaine per patch?

2) Your labeling states "...only 11 ± 4% of the dose applied is expected to be absorbed. At least 82% (115 mg) of lidocaine..." while the RLD's states "...only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine..." Why is your drug product's absorption profile different than the RLD's? Please submit the rationale.

In response to the above deficiency comments, the firm responded as follows:

1) *The Mylan patch contains 140 mg per patch but delivers the same dose as the RLD that contains 700 mg per patch. Both patches are formulated at the same drug concentration (i.e. 50 mg lidocaine per gram adhesive, or 5%), and are the same size (i.e. 140 cm2). However, given that the RLD claims to deliver only 3 ± 2% of the 700 mg of lidocaine contained in the patch, the Mylan patch was developed to contain only the amount of lidocaine needed for the patch to be therapeutically equivalent to the RLD. This was done by keeping the same lidocaine concentration in the adhesive matrix (i.e. 5%), but reducing the thickness of the adhesive layer from 100 mg/cm2 (about 1.0 mm thick) to 20 mg/cm2 (about 0.2 mm thick). The approach taken by Mylan in the development of the Lidocaine patch is aligned with the Agency's Guidance for Industry, Residual Drug in Transdermal and Related Drug Delivery Systems, August 2011, in that the amount of residual drug in transdermal products be minimized consistent with the current state of technology.*
Therapeutic equivalence was confirmed in a single-dose, fasting, two-way crossover, in vivo bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, Lidoderm® Patch 5% (LIDO-1037). Thus, Mylan's Lidocaine Patch 5% and the RLD deliver at the same rate and extent, thereby, producing bioequivalent plasma concentration vs. time profiles. Please refer to Section 5.3.1.2 (Sequence 0000) for more information concerning this study.

2) The absorption of lidocaine is no different from the Mylan Lidocaine Patch 5% or the RLD as demonstrated by the single-dose, fasting, two-way crossover, in vivo bioequivalence study comparing Lidocaine Patch 5% to the Reference Listed Drug, Lidoderm® Patch 5% (LIDO-1037). The differences noted by the reviewer relate to the lower total amount of drug in the Mylan Lidocaine patch compared to the RLD.
This results in different amounts of residual drug in the patches between the two products as illustrated in the following table.

	Mylan Lidocaine Patch 5%	*RLD*

[9] DARRTS: ANDA 202346; VU, THUYANH 08/11/2011 N/A 08/11/2011 REV-LABEL-01(General Review) Original-1 Archive

Total Lidocaine per Patch	*140 mg*	*700 mg*
Lidocaine Dose Absorbed	*15 mg ± 6***	*21 mg ± 11*
Fraction of the original dose absorbed	*15 ± 6 mg / 140 mg =* ***11 ± 4%***	*21 ± 11 mg / 700 mg =* ***3 ± 2%***
Minimum Residual Lidocaine	*140 mg – 25 mg*** =* ***115 mg***	***665 mg***
Minimum Residual Lidocaine (%)	*115 mg / 140 mg =* ***82%***	*665 mg / 700 mg =* ***95%***

**Note: These values were taken from the RLD labeling that states a Dose Absorbed of 64 ± 32 mg for three-patch wear, or about 21 ± 11 mg absorbed per patch, and residual drug of at least 95% (665 mg).*
***Note: From residual patch analyses performed as part of LIDO-1037.*
****Note: The maximum depletion measured in the residual patch analysis from LIDO-1037 was 23.8 mg, which was rounded to 25 mg for use in the labeling.*

The labeling reviewer reviewed the firm's response and had no further questions about the differences in the labeling between the test and RLD products as of 2/11/2013.

4. The DB reviewer consulted the Division of Chemistry with regard to the pharmaceutical equivalency between the test and RLD products which have differences in the thickness and the total weight of the patch. The chemistry reviewer noted the differences and did not have concern about the differences from chemistry point of view (Please see Section 4.6 Appendix email communications). The chemistry reviewer also did not have concerns that cutting the patch would affect the drug delivery[10].

5. Although there exist the differences in the formulation design and reduced amount of drug in the patch between the test and RLD products, according to the PK BE study LIDO-1037, the 90% confidence intervals for lnAUC0-t, lnAUCi and lnCmax of lidocaine met the acceptable criteria of 80-125%. The test and reference products are bioequivalent.

6. The maximum level for Polyisobutylene is listed as 119 mg in IIG database. The (b) (4) (b) (4) in the Lidocaine Patch exceeds the maximum level listed in the IIG.

7. Pigmented Polyethylene / Polyester Film (MEDIFLEX® 1501) is not listed in the IIG database. (b) (4)

[10] DARRTS: ANDA 202346; Turner Betty B 11/25/2012 N/A 11/25/20112 REV-LABEL-01(General Review) Original-1 Archive
[11] DARRTS: NDA (b) (4) MITRA, AMIT K (b) (4) REV-QUALITY-03(General Review) Original-1 (Type 1 NME and Type 4 New Combination) Archive

(b) (4), the reviewer can't determine whether the ingredients used in the backing film in (b) (4) are the same as Mediflex® 1501 used in the Licodaine Patch. However, since the backing film does not pose direct skin contact, it should not be viewed in terms of a true maximum daily intake.

8. Silicone Coated Polyester Film (MEDIRELEASE® 2249) is present to protect the adhesive matrix during storage. It is removed prior to use and is not part of the drug product applied to the patient. Therefore, silicone coated polyester film should not be viewed in terms of a true maximum daily intake, either.

9. The (b) (4) Brown Ink is not listed in the IIG database; (b) (4) . Per the DB practice, trace amounts of (b) (4) (b) (4) Brown Ink used in Mylan's Lidocaine Patch 5% do not warrant further safety evaluation.

10. At the request of OGD's Regulatory Support Branch, a pharm/tox consult review has been done to evaluate acceptability of polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film in Mylan's Lidocaine Patch 5%. The firm conducted USP biological reactivity tests (USP<87> and <88>) to address concerns of safety of Polyisobutylenes. Although these studies lack clinical pathology, histopathology and toxicokinetic evaluations, the pharm/tox reviewer considers additional toxicology studies are not needed due to the following reasons:

1.) Polyisobutylenes are inert molecules and are commonly used for Transdermal Delivery Systems (TDS). Since they have high-molecular weight and low solubility in water they have very slow absorption (less likely pass through the skin barrier).
2.) The USP biological data showed no in vitro and/or in vivo biologic reactivity with Polyisobutylenes.
3.) These chemicals are in FDA-approved products.

The firm conducted International Organization for Standardization (ISO) compliant biological tests of material biocompatibility to assess the safety of extracts of as well as whole pigmented polyethylene/polyester film and silicone coated polyester material. The pharm/tox has the following comments:

According to container closure guidance (May 1999), these studies are considered sufficient to provide evidence of acute local safety of the individual chemicals which may migrate into the patch. However these studies provided limited support to evaluate longer term exposures and do not support the absence of genotoxicity of the compounds. Additionally there is a lack of information on identity and potential levels of leachables from this transdermal patch which could potentially be used to address concerns.

In the end of the pharm/tox review, the pharm/tox reviewer provided the following response to the OGD[12]:

• *From the nonclinical pharmacology toxicology perspective, the levels of Polyisobutylenes (adhesive) are acceptable due to the large size of these molecules which is expected to prevent entry through the stratum corneum layer of the skin.*

• *The identity and levels of excipients comprising the backing film and release liner are acceptable since there is no direct skin contact with these excipients.*

• *There is a lack of information on the identity and levels of potential leachables to further assess acceptability of this generic product. To support a comprehensive evaluation of safety, the ANDA submission should contain information on potential leachables through conduct of extractable and, if necessary, leachable studies. A toxicological risk assessment of identified substances which determines the safe level of exposure via the dermal route of administration should be provided. The approach for toxicological evaluation of the safety of extractables or leachables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (i.e. chronic or short-term usage).*

11. According to the chemistry review of ANDA 202346[13], the chemistry reviewer provided the following comments with regard to the formulation of the test product:

Polyisobutylene (b) (4) (b) (4) *outside the IIG limits for the transdermal route of administration. The adhesive levels, components of the backing membrane and release liner are found acceptable as per the consult review. The consult review asked for extractable/leachable information of the adhesives. Since PIB adhesives have been used in approved ANDA or NDA products leachable/extractable information may not be required. In addition, the irritation and sensitization study will be reviewed by Bioequivalence.*

12. The irritation and sensitization study are reviewed by the Division of Clinical Review instead of the Division of Bioequivalence. Currently, the clinical review of irritation and sensitization study is still pending.

In the fasting PK study LIDO-1037, irritation after patch removal was also assessed as a secondary objective. The mean (± SD) cumulative irritation score was 0.45 ± 0.67 and 0.69 ± 0.66 for the test and RLD products, respectively. Barely perceptible erythema (on average) was seen with both treatments a half hour after patch removal. Also, according to the adverse event report in PK study LIDO-1037, the observed adverse effect at the administration site (application site erythema, application site pain, application site pruritus, feeling hot) was comparable during the fasting PK study for the test and RLD products.

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[12] DARRTS ANDA 202346; EMAMI, ARMAGHAN 04/22/2011 N/A 04/22/2011 CONSULT REV-NONCLINICAL-01(General Consult Review) Original-1 Archive

[13] DARRTS: ANDA 202346; LI, XIHAO 12/30/2011 N/A 12/30/2011 REV-QUALITY-03(General Review) Original-1 Archive

13. The formulation of the test product is deemed acceptable.

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?	Above IIG (per day) Limit
If no, are additional data or Pharm/Tox consult necessary?	A Pharm/Tox consult review has been done (DARRTS: ANDA 202346; EMAMI, ARMAGHAN 04/22/2011 N/A 04/22/2011 CONSULT REV-NONCLINICAL01(General Consult Review) Original-1 Archive)
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?	N/A
Are all strengths of the RLD product dose-proportional?	N/A
Are all strengths of the test formulation acceptable	N/A
Additional Attachment for Formulation Calculations	N/A

4.3 Dissolution Data

Dissolution Review Path	DARRTs: ANDA 202346; Munshi, Utpal M; 6/02/2011;REV-BIOEQ-02 (Dissolution Review); Original-1; Archive

Table 33. Dissolution Data

Dissolution Conditions	Apparatus:	5 (paddle over disk – transdermal sandwich)
	Speed of Rotation:	50 rpm
	Medium:	10 mM Sodium Acetate Buffer, pH 4.0
	Volume:	500 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	1.5 Hours: (b) (4) %, 6 Hours: (b) (4) %, 12 Hours: (b) (4) %, 24 Hours: (b) (4) %	
Dissolution Testing Site (Name, Address)	Mylan Technologies, 110 Lake Street, Saint Albans, Vermont 05478	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength	No. of Dosage Units		Collection Times (hours)				Study Report Location
						1.5 Hours	6 Hours	12 Hours	24 Hours	
N/A	Aug. 2010	Lidocaine Patch Lot R6B0017 March 29, 2010	5%	12	Mean %	7.1	11.7	16.1	22.6	3.2.P.5.4 Batch Analysis
					Range	(b) (4)				
					%CV	4.8	2.5	1.7	1.4	
N/A	Aug. 2010	LIDODERM® Patch Lot 97278 08/10	5%	12	Mean %	39.7	73.7	90.6	98.4	
					Range	(b) (4)				
					%CV	3.7	1.2	1.5	2.2	

(b) (4)

Reviewer's Comments:
1. The labeled amount in RLD is 700 mg/140 sq cm (10 x 14 cm). The labeled amount in Mylan's proposed test product is 140 mg/140 sq cm.

2. The in vitro dissolution testing data has been previously reviewed and found adequate. The dissolution reviewer commented that *the FDA-recommended method is actually a reasonably accurate indicator of in vivo performance of the test product*.

3. The firm has conducted **acceptable** comparative dissolution testing on the Test and Reference Products using the FDA-recommended method (500 mL 10mM Acetic Acid/Sodium Acetate Buffer, pH 4.0 with USP Apparatus V (Paddle over Disk) at 50 rpm). The DB I accepted the firm proposed specifications: 1.5 h (b) (4) %; 6 h: (b) (4) %; 12 h: (b) (4) %; 24 h: (b) (4) %. (DARRTS: ANDA 202346; Munshi, Utpal M; 6/02/2011; REV-BIOEQ-02 (Dissolution Review); Original-1; Archive).

4.4 Review of the OSI Inspection Report for the Clinical Site

The clinical study of ANDA 202346 was conducted at Cetero Research (4801 Amber Valley Pkwy, Fargo, ND 58104). The analytical study of ANDA 202346 was conducted at Mylan Pharmaceuticals Inc. (3711 Collins Ferry Rd, Morgantown, WV 26505).The fasting BE study was conducted from May 09, 2010 to May 18, 2011. The dates of the analytical study encompassed June 2, 2010 to June 9, 2010 for the fasting study.

