CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215401Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM TO FILE

Date: March 11, 2022 **Date consulted**: August 9, 2021

From: Denise Pica-Branco, Ph.D. Senior Regulatory Health Project Manager
Pediatrics and Maternal Health
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of Regulatory Operations

Through: Rosemary Addy, MHS, Supervisory Consumer Safety Officer
Pediatrics and Maternal Health
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of Regulatory Operations

To: Shin-Ye Sandy Chang PharmD
Division of Neurology 1 (DN1)
Office of New Drugs (OND)

Subject: 505(b)(2)

Sponsor: Noven Pharmaceuticals, Inc

Drug: Xelstrym (d-Amphetamine Transdermal System)

NDA: 215401

Indication: Attention Deficit Hyperactivity Disorder

Materials Reviewed:

file:////CDSESUB1/evsprod/NDA215401/0001
drugs@fda
orange book

Consult Question:

"On July 29, 2021, DP took an approval action on Vyvanse S-046, submitted in response

to WR, to add safety information in pediatric patients ages 4 to less than 6 w/ ADHD. With this approval, the following limitation of use statement was added "Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older". DP would like DPMH to provide input on the impact of the pediatric exclusivity granted on July 27, 2021, for Vyvanse on the labeling for Xelstrym.

In preparing this response, DPMH consulted other offices, including the Office of Regulatory Policy.

Noven Pharmaceuticals submitted a new drug application (NDA) for XELSTRYM (dextroamphetamine transdermal system; d-ATS) (NDA 215401), a transdermal patch for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older via the 505(b)(2) pathway. Xelstrym relies on FDA's finding of safety and/or effectiveness for the listed drugs Adderall XR (NDA 021303) and Vyvanse (NDA 021977). There is no 3-year or 7-year exclusivity listed in the Orange Book for Vyvanse and Adderall XR. However, a supplement (s-046) was approved for Vyvanse on July 29, 2021, for the addition of safety information in pediatric patients ages four to less than 6 with Attention Deficit Hyperactivity Disorder. Even if the supplement for Vyvanse received 3-year exclusivity (to which pediatric exclusivity would attach), the approval of Xelstrym would not implicate that exclusivity because Xelstrym and Vyvanse have different active moieties (i.e., dextroamphetamine and lisdexamfetamine, respectively) and are different drugs. Assuming arguendo 3-year exclusivity associated with the Vyvanse supplement was implicated, CDER determines pursuant to section 505A(o) of the Federal Food, Drug, and Cosmetic Act, that the pediatric safety information (regarding FDA's finding of safety for Vyvanse as reflected in its labeling) is necessary to assure safe use, and approval of Xelstrym would not be precluded.

DPMH RPM:	Denise Pica-Branco
DPMH SCSO:	Rosemary Addy
DPMH Reviewer:	Ethan Hausman
DPMH MTL:	Shetarra Walker
DPMH Deputy Director:	John Alexander
ORP	Nisha Shah
ORP	Reena Raman

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/s/

DENISE J PICA-BRANCO
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 17, 2022
To:	ShinYe (Sandy) Chang Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Domenic D'Alessandro, PharmD, MBA, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide and Instructions for Use (IFU)
Drug Name (established name):	XELSTRYM (dextroamphetamine)
Dosage Form and Route:	transdermal system, CII
Application Type/Number:	NDA 215401
Applicant:	Noven Pharmaceuticals, Inc.

1 INTRODUCTION

On February 22, 2021, Noven Pharmaceuticals Inc., submitted for the Agency's review an original New Drug Application (NDA-215401) for XELSTRYM (dextroamphetamine) transdermal system, CII, also referred to as d-ATS, for the proposed indication of use for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on March 2, 2021 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for XELSTRYM (dextroamphetamine) transdermal system, CII.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on January 31, 2022.

2 MATERIAL REVIEWED

- Draft XELSTRYM (dextroamphetamine), MG and IFU received on February 22, 2021 and received by DMPP and OPDP on February 10, 2022.
- Draft XELSTRYM (dextroamphetamine), Prescribing Information (PI) received on February 22, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 10, 2022.
- Approved DYANAVEL XR (amphetamine) comparator labeling dated November 04, 2021.
- Approved VYVANSE (lisdexamfetamine dimesylate) comparator labeling dated November 2, 2021.
- Approved SECUADO (asenapine) transdermal system, comparator labeling dated October 11, 2019.
- DMEPA XELSTRYM (d-amphetamine transdermal system) 5 mg, 10 mg, 15 mg, 20 mg, Human Factors Study Report and Labels and Labeling Review dated January 31, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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SHARON R MILLS
02/17/2022 09:28:43 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 14, 2022

To: Cathy A. Southammakosane, M.D., Clinical Reviewer
Division of Psychiatry (DP)

Sandy Chang, PharmD, Regulatory Project Manager, (DP)

Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, (DP)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for XELSTRYM™ (dextroamphetamine) transdermal system, CII

NDA: 215401

In response to DP's consult request dated March 2, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for XELSTRYM™ (dextroamphetamine) transdermal system, CII.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DP (Sandy Chang) on February 10, 2022, and are provided below.