The last inspection of the clinical site, conducted by the Office of Scientific Investigations (OSI) was a routine inspection requested for NDA202834. The inspection was completed on August 29, 2012, and the outcome was No Action Indicated (NAI). The inspection of the clinical site was also requested on 2/11/2012 for the current ANDA 202346 for the Cumulative Irritation and Sensitization Study (LIDO-1046) and Adhesion Study (LIDO-1044). The inspection was completed on February 3. 2012 and the outcome was Voluntary Action Indicated (VAI). No Form FDA 483 was issued but the following observations were verbally communicated to the management of the clinical site[14]:

1. ***Record review of computer generated pharmacy Drug Inventory control records for Study LIDO-1044 reveals the pharmacy's record of the randomization codes for placement of the patches on subjects has been "over" written manually and changed by pharmacy staff to reflect the correct placement as set in the protocol. The firm's SOPs and computer program, called "Study Monitor Program" are incomplete, in that; there is no current computer program that will print in and for pharmacy the protocol placement of the patches; and the SOPs fail to provide guidance for randomization documentation of dermatological studies. In addition, pharmacy has no applicable guidelines for the dermatology studies to follow.***

2. ***Case document review for Subject (b) (6) for Study RI0-0159, LIDO-1046 shows a positive HCG on final-exit of study. The documents for the follow up of this pregnant subject were incomplete in that; documentation of final outcome of pregnancy was not in study files and SOPs are vague and do not address pregnancy follow up or guidance for where the final documentation should be placed when subjects are found pregnant at the end of a study. Subject's medical records noted a viable newborn delivered on (b) (6). The inspector explained to the management that case files should contain a complete final outcome-history of all subjects and the SOPs should address this matter.***

The OSI concluded that following the inspection of the clinical site for Studies LIDO-1044 and LIDO-1046, no major objectionable conditions were observed and form FDA 483 was not issued. These studies are recommended to be accepted for review.

Observation 1 was related to the incomplete "Study Monitor Program" and lack of effective SOPs for dermatology studies in pharmacy. The reviewer considers this finding is systemic and may affect other dermatological studies conducted at this clinical site. The Project Manager should assign all related ANDAs for **transdermal patch products only**, for review to determine

[14] DARRTs: ANDA 202346; LEE, JANGIK I
02/03/2012 N/A 02/03/2012 FRM-ADMIN-01(Memorandum to File) Original-1 Archive

the acceptability of other dermatological studies conducted at the same clinical facility. For the current application, since the OSI did not indicate concerns for data integrity because of this practice, the firm will not be asked for further evaluation of the impact of observation 1.

4.4.1 Parent ANDA Reviewer Comment for Related ANDAs for Dermatological Products Only:

This OSI finding # 1 is considered systemic. Reviewers of related ANDAs should evaluate the impact of this finding on his/her own respective ANDA.

☐ **Isolated**	☒ **Systemic**

Observation 2 was regarding the incomplete documentation for subjects who were found pregnant at the end of study RI0-0159. Since there was no subject found pregnant in the PK study LIDO-1037 in the current application, the reviewer considers this finding will not be systemic and have impact on the outcome of study LIDO-1037 or other ANDAs.

☒ **Isolated**	☐ **Systemic**

4.5 Review of OSI Inspection Findings for the Analytical Site

The last inspection of the analytical site was a routine inspection requested for ANDA200462. The OSI inspection was completed on 9/15/2010 and the outcome was VAI. A Form FDA-483 was issued to the analytical site with the following findings:

1. ***For ropinirole (study #s ROPI-08204 and ROPI-08205) studies, only 5% of samples were repeated for incurred sample reanalysis (ISR). The firm's SOP L-324-01 for ISR effective date March 10, 2009, requires a fixed percentage (5%) of the total samples to be reanalyzed, irrespective of sample size.***

2. ***Stability of processed samples was determined with only mid level QCs during pre-study validation for ropinirole (study#s ROPI08204 AND ROPI08205) studies. Processed stability was not evaluated with low and high QC concentrations.***

3. ***Failure to document all aspects of study conduct.***

No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes (including PLE#s: 5176, 5187, 5032, 5168, 5081, 5199, 5069, 5177, 5138, and 5172) during ropinirole (study #s ROPI08204 and ROPI08205) studies.

The parent ANDA reviewer from DB II reviewed the OSI inspection report for the analytical site but did not evaluate whether those findings are systemic or specific to the audited studies[15].
Per the DBs practice, the firm should be asked to evaluate the impact of each of these findings on the current application. However, for the current application, the firm has provided the ISR data.. Similar to the OSI observation #1, only 5% of the samples were reanalyzed for ISR. Currently, the DB does not have an official policy on the number of samples to be used for conducting ISR. Therefore, the firm will not be asked to address finding # 1. The firm will be asked to evaluate the impact of findings # 2and 3 on the current application.

[15] DARRTS: ANDA 200462; REN, PING
12/22/2010 N/A 12/22/2010 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive

4.6 Appendix

From: Li, Xihao
To: Wang, Rong
Cc: Rege, Bhagwant; Tampal, Nilufer; Nguyen, Hoainhon T
Subject: RE: Re ANDA 202346 (Lidocaine Patch, 5%)
Date: Wednesday, January 30, 2013 4:18:59 PM

Hi Rong,
Chemistry has finished the first cycle review on this ANDA and we also noted the difference of the ANDA with the RLD you mentioned. The formulation design of the ANDA of the RLD is different and we think that should be fine from chemistry point of view.
Bhagwant, please correct me if wrong.
Thanks,
Xihao

From: Wang, Rong
Sent: Tuesday, January 29, 2013 3:52 PM
To: Li, Xihao
Cc: Rege, Bhagwant; Tampal, Nilufer; Nguyen, Hoainhon T
Subject: Re ANDA 202346 (Lidocaine Patch, 5%)

Dr. Li,
I'm the primary bioreviewer for ANDA 202346 (Lidocaine Patch, 5%) from DBI. I have a question regarding the test product.
The test product, Mylan's Lidocaine Patch, has the same strength (5%) and the same surface area (10 cm x 14 cm) as the RLD product. However, it was also noted that the thickness of the patch (test product 0.2 mm vs RLD product 1 mm) and the weight of the patch (test product (b) (4) mg/patch vs RLD product 14000 mg/patch) are different between the test and RLD products. Would you please confirm whether the test product is considered pharmaceutical equivalent to the RLD product in spite of the aforementioned differences?
Thank you very much.
Rong

4.7 SAS Output

4.7.1 Fasting Study Data

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
1	(b) (6)	1	1	1	A	0	0.000	1.522	26.160	45.740	54.91	59.57	66.78	61.25	64.08	58.68	57.49	64.83	53.04	34.08	26.30	15.280	2.703
2		1	1	2	B	0	0.000	1.448	13.980	31.340	40.06	50.05	52.94	59.94	51.67	52.23	59.80	55.58	46.10	36.19	27.11	15.680	2.551
3		1	2	1	B	0	0.000	1.336	11.070	29.070	44.19	55.40	57.46	67.30	74.89	76.25	80.23	74.89	56.02	55.59	44.61	23.370	4.762
4		1	2	2	A	0	0.000	1.851	20.190	42.900	61.50	78.47	75.57	81.64	68.77	75.36	92.32	101.30	67.50	51.02	31.71	15.290	1.992
5		1	1	1	A	0	0.000	6.068	27.170	34.590	39.80	43.19	44.54	54.19	46.01	48.43	48.30	47.79	45.52	35.68	24.60	13.880	2.169
6		1	1	2	B	0	0.000	2.607	13.980	25.850	39.63	47.13	51.57	53.83	53.86	55.55	58.50	61.32	49.12	35.67	29.84	21.300	4.965
7		1	2	1	B	0	0.000	1.273	14.310	26.730	35.71	45.90	52.54	52.98	45.29	48.53	48.50	51.85	39.11	33.05	27.49	16.430	2.452
8		1	2	2	A	0	0.000	4.666	33.340	49.370	63.98	82.70	74.53	69.71	60.64	64.96	58.62	60.87	48.10	38.85	25.88	13.160	1.351
9		1	2	1	B	0	0.000	0.000	8.546	21.130	32.49	41.22	52.86	65.71	57.73	58.97	59.46	59.41	43.14	34.15	24.48	15.430	4.059
10		1	2	2	A	0	0.000	1.098	20.200	40.150	46.74	56.13	65.51	74.79	61.19	60.36	76.71	61.20	44.19	32.60	23.10	10.250	1.830
11		1	1	1	A	0	0.000	0.000	18.160	41.800	46.60	55.24	59.98	60.98	51.20	48.44	50.05	53.73	38.05	24.81	17.27	7.720	1.145
12		1	1	2	B	0	0.000	0.000	9.966	21.860	27.82	36.24	45.68	45.44	37.03	37.70	41.13	42.71	37.10	28.77	20.95	10.480	2.188
13		1	1	1	A	0	0.000	1.425	16.980	35.450	50.21	56.12	51.02	55.80	54.10	51.33	54.37	66.16	52.79	37.29	23.72	10.520	1.920
14		1	1	2	B	0	0.000	0.000	4.789	14.160	19.67	25.19	30.81	36.67	32.60	33.90	39.37	44.49	33.46	27.79	22.31	13.110	3.351
15		1	2	1	B	0	0.000	2.540	15.240	26.150	31.95	42.48	55.53	63.86	55.76	58.86	68.17	65.65	51.87	48.20	36.36	20.140	4.333
16		1	2	2	A	0	0.000	0.000	10.590	22.470	29.45	44.43	50.65	62.94	52.58	49.79	57.38	65.89	50.18	38.84	26.12	14.650	2.864
17		1	2	1	B	0	0.000	1.296	15.950	41.180	54.66	64.31	67.42	66.01	62.96	63.36	63.79	65.67	60.52	47.27	33.71	25.090	4.704
18		1	2	2	A	0	0.000	1.300	20.680	38.730	55.44	64.55	72.53	69.20	58.97	61.78	64.09	83.65	78.26	54.40	36.37	22.930	3.892
19		1	1	1	A	0	5.368	21.920	64.120	75.930	97.52	109.80	91.40	90.65	72.15	81.36	75.83	96.69	65.32	50.33	35.99	20.210	3.859
20		1	1	2	B	0	1.557	7.983	38.200	69.670	94.99	113.40	116.60	119.40	99.81	98.23	108.30	125.00	81.76	77.33	56.22	35.280	6.703
21		1	2	1	B	0	0.000	3.524	14.920	23.430	24.83	31.94	29.56	31.75	28.31	33.27	37.54	34.43	30.12	24.34	16.47	9.488	2.068
22		1	2	2	A	0	0.000	4.199	25.670	35.660	35.85	35.21	34.38	38.82	33.96	34.62	35.63	34.41	39.66	27.21	15.83	7.937	0.000

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
23	(b) (6)	1	1	1	A	0	0.000	1.489	12.420	18.740	20.13	25.29	31.09	32.61	25.84	29.00	31.22	39.42	33.61	31.32	23.74	14.650	1.742
24		1	1	2	B	0	0.000	0.000	13.120	28.490	39.81	49.63	61.11	65.01	52.37	60.07	67.90	76.21	54.43	43.60	32.13	18.210	2.658
25		1	2	1	B	0	0.000	7.771	32.450	52.490	65.85	78.41	94.82	93.59	87.11	91.83	83.93	69.69	43.95	33.64	23.66	13.240	1.042
26		1	2	2	A	0	0.000	4.337	35.690	61.850	66.42	70.88	75.21	85.68	68.51	60.10	52.89	68.86	45.69	27.83	17.69	7.789	0.000
27		1	1	1	A	0	0.000	0.000	12.820	18.210	23.20	32.96	42.60	43.12	38.51	37.59	38.54	45.92	35.52	29.84	22.04	11.210	1.653
28		1	1	2	B	0	0.000	0.000	3.490	6.894	10.87	17.50	21.04	25.48	24.62	26.95	27.11	34.03	29.07	27.38	20.60	12.560	2.344
29		1	2	1	B	0	0.000	1.642	15.080	28.800	45.25	50.93	57.47	70.16	60.58	57.22	59.45	53.97	40.33	31.55	21.49	9.669	1.301
30		1	2	2	A	0	0.000	1.605	20.660	40.200	47.99	55.53	56.31	61.96	57.25	48.59	47.52	48.15	39.88	27.29	17.80	8.194	0.000
31		1	1	1	A	0	0.000	0.000	8.915	22.180	30.45	33.18	39.85	47.28	37.96	39.48	45.38	52.31	41.10	29.97	20.00	10.290	1.717
32		1	1	2	B	0	0.000	1.369	7.601	15.110	26.02	30.33	34.36	41.80	39.71	42.81	50.70	51.66	38.02	33.49	27.33	15.100	3.009
33		1	1	1	A	0	0.000	1.431	15.680	32.500	38.96	40.42	45.26	46.05	39.57	38.02	42.84	41.93	34.98	24.19	16.42	8.542	.
34		1	1	2	B	0	0.000	4.377	43.300	73.100	81.72	85.75	100.20	92.07	84.84	85.82	91.87	87.52	54.09	36.59	24.03	11.290	1.545
35		1	2	1	B	0	0.000	2.902	17.520	36.850	50.26	51.87	58.35	75.10	75.07	82.24	77.96	74.74	56.85	44.87	32.03	18.130	2.995
36		1	2	2	A	0	0.000	5.192	28.310	54.220	68.89	68.53	74.06	79.88	69.87	62.50	64.20	68.90	43.42	30.97	20.65	10.610	1.247
37		1	1	1	A	0	0.000	12.590	58.240	65.020	73.66	73.88	79.25	79.38	64.75	61.15	65.56	62.57	56.31	37.59	25.98	14.910	2.327
38		1	1	2	B	0	0.000	3.410	26.470	42.180	49.71	59.26	66.60	64.45	68.35	71.13	74.93	72.19	52.57	42.05	29.20	17.900	2.689
39		1	2	1	B	0	0.000	7.033	37.610	56.320	71.34	81.37	97.55	104.50	87.01	73.03	70.70	63.15	44.96	29.90	20.98	12.350	1.046
40		1	2	2	A	0	0.000	7.525	34.220	41.440	50.42	49.78	52.46	56.54	53.13	44.31	41.34	46.36	37.52	25.53	16.88	8.997	0.000
41		1	2	1	B	0	0.000	0.000	9.988	27.720	37.63	39.84	45.99	50.14	51.18	49.17	54.33	55.22	39.71	31.41	22.26	12.730	2.060
42		1	2	2	A	0	0.000	0.000	13.020	41.200	41.96	49.03	59.48	49.41	50.37	47.59	49.41	59.46	45.83	32.81	20.18	9.788	1.240
43		1	1	1	A	0	0.000	3.949	26.800	48.990	64.08	75.61	63.22	67.87	64.69	64.28	72.75	79.97	52.76	34.18	22.24	9.078	1.111
44		1	1	2	B	0	0.000	1.136	10.590	22.870	31.64	37.81	43.14	53.72	49.57	51.49	56.08	50.37	39.25	33.80	29.27	15.940	3.091
45		1	2	1	B	0	0.000	2.302	19.900	48.560	56.96	65.20	73.18	80.92	77.04	74.10	69.19	60.31	46.22	33.29	24.75	13.190	2.489
46		1	2	2	A	0	0.000	1.361	19.090	38.120	42.71	47.20	47.97	49.42	45.54	47.67	57.46	58.87	41.53	28.57	20.97	10.840	1.428
47		1	1	1	A	0	0.000	1.220	16.730	30.150	35.61	47.51	48.87	50.35	48.59	46.48	46.91	53.67	42.84	31.97	20.05	11.730	1.235
48		1	1	2	B	0	0.000	3.269	24.540	46.460	61.25	67.46	73.89	78.76	81.07	78.18	77.93	79.42	50.78	42.76	27.09	16.060	1.599

Obs	sub	GRP	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
49	(b) (6)	1	1	1	A	0	1.748	14.110	47.530	63.810	77.36	76.25	78.23	80.58	74.92	67.15	77.96	80.75	52.83	32.06	22.53	10.980	1.277
50		1	1	2	B	0	1.133	9.208	46.920	79.930	109.20	119.70	132.50	175.20	147.10	129.00	128.50	111.30	74.69	53.44	38.55	22.230	2.464
51		1	2	1	B	0	0.000	8.669	39.230	40.500	55.89	59.25	58.73	74.32	66.62	60.54	60.52	51.37	35.95	30.40	21.30	10.650	1.298
52		1	2	2	A	0	1.339	16.970	58.990	46.460	58.14	69.37	67.72	60.11	52.76	49.01	44.13	40.82	30.43	20.52	13.91	6.670	0.000
53		1	1	1	A	0	0.000	13.220	55.410	69.340	83.64	94.35	86.35	88.61	78.28	86.41	81.62	80.14	66.25	42.83	28.66	14.470	4.045
54		1	1	2	B	0	0.000	6.493	30.810	47.090	60.69	73.15	87.40	99.89	91.84	106.30	107.60	110.80	74.91	59.00	38.35	19.080	3.691
55		1	1	1	A	0	0.000	2.524	22.160	41.020	55.81	63.39	64.76	65.14	59.89	60.19	57.59	58.83	45.85	28.00	20.08	10.350	0.000
56		1	1	2	B	0	0.000	0.000	9.810	24.700	36.75	45.00	50.48	57.25	51.75	52.37	54.92	50.68	39.16	31.67	20.76	10.890	1.401
57		1	2	1	B	0	0.000	14.070	51.130	79.600	97.47	112.10	124.40	145.20	118.20	116.90	111.90	98.12	64.51	43.75	26.65	12.660	1.469
58		1	2	2	A	0	1.666	20.590	100.900	125.400	120.50	127.60	130.20	128.80	96.66	98.34	107.60	111.70	70.07	47.96	28.52	13.600	1.542

Obs	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	trt
1	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
2	15	18	0	1.00	2	4.00000	6.06667	7.00	8	9	10	11.0833	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
3	15	18	0	1.05	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0667	18.0000	20.0	24.0000	36.0000	2
4	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
5	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
6	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
7	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
8	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
9	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
10	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.05	14	16.0000	18.0000	20.0	24.0000	36.0000	1
11	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
12	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0667	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
13	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
14	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2

Obs	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	trt
15	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
16	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0667	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
17	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
18	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0667	20.0	24.0000	36.0000	1
19	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
20	15	18	0	1.10	2	4.06667	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
21	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
22	14	17	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
23	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
24	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
25	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
26	14	17	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
27	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
28	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
29	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
30	14	17	0	1.00	2	4.00000	6.00000	7.05	8	9	10	11.0833	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
31	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
32	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
33	14	17	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
34	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
35	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
36	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
37	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
38	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
39	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
40	14	17	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1

Obs	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	trt
41	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
42	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
43	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
44	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	35.3667	2
45	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
46	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
47	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
48	15	18	0	1.00	2	4.00000	6.00000	7.05	8	9	10	11.0500	12.05	13.00	14	16.0000	18.0000	20.0	24.0667	36.0000	2
49	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
50	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
51	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
52	14	17	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
53	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1
54	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
55	14	17	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.1	24.0000	36.0000	1
56	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
57	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.05	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	2
58	15	18	0	1.00	2	4.00000	6.00000	7.00	8	9	10	11.0000	12.00	13.00	14	16.0000	18.0000	20.0	24.0000	36.0000	1

Fasting Pharmacokinetic Dataset

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
1	(b) (6)	1	1	1	1	1034.82	1053.93	66.78	9.00	4.90118	0.14142
2		2	1	2	1	913.31	930.59	59.94	10.00	4.69591	0.14761
3		1	2	2	1	1259.53	1270.77	101.30	14.00	3.91181	0.17719

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
4	(b) (6)	2	2	1	1	1209.00	1243.60	80.23	13.00	5.03668	0.13762
5		1	1	1	1	871.73	885.80	54.19	10.00	4.49671	0.15415
6		2	1	2	1	981.99	1026.78	61.32	14.00	6.25296	0.11085
7		1	2	2	1	1079.11	1086.37	82.70	8.00	3.72787	0.18594
8		2	2	1	1	850.79	867.43	52.98	10.00	4.70388	0.14736
9		1	2	2	1	951.34	962.86	76.71	13.05	4.36135	0.15893
10		2	2	1	1	882.16	917.18	65.71	10.00	5.98130	0.11589
11		1	1	1	1	798.27	805.00	60.98	10.00	4.07632	0.17004
12		2	1	2	1	679.64	695.05	45.68	9.00	4.88032	0.14203
13		1	1	1	1	908.46	920.37	66.16	14.00	4.29841	0.16126
14		2	1	2	1	630.18	658.64	44.49	14.00	5.88608	0.11776
15		1	2	2	1	892.16	912.32	65.89	14.00	4.87775	0.14210
16		2	2	1	1	1044.94	1077.44	68.17	13.00	5.19864	0.13333
17		1	2	2	1	1256.06	1283.02	83.65	14.00	4.80217	0.14434
18		2	2	1	1	1182.28	1219.42	67.42	9.00	5.47271	0.12666
19		1	1	1	1	1568.23	1595.53	109.80	8.00	4.90276	0.14138
20		2	1	2	1	1939.51	1989.21	125.00	14.00	5.13998	0.13485
21		1	2	2	1	608.32	647.26	39.66	16.00	3.40077	0.20382
22		2	2	1	1	585.76	601.19	37.54	13.00	5.17372	0.13397
23		1	1	1	1	638.23	648.98	39.42	14.00	4.27744	0.16205
24		2	1	2	1	1033.27	1050.34	76.21	14.00	4.45191	0.15570
25		1	2	2	1	969.33	1004.77	85.68	10.00	3.15393	0.21977

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
26	(b) (6)	2	2	1	1	1193.70	1199.06	94.82	9.00	3.56560	0.19440
27		1	1	1	1	674.79	685.05	45.92	14.00	4.30191	0.16113
28		2	1	2	1	511.18	528.37	34.03	14.00	5.08202	0.13639
29		1	2	2	1	755.70	796.94	61.96	10.00	3.48794	0.19873
30		2	2	1	1	851.23	858.61	70.16	10.00	3.93515	0.17614
31		1	1	1	1	697.91	708.87	52.31	14.00	4.42710	0.15657
32		2	1	2	1	747.00	769.23	51.66	14.00	5.12025	0.13537
33		1	1	1	1	620.96	669.42	46.05	10.00	3.93266	0.17625
34		2	1	2	1	1309.41	1318.29	100.20	9.00	3.98542	0.17392
35		1	2	2	1	1040.11	1047.14	79.88	10.00	3.90853	0.17734
36		2	2	1	1	1140.17	1160.20	82.24	12.00	4.63549	0.14953
37		1	1	1	1	1223.36	1238.55	79.38	10.00	4.52505	0.15318
38		2	1	2	1	1120.21	1137.96	74.93	13.00	4.57356	0.15156
39		1	2	2	1	754.14	804.54	56.54	10.00	3.88301	0.17851
40		2	2	1	1	1168.21	1173.80	104.50	10.00	3.70091	0.18729
41		1	2	2	1	827.84	834.78	59.48	9.00	3.87536	0.17886
42		2	2	1	1	795.89	809.58	55.22	14.00	4.60842	0.15041
43		1	1	1	1	1045.35	1051.24	79.97	14.00	3.67227	0.18875
44		2	1	2	1	830.14	852.06	56.08	13.00	4.91471	0.14104
45		1	2	2	1	822.07	830.62	58.87	14.00	4.14884	0.16707
46		2	2	1	1	1056.87	1074.19	80.92	10.00	4.82263	0.14373
47		1	1	1	1	796.36	803.28	53.67	14.00	3.88212	0.17855

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
48	(b) (6)	2	1	2	1	1168.19	1177.03	81.07	11.05	3.83487	0.18075
49		1	1	1	1	1200.14	1207.26	80.75	14.00	3.86819	0.17919
50		2	1	2	1	1901.36	1915.72	175.20	10.00	4.03780	0.17166
51		1	2	2	1	833.90	869.11	69.37	8.00	3.65887	0.18944
52		2	2	1	1	954.73	962.14	74.32	10.00	3.95894	0.17508
53		1	1	1	1	1398.30	1430.12	94.35	8.00	5.45305	0.12711
54		2	1	2	1	1492.72	1517.23	110.80	14.00	4.60196	0.15062
55		1	1	1	1	854.17	911.10	65.14	10.00	3.81230	0.18182
56		2	1	2	1	780.68	788.85	57.25	10.00	4.04381	0.17141
57		1	2	2	1	1839.37	1847.60	130.20	9.00	3.69707	0.18749
58		2	2	1	1	1622.84	1630.75	145.20	10.00	3.73594	0.18553

4.7.2 Fasting Study Codes

4.7.3 Fasting Study Output

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	29	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 28 29 30
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	58
Number of Observations Used	58

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	30	4.20029031	0.14000968	4.09	0.0002
Error	27	0.92365969	0.03420962		
Corrected Total	57	5.12395000			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.819737	2.689912	0.184958	6.876004

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01096631	0.01096631	0.32	0.5759
sub(seq)	27	4.11949584	0.15257392	4.46	0.0001
per	1	0.00295591	0.00295591	0.09	0.7710
trt	1	0.06687225	0.06687225	1.95	0.1735

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01096631	0.01096631	0.32	0.5759
sub(seq)	27	4.11949584	0.15257392	4.46	0.0001
per	1	0.00206287	0.00206287	0.06	0.8079
trt	1	0.06687225	0.06687225	1.95	0.1735

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01096631	0.01096631	0.07	0.7907

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.06795123	0.04860137	-1.40	0.1735

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	30	4.05616858	0.13520562	4.40	0.0001
Error	27	0.83059438	0.03076275		
Corrected Total	57	4.88676296			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.830032	2.542812	0.175393	6.897606

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01144932	0.01144932	0.37	0.5469
sub(seq)	27	3.97953672	0.14739025	4.79	<.0001
per	1	0.00477392	0.00477392	0.16	0.6967
trt	1	0.06040862	0.06040862	1.96	0.1725

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01144932	0.01144932	0.37	0.5469
sub(seq)	27	3.97953672	0.14739025	4.79	<.0001
per	1	0.00366960	0.00366960	0.12	0.7325
trt	1	0.06040862	0.06040862	1.96	0.1725

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01144932	0.01144932	0.08	0.7826

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.06458383	0.04608790	-1.40	0.1725

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	30	4.89498971	0.16316632	2.86	0.0036
Error	27	1.53885708	0.05699471		
Corrected Total	57	6.43384679			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.760819	5.625397	0.238736	4.243890

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.10836337	0.10836337	1.90	0.1793
sub(seq)	27	4.72047361	0.17483236	3.07	0.0024
per	1	0.02356866	0.02356866	0.41	0.5256
trt	1	0.04258407	0.04258407	0.75	0.3950

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10836337	0.10836337	1.90	0.1793
sub(seq)	27	4.72047361	0.17483236	3.07	0.0024
per	1	0.02140771	0.02140771	0.38	0.5451
trt	1	0.04258407	0.04258407	0.75	0.3950

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10836337	0.10836337	0.62	0.4380

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.05422480	0.06273236	-0.86	0.3950

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	0.98
2		1	0.99
3		1	0.98
4		1	0.99
5		1	0.99
6		1	0.99
7		1	0.99
8		1	0.98
9		1	0.98
10		1	0.98
11		1	0.94
12		1	0.98
13		1	0.96
14		1	0.99
15		1	0.95
16		1	0.98
17		1	0.93
18		1	0.99
19		1	0.99
20		1	0.94
21		1	0.99
22		1	0.99
23		1	0.99
24		1	0.99
25		1	0.99
26		1	0.96
27		1	0.98
28		1	0.94

Obs	sub	trt	AUCRATIO
29	(b) (6)	1	1.00
30		2	0.98
31		2	0.97
32		2	0.96
33		2	0.98
34		2	0.96
35		2	0.98
36		2	0.96
37		2	0.97
38		2	0.97
39		2	0.98
40		2	0.97
41		2	0.98
42		2	1.00
43		2	0.97
44		2	0.99
45		2	0.97
46		2	0.99
47		2	0.98
48		2	0.98
49		2	1.00
50		2	0.98
51		2	0.97
52		2	0.98
53		2	0.99
54		2	0.99
55		2	0.99
56		2	0.98
57		2	0.99

Obs	sub	trt	AUCRATIO
58	(b) (6)	2	1.00

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	1.13	1.13	1.11	0.90	0.96	1.04
	2	1.04	1.02	1.26	1.08	1.29	0.78
	1	0.89	0.86	0.88	0.71	1.39	0.72
	2	1.27	1.25	1.56	0.80	1.26	0.79
	2	1.08	1.05	1.17	1.31	1.37	0.73
	1	1.17	1.16	1.33	1.11	1.20	0.84
	1	1.44	1.40	1.49	1.00	1.37	0.73
	2	0.85	0.85	0.97	1.08	1.07	0.94
	2	1.06	1.05	1.24	1.56	1.14	0.88
	1	0.81	0.80	0.88	0.57	1.05	0.95
	2	1.04	1.08	1.06	1.23	1.52	0.66
	1	0.62	0.62	0.52	1.00	1.04	0.96
	2	0.81	0.84	0.90	1.11	1.13	0.88
	1	1.32	1.30	1.35	1.00	1.18	0.85
	2	0.89	0.93	0.88	1.00	1.13	0.89
	1	0.93	0.92	1.01	1.00	1.16	0.86
	1	0.47	0.51	0.46	1.11	1.01	0.99
	2	0.91	0.90	0.97	0.83	1.19	0.84
	1	1.09	1.09	1.06	0.77	1.01	0.99
	2	0.65	0.69	0.54	1.00	0.95	1.05
	2	1.04	1.03	1.08	0.64	1.19	0.84
	1	1.26	1.23	1.43	1.08	1.34	0.75
	2	0.78	0.77	0.73	1.40	1.16	0.86

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	0.68	0.68	0.66	1.27	0.99	1.01
	1	0.63	0.63	0.46	1.40	1.04	0.96
	2	0.87	0.90	0.93	0.80	1.08	0.92
	1	0.94	0.94	0.85	0.57	0.84	1.18
	1	1.09	1.15	1.14	1.00	1.06	0.94
	2	1.13	1.13	0.90	0.90	1.01	0.99

4.8 Communication Related to the OSI Inspection Status

Archived: Tuesday, November 27, 2012 3:56:06 PM
From: Chang, Sherry
Sent: Wednesday, November 21, 2012 10:37:18 AM
To: Wang, Rong
Cc: Chang, Sherry
Subject: RE: OSI status for ANDA 202346
Importance: Normal

Hello Rong,

For Study Numbers LIDO-1037, LIDO-09255, LIDO-1044, and LIDO-1046

1. OSI Inspection History of the Clinical site: Cetero Research (formerly PRACS), 4801 Amber Valley Pkwy, Fargo, ND 58104.
A routine inspection for NDA 21342 was completed on 10/7/2010, NAI.
A routine inspection for NDA 201194 was completed on 2/3/2011, NAI.
A routine inspection for NDA 202133 was completed on 8/12/2011, NAI.
A routine inspection for ANDA 202346 was completed on 2/3/2012, VAI.
A routine inspection for NDA 22497 was completed on 10/3/2011, NAI.
A routine inspection for NDA 203202 was requested on 10/28/2011, NAI.
A routine inspection for NDA 202834 was completed on 8/29/2012, NAI.
2. OSI Inspection History of the Analytical site: Mylan Pharmaceuticals Inc., 3711 Collins Ferry Rd, Morgantown, WV 26505.
A routine inspection for ANDA 200462 was completed on 9/15/2010, VAI.

For Study Number LIDO-09254

1. OSI Inspection History of the Clinical site: Cetero Research (formerly PRACS), 625 Demers Avenue, East Grand Forks, MN 56721.
(b) (4)

2. OSI Inspection History of the Analytical site: Mylan Pharmaceuticals, Inc., 3711 Collins Ferry Road, Morgantown, WV 26505.

A routine inspection for ANDA 200462 was completed on 9/15/2010, VAI.
Please let me know if you need further assistance.
Have a great Thanksgiving.
Thank you,
Sherry

From: Wang, Rong
Sent: Tuesday, November 20, 2012 4:22 PM
To: Chang, Sherry
Subject: OSI status for ANDA 202346
Sherry,
I will be working on the review for ANDA 202346. Could you please help me find the information about most updated OSI status for ANDA 202346 (please see below)? Thank you very much.
Rong

ANDA No.	202346			
Drug Product Name	Lidocaine Patch			
Strength(s)	5%			
Applicant Name	Mylan Technologies Inc			
Applicant Address	110 Lake St. St. Albans, VT 05478			
US Agent Name and the mailing address	S. Wayne Talton Vice President, Regulatory Affairs 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310			
US agent's Telephone Number	304-599-2595 ext. 6551			
US Agent's Fax Number	304-285-6407			
Original Submission Date(s)	10/26/2010			
Submission Date(s) of Amendment(s) Under Review	10/26/2010 (Original Submission)			
First Generic (Yes or No)	No			
Reviewer	Rong Wang Pharm.D., Ph.D.			
Study Number (s)	**LIDO-1037**	LIDO-09255	LIDO-1044	LIDO-1046
Study Type (s)	**Fasting**	Adhension	Adhension	Cumulative

	(Pivotal)	(Pilot)		Irritation and Sensitization
Strength (s)	**5%**	5%	5%	5%
Clinical Site	Cetero Research			
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104			
Analytical Site	Mylan Pharmaceuticals, Inc. Bioanalytical Department			
Analytical Site Address	3711 Collins Ferry Road Morgantown, WV 26505			
Study Number (s)	**LIDO-09254**			
Study Type (s)	**Fasting (Pilot)**			
Strength (s)	**5%**			
Clinical Site	Cetero Research			
Clinical Site Address	625 Demers Avenue East Grand Forks, MN 56721			
Analytical Site	Mylan Pharmaceuticals, Inc. Bioanalytical Department			
Analytical Site Address	3711 Collins Ferry Road Morgantown, WV 26505			
OSI Status				
OVERALL REVIEW RESULT				
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**			
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**	
1, 2	**Fasting Study**	**5%**		

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 202346

APPLICANT: Mylan Technologies Inc

DRUG PRODUCT: Lidocaine Patch, 5%

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet and has identified the following deficiencies.

1. For the bioequivalence (BE) study LIDO-1037, you reported the "apparent dose" delivered. However, the validity of your reported data for the "apparent dose" delivered cannot be confirmed as the study report did not include the complete analytical report, validation report, and the detailed experimental procedures. Please provide this information. Please provide your analysis to show that the "apparent dose" delivered for your test product was comparable to the reference product.

2. We note that a number of subjects in the study LIDO-1037 were evaluated with adhesion score as 1 or 2 at some time points during the study. According to the protocol, score 1 means >=75% to <90% adhered (some edges only lifting off the skin) and score 2 means >=50% to 75% adhered (less than half the system lifting off the skin). You submitted the adhesion scores at 3 time points (4, 8 and 12 hours (± 10 minutes) after patch application) for each patch applied for all the subjects. However, you did not provide statistical summary data of the adhesion scores for the test and reference patches (Mean, SD, Minimum, Median, Maximum, confidence interval etc.) and the acceptance criterion for comparable adhesion of the test and reference products. Please provide this information.

3. The FDA's Office of Scientific Investigations (OSI) previously conducted an inspection at the analytical site, Mylan Pharmaceutical Inc (3711 Collins Ferry Rd, Morgantown, WV 26505), for a different application. This analytical site is the same as that used for the BE study LIDO-1037 in your application. The FDA Form 483 issued to the analytical site at the end of the inspection noted the following:

   1) *Stability of processed samples was determined with only mid level QCs during pre-study validation for the audited studies. Processed stability was not evaluated with low and high QC concentrations.*

   2) *Failure to document all aspects of study conduct.*

      No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes during the audited studies.

Please address the impact of each of these findings on the study in your current application.

4. You approved the bioanalytical method validation report on June 15, 2010, after the completion date of the sample analysis on June 9, 2010 for the study LIDO-1037. The analytical method is considered validated only after the method validation report is approved by signatory authority. For future submission, please ensure a validated analytical method is used for study sample analysis.

5. For better understanding for your formulation and dissolution method development and optimization, please provide individual concentration and pharmacokinetic data of pilot study LIDO-09254 and the dissolution testing data for all formulations used in this study, if available.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.9 Outcome Page

ANDA: 202346

5 *COMPLETED ASSIGNMENT FOR 202346 ID: 18527*

Reviewer: Wang, Rong **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Lidocaine Patch, 5% Mylan Technologies Inc

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
18527	10/26/2010	Bioequivalence Study (REGULAR)	Fasting Study	1	1
18527	10/26/2010	Bioequivalence Study (REGULAR)	Non-Failed Extra Study	1	1
				Total:	2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RONG WANG
02/12/2013

NILUFER M TAMPAL
02/12/2013

HOAINHON N CARAMENICO
02/13/2013

DALE P CONNER
02/25/2013

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202346			
Drug Product Name	Lidocaine Patch			
Strength (s)	5%			
Applicant Name	Mylan Technologies, Inc.			
Address	110 Lake St. St. Albans, VT 05478			
Applicant's Point of Contact	For electronic components of the application: Jerry Toppins; All other correspondence to S. Wayne Talton			
Contact's Phone Number	JT: 304-599-2595; SWT: 304-599-2595			
Contact's Fax Number	304-285-6407			
Submission Date(s)	October 22, 2010 and February 8, 2011			
First Generic	Yes			
Reviewer	Utpal M. Munshi			
Study Number (s)	LIDO-1037	LIDO-09255 (clinical site only, no analytical site used)	LIDO-1044 (clinical site only, no analytical site used)	LIDO-1046(clinical site only, no analytical site used)
Study Type (s)	Fasting	Adhesion	Adhesion	Cumulative Irritation and Sensitization
Strength(s)	5%	5%	5%	5%
Clinical Site	Cetero Research			
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104			
Analytical Site	Mylan Pharmaceuticals, Inc. Bioanalytical Department			
Analytical Address	3711 Collins Ferry Road Morgantown, WV 26505			
Study Number (s)	LIDO-09254			
Study Type (s)	Fasting			
Strength (s)	5%			
Clinical Site	Cetero Research			
Clinical Address	625 Demers Avenue East Grand Forks, MN 56721			
Analytical Site	Mylan Pharmaceuticals, Inc. Bioanalytical Department			
OUTCOME DECISION	**ADEQUATE (NOTE TO THE PROJECT MANAGER, Please relay information in footnote #4 to the Division of Chemistry).**			

I. EXECUTIVE SUMMARY

This is a review of the *in vitro* drug release testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm has conducted comparative *in vitro* drug release testing on the Test and Reference products using this method. The testing and proposed specifications are **adequate.**

The firm failed to submit SAS transport files for adhesion study # LIDO-1044. The firm is asked to submit these files.

The DBE will review the fasting, adhesion, and cumulative irritation/sensitization studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			x	☐	☐
Did the firm use the USP dissolution method			☐	☐	x
Did the firm use 12 units of both test and reference in dissolution testing			x	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			x	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	x	☐
Is FDA method in the public dissolution database (on the web)			x	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	x	☐	☐
		Plasma concentrations	x	☐	☐
	Fed BE study	PK parameters	☐	☐	x
		Plasma concentrations	☐	☐	x
	Cumulative Irritation and Sensitization Study	Summary	x	☐	☐
		Irritation Data	x	☐	☐
	Adhesion Study	Summary	☐	x	☐
		Adhesion Data	☐	x	☐
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			x	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			x	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DRUG RELEASE DATA

Dissolution Conditions	Apparatus:	5 (paddle over disk – transdermal sandwich)
	Speed of Rotation:	50 rpm
	Medium:	10 mM Sodium Acetate Buffer, pH 4.0
	Volume:	500 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	1.5 Hours: (b) (4)%, 6 Hours: (b) (4)%, 12 Hours: (b) (4)%, 24 Hours: (b) (4)%	
Dissolution Testing Site (Name, Address)	Mylan Technologies, 110 Lake Street, Saint Albans, Vermont 05478	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength	No. of Dosage Units		Collection Times (hours)				Study Report Location
						1.5 Hours	6 Hours	12 Hours	24 Hours	
N/A	Aug. 2010	Lidocaine Patch Lot R6B0017 March 29, 2010	5%	12	Mean	7.1	11.7	16.1	22.6	3.2.P.5.4 Batch Analysis
					Range	(b) (4)				
					%CV	4.8	2.5	1.7	1.4	
N/A	Aug. 2010	LIDODERM® Patch Lot 97278 08/10	5%	12	Mean	39.7	73.7	90.6	98.4	
					Range	(b) (4)				
					%CV	3.7	1.2	1.5	2.2	

(b) (4)

Note: The recommended sampling times (minutes) in FDA's external dissolution database are: 10, 20, 30, 60, 120, and 180.

II. COMMENTS:

1. As noted on the first page of this review, the firm has submitted 5 different studies. Of these studies, study # s 09255 (adhesion) and 09254 (fasting) were pilot studies.

2. The firm did not submit adhesion study data (# LIDO-1044) in SAS transport format.

3. The reviewer has confirmed that the summary *in vitro* drug release data table provided by the firm accurately reflects the individual unit data.

4. The reviewer has confirmed that the sponsor's *in vitro* drug release testing was performed on the same lots of the Test (R6B0017) and Reference (97278) products used in fasting study # LIDO-1037, adhesion study # LIDO-1044, and cumulative irritation/sensitization study # LIDO-1046. The RLD lot was unexpired at the time of the *in vitro* drug release testing. The *in vitro* release testing for the Test product lot was performed 5-6 months after manufacture.

5. Based on the FDA internal and external dissolution databases as of April 25, 2011, the following are the FDA-recommended method and specification for the Lidocaine Topical Patch, 5%[1].

Apparatus: V (Paddle over Disk)
Speed: 50 rpm
Medium: Acetic Acid/Sodium Acetate Buffer, pH 4.0
Temperature: 32°C
Volume: 500 mL
Sampling Time Points: 10, 20, 30, 60, 120, and 180 minutes

Specification: NLT (b) (4) *per patch at 30 minutes.*

NOTE: The labeled amount in RLD is 700 mg/140 sq cm (10 x 14 cm). In the current submission, Mylan did not follow the recommended sampling times above. Mylan collected the samples at 1.5 hours, 6 hours, 12 hours, and 24 hours. The labeled amount in Mylan's proposed test product is 140 mg/140 sq cm.

[1] This reviewer was not able to confirm if the method stated in the DBE dissolution databases is that currently used by the innovator for the RLD product. However, based on information in DARRTS, the reviewer could confirm that the specification of NLT (b) (4) in 30 minutes is that currently used by the innovator (DARRTS, NDA 020612, REV-QUALITY-03, Final Date of 06/28/02).

6. Using the FDA-recommended method, it is seen that nearly 100% of Label Claim is released at the 24h sampling time point for the Reference product, whereas only ~20% of Label Claim is released for the Test product at this time point. While the Test product undergoes incomplete release as compared to the Reference product, it is important to note that the FDA-recommended method is actually a reasonably accurate indicator of *in vivo* performance of the Test product. This conclusion is based on the following:

a) Given that one patch of the Test product contains 140 mg of lidocaine[2], 0.20 x 140 mg, or approximately 28 mg of lidocaine is released from the Test product by the 24 h time point.

b) Per the RLD label[3], an average of 21 mg of lidocaine is released *in vivo* from the RLD patch over a period of 12 h. Assuming that the Test and Reference products are bioequivalent, it follows that the Test product will have a similar *in vivo* release profile.

c) Based on the discussion in point a) above, the *in vitro* release data for the Test product indicate a release of approximately 22.4 mg of lidocaine from a patch at the 12 h time point (i.e., 0.16 x 140 mg). This is a reasonable estimation of the *in vivo* release of lidocaine from the Test product based on point b) above. In contrast, the Reference product releases 630 mg[4] of lidocaine at the 12 h time point *in vitro*. As a result, it is evident that the FDA-recommended method is not nearly as accurate an indicator of the *in vivo* performance of the RLD as compared to that of the Test product.

Taking the above discussion together with the fact that the method has low variability and is discriminating[5], the FDA-recommended method as applied to the Test product is **acceptable.**

7. The specifications proposed by the firm are stringent with respect to the proposed range at each time point as well as the number of time points used. The proposed specifications should therefore provide adequate quality control of the Test product. The specifications proposed by the firm are therefore **acceptable**.

---

[2] Section 2.3.P.1 of the submission

[3] Drugs@FDA database. Label approved 04/13/2010

[4] The RLD label indicates that 700 mg of lidocaine is contained within the 140 cm2 patch. This is in contrast to the 140 mg of lidocaine contained with one 140 cm2 patch of the Test product. In this regard, it is noted that the Individual Product Guidance states that the Test product should have the same total amount of Lidocaine as the RLD. The Division of Chemistry should be notified of this issue.

[5] The RLD and Test products have different formulations (per the RLD label and section 2.3.P.1 of the submission). The different i*n vitro* release profiles for the two formulations support this fact.

III. DEFICIENCY COMMENTS:

The firm did not submit SAS transport files for adhesion study # LIDO-1044. The firm will be asked to submit these files.

IV. RECOMMENDATION:

The firm's *in vitro* drug release testing is **adequate.**

BIOEQUIVALENCE DEFICIENCY

ANDA: 202346

APPLICANT: Mylan

DRUG PRODUCT: Lidocaine Topical Patch, 5 %

The Division of Bioequivalence (DBE) has completed its review of the drug release testing portion of your submission(s) acknowledged on the cover sheet. The review of the *in vivo* fasting bioequivalence study, adhesion study, and the cumulative irritation/sensitization study will be conducted later. The following deficiency has been identified:

You did not submit SAS transport files for the adhesion study # LIDO-1044. Please submit these files.

The DBE acknowledges that you will use the following *in vitro* drug release method and specifications for your product:

Apparatus: V (Paddle over Disk)
Speed: 50 rpm
Medium: Acetic Acid/Sodium Acetate Buffer, pH 4.0
Temperature: 32°C
Volume: 500 mL

Specifications:
1.5 h: (b) (4) %
6 h: (b) (4) %
12 h: (b) (4) %
24 h: (b) (4) %

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 202346

Completed Assignment for 202346 ID: 13849

Reviewer: Munshi, Utpal **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Lidocaine, Mylan, Dissolution-Only, DBE I

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
13849	10/22/2010	Dissolution Data	Dissolution Review	1	1
13849	2/8/2011	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	1

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/s/

UTPAL M MUNSHI
06/02/2011

YIH CHAIN HUANG
06/02/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/02/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

OTHER REVIEWS

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 3, 2012

TO: John Peters, M.D.
Acting Associate Director for Medical Affairs
Office of Generic Drugs

FROM: Jangik I. Lee, Pharm.D., Ph.D.
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering ANDA 202-346, Lidocaine Topical Patch, 5% sponsored by Mylan Technologies, Inc.

At the request of the Office of Generic Drugs (OGD), the Division of Bioequivalence and GLP Compliance (DBGC) conducted the audit of the clinical portion of the following studies:

Study 1: LIDO-1046
Study Title: "Comparative Evaluation of the Cumulative Irritation and Sensitization Potential of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers"

Study 2: LIDO-1044
Study Title: "Single-Dose Adhesion Study of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers"

The clinical portion of the studies was conducted at Cetero Research in Fargo, ND. Following the inspection, no Form FDA 483 was issued for either study. However, the following verbal observations communicated to the firm and our evaluations follow.

1. **Record review of computer generated pharmacy Drug Inventory control records for Study LIDO-1044 reveals the pharmacy's**

record of the randomization codes for placement of the patches on subjects has been "over" written manually and changed by pharmacy staff to reflect the correct placement as set in the protocol. The firm's SOPs and computer program, called "Study Monitor Program" are incomplete, in that; there is no current computer program that will print in and for pharmacy the protocol placement of the patches; and the SOPs fail to provide guidance for randomization documentation of dermatological studies. In addition, pharmacy has no applicable guidelines for the dermatology studies to follow.

The firm’s management promised immediate correction, including possibly applying Fargo site-specific SOPs to both pharmacokinetic and dermatological studies (e.g., irritation, sensitization, and adhesion).

2. **Case document review for Subject (b) (6) for Study RI0-0159, LIDO-1046 shows a positive HCG on final-exit of study. The documents for the follow up of this pregnant subject were incomplete in that; documentation of final outcome of pregnancy was not in study files and SOPs are vague and do not address pregnancy follow up or guidance for where the final documentation should be placed when subjects are found pregnant at the end of a study. Subject's medical records noted a viable newborn delivered on (b) (6) The inspector explained to the management that case files should contain a complete final outcome-history of all subjects and the SOPs should address this matter.**

The management promised correction to the inspector.

CONCLUSION

Following the inspection of the clinical site for Studies LIDO-1044 and LIDO-1046, no major objectionable conditions were observed, and Form FDA 483 was not issued. DBGC recommends that the studies be accepted for review.

After you have reviewed this transmittal memorandum, please append it to the original ANDA submission.

FINAL CLASSIFICATIONS

VAI - Cetero Research in Fargo, ND (FEI #1720861)

cc:
OSI: Ball/Moreno
DBGC: Taylor/Haidar/Dejernett/CF
OGD: Peters/Patel
MIN-DO: Smith/Harold
Draft: JIL 1/27/2012
Edit: MFS 1/27/2012
OSI: File BE6184; O:\BIOEQUIV\EIRCOVER\202346Myl.Lid.doc
FACTS: 1265645

EMAIL: CDER OSI PM TRACK

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/s/

JANGIK I LEE
02/03/2012

MICHAEL F SKELLY
02/03/2012
Skelly signing on behalf of Dr. Haidar

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202346

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: Potter Team: **Approval Date:**

☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☒ **No)** ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 202346 Applicant: Mylan Technologies Inc. Established Product Name: Lidocaine Topical Patch, 5%.

Basis of Submission (RLD): Lidoderm

(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ☒ *No)*

Does the ANDA contain REMS? ☐ **Yes** ☒ **No** *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 8/4/2015**

☐ Date last Complete Response (CR) letter was issued -- Date 4/24/2015

☐ Previously reviewed and tentatively approved (if applicable) --- Date _____

Date of Application 10/25/2010	Original Received Date 10/26/2010	Date Acceptable for Filing 20/26/201

YES	NO	
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A) Date of Acceptable Quality 8/6/2015 Date of Acceptable Dissolution 2/25/2013 Date of Acceptable Bioequivalence 11/24/2014 Date of Acceptable Labeling 3/10/2015 If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 5/31/2013 Date of Acceptable REMS N/A
☐	☒	Are consults pending for any discipline?
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed and that all disciplines completed new reviews ☐
☐	☒	Is there a pending Citizen Petition (CP)?
☒	☐	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: _____ Re-evaluation Date: 12/31/2015
☒	☐	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable
☐	☒	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed _____
Draft Approval/Tentative Approval Letter		
☒	☐	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task
Review Discipline/Division Endorsements		
☒	☐	Division of Legal and Regulatory Support Endorsement completed, Date 8/6/2015
☒	☐	Paragraph IV Evaluation completed (if applicable), Date 8/7/2015
☒	☐	Quality Endorsement completed, Date 8/6/2015
☒	☐	Bioequivalence Endorsement completed, Date 8/7/2015
☒	☐	Labeling Endorsement completed, Date 8/6/2015
☐	☐	REMS Endorsement (if applicable), Date N/A
RPM Team Leader Endorsement and Action Package Verification		
☒	☐	RPM Team Leader Endorsement completed, Date 8/7/2015
Final Decision and Letter Sign-off		
☒	☐	Final Decision recommending approval/tentative approval completed, Date 8/7/2015
☒	☐	Approval/Tentative Approval letter electronically signed, Date: 8/7/2015
Project Close-Out		
☒	☐	Notify applicant of approval and provide a courtesy copy of the electronically signed letter
☐	☒	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed _____
☒	☐	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information

This page to be completed by the RPM

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 8/6/2015
Name/Title: IM for MHS

Contains GDEA certification: Yes ☒ No ☐	
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = _____ NDA# _____ Date Checked _____
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days: Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: 10/17/2013 Is applicant eligible for 180 day Is a forfeiture memo needed: Yes ☐ No ☐ If yes, has it been completed	Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER:	
Comments:	

BOS = Lidoderm (NDA 20612) Application submission 10/26/2010 with PIV certifications to the '529 and '510 patents and PIII certifications to the '738 and '838 patents. Acknowledgment letter signed 1/10/2011.
Amendment 2/2/2011 with copies of PIV RR sent 1/27/2011 to Teikoku Pharma USA (CA), Endo Pharmaceuticals (PA), Birch, Stewart, et al. (VA) and Teikoku Seiyaku (JP) and rc'd 1/28/2011, 1/28/2011, 1/28/2011 and 1/31/2011.
Amendment 4/5/2011 providing a copy of litigation filed 3/14/2011 in USDC of Delaware, CA# 1:11-cv-00220-UNA, on the '510 patent.
Amendment 4/16/2012 Mylan has provided a copy of the Order dated 3/30/2012 by the USDC of Delaware, CA# 11-220, dismissing the plaintiff's complaint without prejudice.
Amendment 6/5/2013 Mylan states Endo filed a Motion to Amend Complaint Pursuant to Rule 15(a) and for Reconsideration Under Rule 59(e) and D. Del. LR 7.15. The motion remained pending until 3/11/2013 when the USDC of Delaware granted the Motion allowing amendment of the complaint (CA# 1:11-cv-00220-GMS). Within the complaint, the court states "…the court does not view its dismissal order or its decision on the present motion as having any immediate effect on thirty month stay." (page 10 of complaint)
Amendment 10/21/2013 with a copy of the Consent Decree and Order dated 10/17/2013 issued by USDC of Delaware to CA# 1:11-cv-00220-GMS stating Mylan does not infringe upon the '510 patent and judgment is entered in favor of Mylan.
The '738, '838 and '510 patents have all expired. The remaining '529 (exp. 10/27/2015) was not the subject of litigation and is therefore not a barrier to approval. Watson/Actavis, ANDA 200675, was the FTF application and eligible for 180-day. However, they did not secure a TA or approval within 30 months of their original submission and 'punt' language was used in the approval letter. In the 9/25/2013 amendment from Watson, they state commercial marketing commenced 9/15/2013. With this marketing, the 180-day has run and expired, whether or not Watson forfeited the exclusivity. Mylan's ANDA is eligible for immediate Full Approval.

2. ***Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

3. ***Quality Endorsement by the Office of Pharmaceutical Science***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

4. ***Bioequivalence Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

5. ***Labeling Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

6. ***REMS Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

7. ***RPM Team Leader Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

8. Final Decision

Date: 8/7/2015
Name/Title: CAH

Para.IV Patent Cert: Yes ☒ ☐ ☐ No ☐
Pending Legal Action: Yes ☐ ☐ No ☒
Petition: Yes ☐ No ☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met ☒ Unmet ☐
Press Release Acceptable ☐
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐

Date PETS checked for first generic drug _____

Comments:

BOS = Lidoderm (NDA 20612), Teikoku. The application was submitted on 10/26/2010 with PIV certifications to the '529 and '510 patents and PIII certifications to the '738 and '838 patents. The applicant states that the applicant was notified and they were sued for infringement on the '510 patent. The 4/16/2012 amendment Mylan has provided a copy of the Order dated 3/30/2012 by the USDC of Delaware, CA# 11-220, dismissing the plaintiff's complaint without prejudice. Amendment 6/5/2013 Mylan states Endo filed a Motion to Amend Complaint Pursuant to Rule 15(a) and for Reconsideration Under Rule 59(e) and D. Del. LR 7.15. The motion remained pending until 3/11/2013 when the USDC of Delaware granted the Motion allowing amendment of the complaint (CA# 1:11-cv-00220-GMS). Within the complaint, the court states "…the court does not view its dismissal order or its decision on the present motion as having any immediate effect on thirty month stay." (page 10 of complaint). Amendment 10/21/2013 with a copy of the Consent Decree and Order dated 10/17/2013 issued by USDC of Delaware to CA# 1:11-cv-00220-GMS stating Mylan does not infringe upon the '510 patent and judgment is entered in favor of Mylan. The '738, '838 and '510 patents have all expired. The remaining '529 (exp. 10/27/2015) was not the subject of litigation and is therefore not a barrier to approval. There are no new patents or exclusivities listed in the OBook (8/7/15). There are no issues listed on the OGD Policy Alert Tracker (8/7/15 update). The clinical evaluation of the skin irritation, sensitization and adhesion study was found adequate by Lee on 5/31/15, Clinical consult on cutting was found adequate. CMC found adequate with a post market commitment – Berendt 8/5/15. The QE was completed by Strasinger and is adequate on 8/5/15. Stats is adequate on 5/28/13, Bio is adequate with fasting study and OSIS adequate – Review by Yu 24 Nov 2014. Dissolutionok 2/25/13.Labeling is adequate by Turner on 11/25/12 with TL endorsement by Skanchy on 8/6/15. The overall manufacturing inspection recommendation is approve through 12/31/15 – See screen shots below. According to OGD policy "Watson/Actavis, ANDA 200675, was the FTF application and eligible for 180-day. However, they did not secure a TA or approval within 30 months of their original submission and 'punt' language was used in the approval letter. In the 9/25/2013 amendment from Watson, they state commercial marketing commenced 9/15/2013. With this marketing, the 180-day has run and expired, whether or not Watson forfeited the exclusivity." Thus, this ANDA is eligible for immediate Full Approval.

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 202346

INFORMATION REQUEST

Mylan Technologies Inc.
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated October 25, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Lidocaine Topical Patch, 5%.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We also refer to your January 7, 2015 submission, containing your response to the Information Request sent out on December 24, 2014.

We request a prompt written response, no later than **March 15, 2015**, in order to continue our evaluation of your ANDA.

A. Deficiencies

1)

(b) (4)

2)

(b) (4)

3)

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
CHEMISTRY
REFERENCE # 77471

Please note, if information or data submitted exceeds the data requested in the Information Request this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA). If the submitted data is determined to be a Tier 2 unsolicited amendment, this may affect the goal date.

If you have any questions, please contact Brijet Burton Coachman, Regulatory Business Project Manager, at (240) 402-4878.

Sincerely,

Brijet N. Burton Coachman -S

Digitally signed by Brijet N. Burton Coachman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=CMS, ou=People, 0.9.2342.19200300.100.1.1=2000028104, cn=Brijet N. Burton Coachman -S
Date: 2015.02.13 12:48:43 -05'00'

Brijet Burton Coachman
Regulatory Business Project Manager
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 05/18/2015 09:37:31 AM
To: Joseph.Sobecki@mylan.com
CC: Wayne.Talton@mylanlabs.com
BCC: andrew.potter@fda.hhs.gov
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 202346

ANDA 202346

NOTIFICATION --
TARGET ACTION DATE

Mylan Technologies Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26404
Attention: Joseph J. Sobecki

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated November 30, 2011, received December 1, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

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 take action on this ANDA. “Action” for these purposes is a complete response, a tentative approval, or a final approval.

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 action 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 take action 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 August 7, 2015.

Please contact your Regulatory Project Manager, Andrew Potter at (240) 402-9266, one month prior to your Target Action Date for an additional status update of your application.

Sincerely,

Andrew Potter, RPM

Division of Project Management
Office of Regulatory Operations
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 202346

NOTIFICATION --
TARGET ACTION DATE

Mylan Technologies Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26404
Attention: Joseph J. Sobecki

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated November 30, 2011, received December 1, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

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 take action on this ANDA. “Action” for these purposes is a complete response, a tentative approval, or a final approval.

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 action 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 take action 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 April 20, 2015.

Please contact your Regulatory Project Manager, Andrew Potter at (240) 402-9266, two weeks prior to your Target Action Date for an additional status update of your application.

Sincerely,

Andrew Potter

Division of Project Management
Office of Regulatory Operations
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 202346

INFORMATION REQUEST

Mylan Technologies Inc.
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated October 25, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Lidocaine Topical Patch, 5%.

We also refer to your November 5, 2014 submission, containing your response to the Easily Correctable Deficiency sent out on October 23, 2014.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than **January 12, 2015**, in order to continue our evaluation of your ANDA.

A. Deficiencies

(b) (4)

1)

2)

(b) (4)

3)

4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1) (b) (4)

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
CHEMISTRY
REFERENCE # 60813

Please note, if information or data submitted exceeds the data requested in the Information Request this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA). If the submitted data is determined to be a Tier 2 unsolicited amendment, this may affect the goal date.

If you have any questions, please contact Brijet Burton Coachman, Regulatory Business Project Manager, at (240) 402-4878.

Sincerely,

Brijet N. Burton Coachman -S

Digitally signed by Brijet N. Burton Coachman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=CMS, ou=People, 0.9.2342.19200300.100.1.1=2000028104, cn=Brijet N. Burton Coachman -S
Date: 2014.12.24 11:26:52 -05'00'

Brijet Burton Coachman
Regulatory Business Project Manager
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2014-0912	
TO *(Division/Office)* OGD: Division of Clinical Review (DCR): Nitin Patel			FROM: Robert Berendt, Ph. D., CMC Reviewer, Chemistry 5	
DATE: 3/28/2014	IND NO.	ANDA NO. 202346	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 10/28/2013,
NAME OF DRUG Lidocaine topical patch, 5%		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Local anesthetic	DESIRED COMPLETION DATE 5/27/2014
NAME OF FIRM Mylan Technologies, Inc.				

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY _____
Γ PRE NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICIENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

□ DISSOLUTION
□ PROTOCOL-- BIOPHARMACEUTICS
□ IN--VIVO WAIVER REQUEST
□ DEFICIENCY LETTER RESPONSE
□ BIOAVAILABILITY STUDIES
□ PHASE IV STUDIES

IV.DRUG EXPERIENCE

□ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
□ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
□ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
□ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
□ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
□ SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL □ PRECLINICAL

COMMENTS
OGD is requesting a clinical assessment of the ANDA 202346 lidocaine topical patch, 5%. The chemistry review team is concerned (b) (4) (b) (4) (b) (4) Please contact the CMC primary reviewer, Robert Berendt (robert.berendt@fda.hhs.gov, 240-276-8333), to cal reviewer for assessment.

Please compare the RLD and proposed ANDA 202346 topical patches and assess the acceptability of the ANDA product (b) (4) (b) (4) (b) (4) (Please note, clinical assessment of skin irritation, sensitization, and adhesion studies has already been performed (DARRTS, 05/31/2013) and found adequate.)

Please provide an electronic copy of the review to the requestor by email and cc Steven Yang, HFD-617 (Steven.Yang@FDA.HHS.gov) when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* □ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

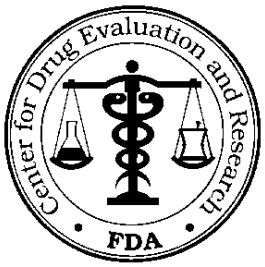
ROBERT T BERENDT
03/28/2014

BHAGWANT D REGE
03/28/2014

STEVEN W YANG
03/31/2014

FDA FAX

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: MYLAN TECHNOLOGIES INC TEL: 304-599-2595 x 6551

ATTN: S. Wayne Talton FAX: 304-285-6407

This facsimile is in reference to your abbreviated new drug application(s), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

DATE: 2/9/2014

TO: MYLAN TECHNOLOGIES INC

ATTN: S. Wayne Talton

E-Mail: wayne.Talton@mylan.com

FAX: 304-285-6407

RE: Update summary of filed and pending original ANDA(s)

Dear Sir or Madam:

The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is providing you with this one-time communication on the status of your filed and pending original abbreviated new drug application(s) (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act. OGD is providing these updates as an interim measure to help applicants assess the status of their current submissions as we transition towards predictable goal times pursuant to the Generic Drug User Fee Amendments of 2012 (GDUFA).

Your status update is limited to available review information as of January 29, 2014. Any additional information regarding your ANDA collected after this date is neither considered nor provided. Furthermore, your ANDA status is subsequently subject to revision pending additional information or concerns raised by any of the discipline reviews (bioequivalence, clinical, chemistry, microbiology, labeling, facility), other unforeseen legal, scientific or regulatory issues, or inspectional results, which can also impact the status or ability to issue a complete response. Any applicable fees can also affect the status of your ANDA.

OGD is providing your ANDA status update in the attached chart with a list of applicable acronyms. The chart only contains current information regarding discipline review and does not forecast if and when OGD will issue a complete response, tentative approval, or final approval letter.

Please do not respond to this communication by asking FDA or your Regulatory Project Manager for additional or more detailed information. This is a one-time communication intended to assist you to ascertain the current status of submissions. It is not feasible for us to respond to a high volume of follow up inquiries.

Sincerely yours,

CAPT Aaron W. Sigler, USPHS
Chief, Review Support Branch

ANDA	DRUG NAME	CHEM	BIO	MICRO	LABEL	CLINICAL	FACILITY
200910	ETHINYL ESTRADIOL;NORELGESTROMIN	AQ	UR	NA	UR	UR	AC
201675	ESTRADIOL	UR	AQ	NA	AQ	UR	AC
202346	LIDOCAINE	UR	UR	NA	AQ	AQ	AC

CHART ACRONYMS

Column Headings

ANDA - The application number for your Abbreviated New Drug Application
DRUG NAME - The official filed name of the drug associated with the ANDA number
CHEM - Product Quality Chemistry Review
BIO - Bioequivalence Review, typically including OSI, if applicable
MICRO - Microbiology Review
LABEL - Labeling Review
CLINICAL - Clinical Review
FACILITY - Overall Facility inspections summary. All facilities must be acceptable at the time of 29 JAN 14 in order to warrant an adequate notation. If one of more facility is not acceptable then the FACILITY column will be marked as such. OSI information is not considered.

Discipline Notations

IQ	- Inadequate. This particular discipline is currently found to be inadequate.
AQ	- Adequate. This particular discipline was found to be adequate when the information was gathered for this communication.
UR	- Under Review. This particular discipline is currently assigned OR under review with the discipline team.
NR	-Not Reviewed. This particular discipline is either currently not under review or assigned.
NA	- Not applicable. This particular discipline is not required for the approval of this ANDA.

Facility Notations

PN	- Pending, i.e., one or more facilities have been inspected and are pending an outcome.
AC	- All facilities are acceptable at the time of this publication.

*Please note that you may receive your updates in multiple communications over time, based on the number of ANDAs pending in OGD.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SIMON S ENG on behalf of AARON W SIGLER
02/12/2014

Please send an email to the labeling reviewer (betty.turner@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 202346

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8728)

TO: Mylan Technologies Inc.

TEL: (304) 599-2595

ATTN: Joseph J. Sobecki

FAX: (304) 285-6407

FROM: Betty Turner

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

Pages (including cover and signature page): 3

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202346

Date of Submission: August 29, 2011

Applicant's Name: Mylan Technologies, Inc.

Established Name: Lidocaine Patch 5%

Labeling Deficiencies:

GENERAL COMMENTS:

i. Please note your labeling was submitted in draft. Please submit your Pouch, Patch, Carton and Insert labeling in final print.

ii. Please provide your labeling in the Structured Product Labeling (SPL) format.

Revise your labeling, as instructed above, and submit final printed labeling electronically

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

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/

CHI-ANN Y WU
09/19/2012
For Wm. Peter Rickman

CLINICAL BIOEQUIVALENCE INFORMATION REQUEST

ANDA 202346

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Mylan Technologies Inc.

ATTN: S. Wayne Talton
Vice President, Regulatory Affairs

TEL: (304) 599-2595 ext. 6551

FAX: (304) 285-6407

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Sir:

This facsimile is a request for information from the Division of Clinical Review, in reference to your abbreviated new drug application dated October 25, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The information request is presented on the attached ____ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Please direct any questions concerning this communication to the Project Manager identified above.

SPECIAL INSTRUCTIONS:

Your cover letter should clearly indicate that the response is a "Clinical Bioequivalence Response to Information Request". We also request that you include a copy of this communication with your response.

CLINICAL BIOEQUIVALENCE INFORMATION REQUEST TO BE PROVIDED TO THE APPLICANT

ANDA: 202346

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Lidocaine Patch, 5%

In order to facilitate the review of your bioequivalence study for ANDA 202346 submitted for Lidocaine Patch, 5% please provide the following information:

1. Please provide an SOP of the electronic source documentation procedures used in this study. In addition, please provide any information as to whether this electronic source documentation procedure was used in any other approved applications.

2. Please submit irritation data sets for pilot study LIDO-0873. Irritation data for pilot study LIDO-0929 were located within the submission. However, there were no irritation results found for study LIDO-0873.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
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/

NITIN K PATEL
09/17/2012

JOHN R PETERS
09/17/2012

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 202346

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Mylan Technologies Inc.

ATTN: S. Wayne Talton
Vice President, Regulatory Affairs

TEL: (304) 599-2595 ext. 6551

FAX: (304) 285-6407

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Sir:

This facsimile is a request for information from the Division of Clinical Review, in reference to your abbreviated new drug application dated October 25, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The information request is presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a "Clinical Bioequivalency Amendment". We also request that you include a copy of this communication with your response.

Please direct any questions concerning this communication to the Project Manager identified above.

SPECIAL INSTRUCTIONS:

MEMORANDUM

ANDA 202346

To:	**Mylan Technologies Inc.** **ATTN: S. Wayne Talton, Vice President, Regulatory Affairs** **(Telephone: 304-599-2595; Fax: 304-285-6407)**
Drug:	**Lidocaine Patch, 5%**
From:	**Nicole Lee, Pharm.D.** **Clinical Reviewer** **Office of Generic Drugs**
	John R Peters, MD **Director** **Division of Clinical Review** **Office of Generic Drugs**
Date:	**June 20, 2012**
Re:	**Request for Information**

In order to facilitate the review of your bioequivalence study for ANDA 202346 submitted for Lidocaine Patch, 5% please provide the following information:

1. Please submit a justification as to why the skin irritation and sensitization study was conducted with patches worn for 12 hours per 24 hours instead of the full 24 hours as recommended in the FDA Bioequivalence Draft Guidance: "…applied continuously to the same sites and replaced with a new one-fourth patch 3 times weekly."

2. Currently validated sensitization studies use at least a 24 hour contact exposure to induce a reaction. Please provide evidence and documentation that the 12-hour induction period for 21 days is sufficient to elicit acceptable sensitization data.

3. The source data for skin irritation/sensitization scores for each subject could not be located in your Case Report Forms. Please provide the source documentation of each irritation dermal response score, other effect score, and sensitization score for each subject.

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/s/

NITIN K PATEL
06/20/2012

NICOLE LEE
06/20/2012

JOHN R PETERS
06/20/2012

QUALITY DEFICIENCY - MINOR

ANDA 202346

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Mylan Technologies Inc.

TEL: (304) 599-2595 ext. 6551

ATTN: S. Wayne Talton

FAX: (304) 285-6407

FROM: Christina Kirby for Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 25, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

Reference is also made to your amendments dated November 10, and December 15, 2010; and March 8, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

ANDA : **202346**
Applicant: **Mylan Technologies Inc.**
Drug Product: **Lidocaine Patch 5%**

The deficiencies presented below are minor deficiencies:

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9.

10

11

12

13

(b) (4)

14.

15.

16.

17.

18.

19.

20.

21.

22.

23.

24.

25.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional long-term stability data that may be available.

2. Please send us your drug product samples and RLD patch samples for evaluation.

3. Your Labeling and Bioequivalence information is pending review. Deficiencies, if any, will be communicated to you separately.

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BING CAI
12/30/2011

Fax Comments

ANDA 202346

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8991

TO: Mylan Pharmaceuticals, Inc.

TEL: 304-599-2595 ext. 6551

ATTN: Wayne Talton

FAX: 304-285-6407

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%

Pages (including cover):4

SPECIAL INSTRUCTIONS:

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202346 Date of Submission: October 25, 2010

Applicant's Name: Mylan Technologies, Inc.

Established Name: Lidocaine Patch 5%

Labeling Deficiencies:

1. PATCH

   Acceptable in draft.

2. CARTON – (30 patches per carton)

   Please explain why your pouch and carton label states “Lidocaine, USP 140 mg (50 mg per gram adhesive)...” while the reference listed drug (RLD), Lidoderm states “Lidocaine 700 (50 mg per gram adhesive)...” Why does your patch deliver 140 mg per patch while the RLD delivers 700 mg of lidocaine per patch?

3. POUCH

   See CARTON statement.

4. INSERT

   a. See CARTON statement.

   b. CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption,

      Your labeling states “...only 11 ± 4% of the dose applied is expected to be absorbed. At least 82% (115 mg) of lidocaine...” while the RLD’s states “...only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine...” Why is your drug product’s absorption profile different than the RLD’s? Please submit the rationale.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

{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

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/s/

JOHN F GRACE
08/15/2011
for Wm Peter Rickman

BIOEQUIVALENCE AMENDMENT

ANDA 202346

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Mylan Technologies, Inc. TEL: (304) 599-2595

ATTN: Wayne S. Talton FAX: (304) 285-6407

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on October 25, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Topical Patch, 5%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 202346

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Lidocaine Topical Patch, 5 %

The Division of Bioequivalence (DBE) has completed its review of the drug release testing portion of your submission(s) acknowledged on the cover sheet. The review of the *in vivo* fasting bioequivalence study, adhesion study, and the cumulative irritation/sensitization study will be conducted later. The following deficiency has been identified:

You did not submit SAS transport files for the adhesion study # LIDO-1044. Please submit these files.

The DBE acknowledges that you will use the following *in vitro* drug release method and specifications for your product:

Apparatus: V (Paddle over Disk)
Speed: 50 rpm
Medium: Acetic Acid/Sodium Acetate Buffer, pH 4.0
Temperature: 32°C
Volume: 500 mL

Specifications:
1.5 h: (b) (4) %
6 h: (b) (4) %
12 h: (b) (4) %
24 h: (b) (4) %

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

DALE P CONNER
06/20/2011

MEMORANDUM
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 11, 2011

TO: C.T. Viswanathan, PhD
Associate Director - Bioequivalence, Division of Scientific Investigations
WO51, HFD-48

THROUGH: Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs
MPNI, HFD-600

FROM: Nitin K. Patel, PharmD
Medical Affairs Coordinator, Clinical Review Team
Office of Generic Drugs
MPNI, HFD-600
240-276-8887

SUBJECT: Compliance Program 7348.001 – In Vivo Bioequivalence

REQUEST FOR INSPECTION

REFERENCES:

ANDA#	202346
Product	Lidocaine Topical Patch, 5%
Sponsor: full address Phone Fax	Mylan Technologies Inc. 110 Lake St. St. Albans, VT 05478 304-599-2595 802-527-8155
Sponsor Contact Phone Fax	S. Wayne Talton, Vice President, Regulatory Affairs 304-599-2595 802-527-8155
Submission Date	October 25, 2010

PRIORITY: **C**

A (highest) = ready for approval in the office
B = ready for approval, clinical study under review
C = pending clinical review

DUE DATE: May 11, 2011

REASON FOR REQUEST:

X	Not inspected in the last three years
	For Cause/Violative History
	New Sites
	Other

Clinical Studies (two studies conducted at the same site and same investigator)

TITLE:	Comparative Evaluation of the Cumulative Irritation and Sensitization Potential of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers
STUDY #:	LIDO-1046
NUMBER OF STUDY SITES:	1
CROs/SMO:	Not provided with submission

TITLE:	Single-Dose Adhesion Study of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers
STUDY #:	LIDO-1044
NUMBER OF STUDY SITES:	1
CROs/SMO:	Not provided with submission

SITE TO BE INSPECTED	
Site	Cetero Research
Address	4801 Amber Valley Parkway Fargo, ND 58104
Phone	701-239-4750
Investigator (Name/Contact Info)	Alan K. Copa, PharmD
# of subjects	LIDO-1046 (218 subjects); LIDO-1044 (24 subjects)

COMMENTS/ADDITIONAL INFORMATION FOR INSPECTORS:

This ANDA is located in the Electronic Document Room (EDR).

CLINICAL STUDY STATUS:

	Study under review
	Study review completed
	Decision:
X	Other: Review not started.

CLINICAL REVIEWER/CONTACT INFORMATION: Not yet assigned to a clinical reviewer.

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/s/

NITIN K PATEL
02/11/2011

DENA R HIXON
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2011-0485	
TO *(Division/Office)* DACCADP - HFD-170 Thru: Leah Ripper, ODEII - HFD 102			FROM: Ted Palat	
DATE: 1/13/2011	IND NO.	ANDA NO. 202346	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 10/25/2010,
NAME OF DRUG Lidocaine		PRIORITY CONSIDERATION 90 days	CLASSIFICATION OF DRUG Local anesthetic	DESIRED COMPLETION DATE 4/13/2011

NAME OF FIRM Mylan Technologies, Inc.

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY _____
Γ PRE NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICPENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

DISSOLUTION
PROTOCOL-- BIOPHARMACEUTICS
IN--VIVO WAIVER REQUEST
DEFICIENCY LETTER RESPONSE
BIOAVAILABILITY STUDIES
PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
_SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL PRECLINICAL

COMMENTS
The sponsor has submitted pharm/tox data to justify the use of polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film in their formulation. Please review the data and determine if the levels of these ingredients are safe for human use. The data is located in module 2.7.5 Literature-References in the electronic document room (EDR).

Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) on the review when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA 202346
Drug File Folder

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/s/

TED C PALAT
01/13/2011

TRANG Q TRAN
01/13/2011

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.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**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 202346 **FIRM NAME**: MYLAN TECHNOLOGIES INC.

PIV: Yes **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: LIDOCAINE
DOSAGE FORM: PATCH, 5%

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC3 TM 34 ☒ ***Activity***	***Bio Team 6: Bing Li*** ☒ ***Activity***
ANDA/Quality RPM: Leigh Ann Bradford ☒ ***FYI***	Bio PM: Nam J. Chun (Esther) ☐ ***FYI***
Quality Team Leader: Nagavelli, Laxma No assignment needed in DARRTS	***Clinical Endpoint Team Assignment:*** ☒ ***Activity***
Labeling Reviewer: Ann Vu ☒ ***Activity***	***Micro Review (No)*** ☐ ***Activity***

*****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). *****

Letter Date: OCTOBER 25, 2010 **Received Date**: OCTOBER 26, 2010

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 6040400 LOCAL ANESTHETICS, TOPICAL

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

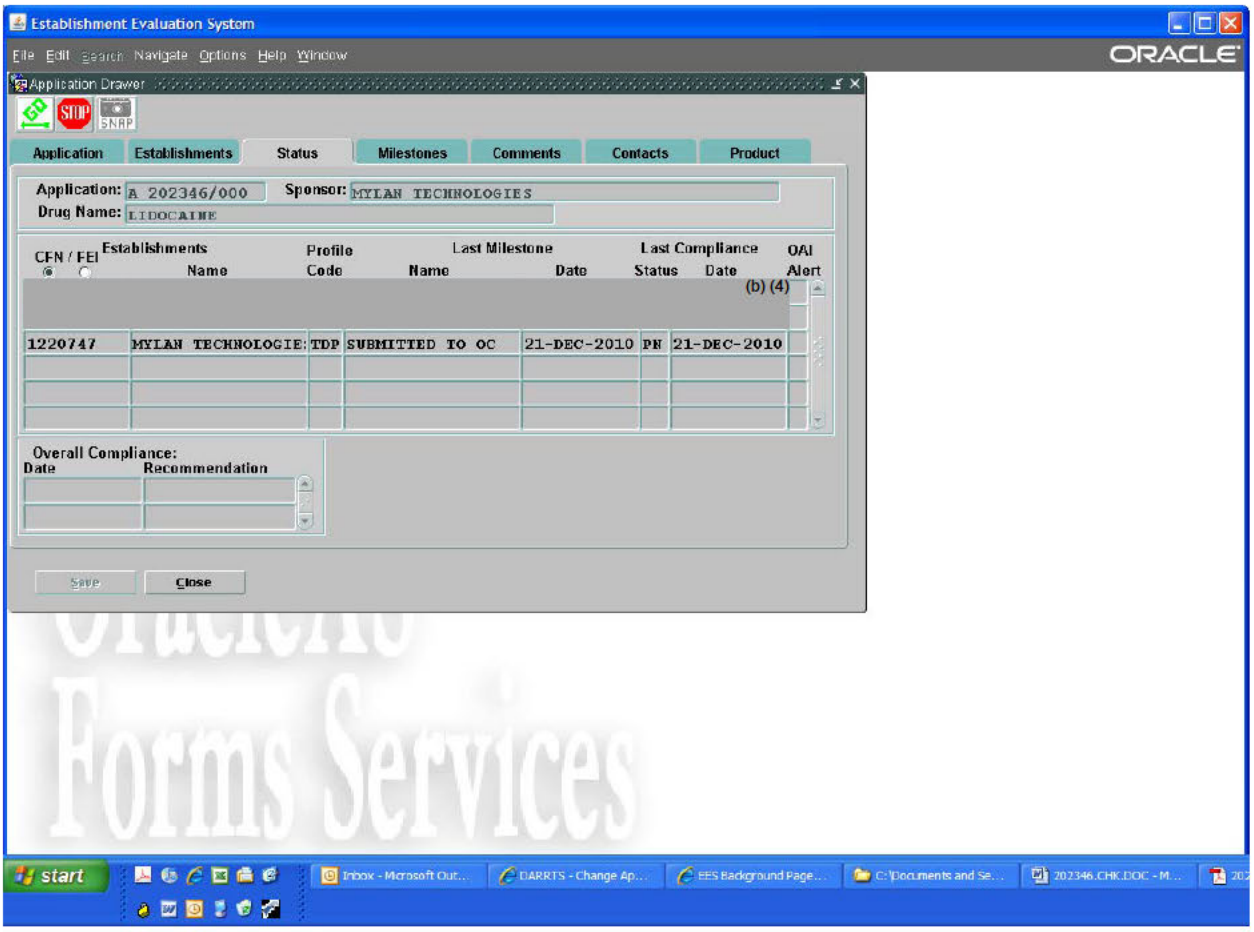
PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Ted Palat **Date 12/21/2010**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

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 (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☐ Yes ☒ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. Requested EER
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA: S. Wayne Talton 304-599-2595

2. pharm/tox data submitted re: Polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film.



CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# _202346_____ **FIRM NAME** Mylan Pharmaceuticals Inc._____

DRUG NAME _Lidocaine Patch 5%_____

DOSAGE FORM __Transdermal Patch_____

Reference Listed Drug (RLD) _Lidoderm® Patch 5%, NDA 020612_____

Requested by: ___Edward Washington_____ Date: _11/8/10_____
Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements** **Please see additional comments to be conveyed to the sponsor for the review.**
	Study does NOT meet statutory requirements
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: **__X_COMPLETE** **__INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA#: 202-346 **FIRM NAME:** Mylan Technologies, Inc.

DRUG NAME: Lidocaine

DOSAGE FORM: Patch, 5% (700 mg/24 hours)

SUBJ: Request for examination of Bioequivalence studies

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: _____
Haritha Mandula, Ph.D.
Reviewer

_____ Date: _____
Bing V. Li, Ph.D.
Team Leader

BIO_1G_CHKLST.dot v.4/4/2003

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status)RX YES	☒
1.2	**Cover Letter** Dated: OCTOBER 25, 2010	☒
1.2.1	**Form FDA 3674 (PDF) YES**	☒
*	**Table of Contents (paper submission only)** YES	☒

1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 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, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** **PIV – '529 and '510, PIII – '738 and '838** 1. Patent number(s) **Patent and Exclusivity Search Results from query on Appl No 020612 Product 001 in the OB_Rx list.**	☒

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020612	001	5411738	May 2, 2012				
N020612	001	5601838	May 2, 2012			U - 488	
N020612	001	5741510	Mar 30, 2014		Y		
N020612	001	5827529	Oct 27, 2015			U - 486	

There is no unexpired exclusivity for this product.

U - 488 METHOD FOR REDUCING THE PAIN ASSOCIATED WITH HERPES-ZOSTER AND POST-HERPETIC NEURALGIA

U - 486 EXTERNAL PREPARATION FOR APPLICATION TO THE SKIN CONTAINING LIDOCAINE-DRUG RETAINING LAYER PLACED ON SUPPORT AND COMPRISES ADHESIVE GEL BASE 1-10% BY WEIGHT OF LIDOCAINE

2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☒
   PIV ☒ (Statement of Notification) ☒
3. Expiration of Patent(s): 10/27/2015
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES no exclusivity

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 Type II DMF No. (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒

1.12.11	**Basis for Submission** **OK** NDA# : 20-612 Ref Listed Drug: LIDODERM Firm: TEIKOKU PHARMA USA ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling** **(Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **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** **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**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **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 **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution 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 YES **2.7.1.4 Appendix** 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 ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) ***2.3.S.2.1 Manufacturer(s) (Lidocaine, USI*** **Name and Address** | (b) (4) 2. Function or Responsibility YES 3. Type II DMF number for API YES 4. CFN or FEI numbers YES	☒
3.2.S.3	**Characterization**	☒
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** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) Mylan commits to resolve any issues identified in the method validations during review or after approval. Sample of the drug substance (Lot 188/1), reference standards and related materials will be made available to the Agency upon request and/or at the time of the pre-approval inspection at the St. Albans, Vermont, facility. **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒

3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

ACCEPTABLE

3.2.P.1 Description and Composition of the Drug Product

☒

1. Unit composition

Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Lidocaine Patch 5%

Components	Pharmaceutical Function	% w/w	mg per patch
Active Ingredient			
Lidocaine, USP	Active Ingredient	5.00	140.00
Inactive Ingredients			
Polyisobutylene (b) (4)	Adhesive	(b) (4)	(b) (4)
Theoretical Total Matrix		100.00	(b) (4)
Components of the Delivery and Packaging System			
Pigmented Polyethylene / Polyester Film (MEDIFLEX® 1501)	Backing	NA	(b) (4)

Components	Pharmaceutical Function	% w/w	mg per patch
Brown Ink (b) (4)	Imprinting Ink	NA	(b) (4)
Silicone Coated Polyester Film (MEDIRELEASE® 2249)	Release Liner	NA	

2. Inactive ingredients and amounts are appropriate per IIG NO, pharmtox data submitted re: Polyisobutylene, pigmented polyethylene/polyester film, and silicone coated polyester film.

(b) (4)

3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) **Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form:** **Name and Address** / **Responsibilities** Mylan Technologies, 110 Lake Street, St. Albans, VT 05478 — Manufacturing, Packaging, Labeling, Quality Control Testing of Components and Finished Dosage Form. A cGMP certification letter is provided in Section 3.2.P.3.1. (b) (4) 2. CGMP Certification: 3. Function or Responsibility YES 4. CFN or FEI numbers YES **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 YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES **Exhibit Lot** / **Commercial Lot** (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation NA 2. Filter validation (if aseptic fill) NA	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **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** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

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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** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers Mylan commits to resolve any issues identified in the method validations during review or after approval. Sample of the drug product (Lots R6B0017, R6B0038 and R6B0039), reference standards and related materials will be made available to the Agency upon request and/or at the time of the pre-approval inspection at the St. Albans, Vermont, facility. **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES. **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes **HOW SUPPLIED:** Lidocaine patch 5% is available as the following: Carton of 30 patches, packaged into individual child-resistant envelopes. NDC 0378-9055-93 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YES, 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

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 YES **Yield and Reconciliation of the Packaging Process for the Exhibit Lots** (b) (4) **3.2.R.1.P.2 Information on Components** YES **3.2.R.2.P Comparability Protocols** NO **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

Parameter	R6B0017	R6B0039	R6B0038	Limit
Yield Target				
Yield (m² % of target)				
Reconciliation Target				
Reconciliation (m² % of target)				

(b) (4)

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒

5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) NA b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) NA **2. Lot Numbers of Products used in BE Study(ies):** **Treatments (Dose, Dosage Form, Route), [Product ID]** A=Lidocaine Patch 5%, Ext. (b) (4) 140 mg lidocaine topical route, Lot# R6A0041 B=Lidocaine Patch 5%, (b) (4) 70 mg lidocaine topical route, Lot# R6A0042 C=Lidocaine Patch 5%, (b) (4) 140 mg lidocaine topical route, Lot# R6A0043 D= Lidoderm® Patch 5% 700 mg lidocaine topical route, Lot #97278 exp. 08/2010 in the Federal registe **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

5.3.1.2 Comparative BA/BE Study Reports

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) ☒

LIDOCAINE PATCH 5%

LIDOCAINE PATCH 5% Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
LIDO-1037 lidocaine				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUC0-t	936.8	1003	0.93	86% – 101%
AUC∞	959.3	1023	0.94	87% – 101%
C_{max}	67.92	71.70	0.95	85% – 105%

*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$
**Used Natural Log Transformed Parameter

2. Summary Bioequivalence tables:
   Table 10. Study Information YES
   Table 12. Dropout Information YES
   Table 13. Protocol Deviations YES

5.3.1.3
In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   Table 11. Product Information YES
   Table 16. Composition of Meal Used in Fed Bioequivalence Study YES

5.3.1.4
Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   Table 9. Reanalysis of Study Samples YES
   Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES
   Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES

5.3.7
Case Report Forms and Individual Patient Listing YES

Firm's Proposed Specifications	**1.5 Hours:** (b) (4)%, **6 Hours:** (b) (4)%, **12 Hours:** (b) (4)
Dissolution Testing Site (Name, Address)	Mylan Technologies, 110 Lake Street, Saint Albans, Vermont 05478

LIDOCAINE PATCH 5%

Study Number	LIDO-1037
Study Title	Single-Dose Fasting Bioequivalence Study of Lidocaine Patch (5%; Mylan) and Lidoderm® Patch (5%; Endo) in Normal Healthy Volunteers
Clinical Site (Name, Address, Phone #)	Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104, USA 701-239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 09-May-2010 Period II: 16-May-2010
Analytical Sites (Name, Address, Phone #)	Bioanalytical Department 3711 Collins Ferry Rd. Morgantown, WV 26505, USA 304-598-5430
Analysis Dates	02-Jun-2010 – 09-Jun-2010
Analytical Director	Patrick Vallano, Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	31 days at -70°C ± 15°C [Date of 1st sample collection – 09-May-2010; Date of last sample extraction – 09-Jun-2010]

5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution:	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** YES/STU/BIO clinical studies pass clinical filing review. 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☒
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐

Study Type	**TRANSDERMAL DELIVERY SYSTEMS** clinical studies pass clinical filing review. 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☒

Updated 10/19/2009

Active Ingredient Search - Windows Internet Explorer

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FDA Home

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Active Ingredient Search Results from "OB_Rx" table for query on "CIDOFOVIR."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020638		Yes	CIDOFOVIR	INJECTABLE; INJECTION	EQ 75MG BASE/ML	VISTIDE	GILEAD

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2010
Patent and Generic Drug Product Data Last Updated: October 28, 2010

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Orange Book Detail Record Search - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020638&TABLE1=OB_Rx

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FDA Home

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "020638."

Active Ingredient:	CIDOFOVIR
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	VISTIDE
Applicant:	GILEAD
Strength:	EQ 75MG BASE/ML
Application Number:	N020638
Product Number:	001
Approval Date:	Jun 26, 1996
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2010
Patent and Generic Drug Product Data Last Updated: October 28, 2010

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Patent and Exclusivity Search Results - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020638&Product_No=001&table1=OB_Rx

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FDA Home

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020638 Product 001 in the OB_Rx list.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020638	001	5142051	Jun 26, 2010				

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.

View a list of all patent use codes
View a list of all exclusivity codes

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/s/

TED C PALAT
01/04/2011

MARTIN H Shimer
01/10/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 202346

Mylan Pharmaceuticals, Inc.
Attention: S. Wayne Talton
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated December 14, 2010 and your correspondence dated December 15, 2010.

NAME OF DRUG: Lidocaine Topical Patch, 5%

DATE OF APPLICATION: October 25, 2010

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 26, 2010

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.

3) 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 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 above the body of the cover letter 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 cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(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 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, Chief, Regulatory Support Branch, at (240) 276-8675.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Leigh Ann Bradford
Project Manager
240-276-8453

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/

MARTIN H Shimer
01/10/2011
Signing for Wm Peter Rickman

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 : October 29, 2010

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 202346 for Lidocaine Patch, 5% 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 202346 for Lidocaine Patch, 5%. 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 October 25, 2010 for its Lidocaine 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/

EDA E HOWARD
11/01/2010