Medication Guide and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 9, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

38 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DOMENIC G DALESSANDRO
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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	January 31, 2022
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 215401
Drug Constituent Name and Strength	Combination Product
Product Type:	Xelstrym (d-amphetamine transdermal system) 5 mg, 10 mg, 15 mg, 20 mg
Device Constituent:	Transdermal system
Rx or OTC:	Rx
Applicant/Sponsor Name:	Noven Pharmaceuticals, Inc. (Noven)
FDA Received Date:	12/06/2021
OSE RCM #:	2021-373-1
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD,MHS,CPH,MCHES

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports and labels and labeling submitted validation study report submitted under NDA 215401 for Xelstrym (d-amphetamine) 5 mg, 10 mg, 15 mg, 20 mg.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed transdermal system device constituent part that is intended to treat Attention Deficit Hyperactivity Disorder (ADHD).

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

We previously reviewed an HF validation study protocol[a] for this product, however, upon review of the HF validation study results[b], we noted that all of our recommendations for the protocol were not implemented, and there were numerous use errors and use diificulties that indicated the user interface was not optimized to support safe and effective use of the product. We sent a Discipline Review Letter[c] on September 02, 2021, indicating that the Applicant should make changes to their user interface and conduct another HF validation study. The Applicant submitted an updated prescribing information (PI) on November 28, 2021 and an HF validation study and updated labels and labeling on December 06, 2021 which are the focus of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C

[a] Flint J. Human Factors validation Study Protocol Review for Xelstrym (d-amphetamine transdermal system) (IND 073862). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020MAR27. RCM No.: 2020-246

[b] Flint J. Human Factors Study Report and Label and Labeling Review for Xelstrym (d-amphetamine transdermal system) (IND 073862). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2021AUG31. RCM No.: 2021-373.

[c] Chang, S. Discipline Review Letter for Xelstrym (d-amphetamine transdermal system) (IND 073862). Silver Spring (MD): FDA, CDER, OND, DP (US);2021SEP02.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	**Details**
Participants	15 Adult ADHD Patients 15 Pediatric ADHD Patients 15 Adult Cargivers of ADHD Patients
Training	No training
Test Environment	Simulated Home environment
Sequence of Study	Simulated Use Scenario 1 Decay Period (1 hour) Simulated Use Scenario 2 Root Cause Analysis Knowledge Assessment Root Cause Analysis of Knowledge Questions

3 RESULTS AND ANALYSES

Table 2 describes the study results, Noven's analyses of the results, and DMEPA 1's analyses and recommendations.

Identified Issues and DMEPA's Findings		
	Identified Issue and Rationale for Concern	**DMEPA's Analysis and Findings**
1.	For the second "Select Application Site" task, there were 4 use errors in the adult ADHD patients group, 3 use errors in the adult caregivers group, and 7 use errors in the pediatric patients group. The subjective data and the Applicant's root cause analysis stated: Test Artifact - Some participants selected the same arm for both patch application scenarios due to convenience during the HF testing. Difficult to find information in the IFU. The Applicant did not provide additional risk mitigations to address these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of Increased irritation/discomfort/ pain. Our review of the study results identified subjective feedback that indicated that information regarding using different application sites was located in the important information section and in step 1 (application); however, the reason "why" they should do so was in the important information section only. We note that the IFU contains instructions and images pertaining to rotating the application site, and we did not identify additional risk mitigations to address this use error. Additionally, we note that this step and the resulting residual risks are similar in nature to other approved transdermal systems, and we find the residual risks acceptable.
2.	For the task "Wash hands after applying the patch" there were 9 use errors in the adult ADHD patients group. Additionally, for the task "Wash hands after disposal" there were 3 use errors in the adult ADHD patients group. The subjective data and the Applicant's root cause analysis stated: Test artifact: Participants knew they were simulating use, and subsequently only stated that they would wash their hands, or did not wash their hands because it was a simulation and there was no risk of contamination. The Applicant did not provide additional risk mitigations to address these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of unintentional exposure to non-user, or inadvertent application of drug to sensitive areas of the body. Our review of the study results identified that some participants skipped the hand washing steps because of the simulated nature of the study (test artifact). We note that the IFU contains instructions and images pertaining to hand washing, and we did not identify additional risk mitigations to address this use error. Additionally, we note that this step and the resulting residual risks are similar in nature to other approved transdermal systems, and we find the residual risks acceptable.
3.	For the task "Patch removal" there was one use error in the adult ADHD patients group, 1 use error in the adult caregivers group, and 4 use errors in the pediatric ADHD patients group. Participants did not fold the patch in half prior to disposal. The subjective data and the Applicant's root cause analysis indicated:	Based on the URRA, if this task is omitted or not performed correctly there is risk of unintentional exposure to nonuser. Our review of the study results identified that most users were aware that they should fold the patch prior to disposal and did so during their first scenario. However, some participants did not fold the patch prior to disposal for the

	Lapse: Most participants folded the patch prior to disposal during the first scenario, but some did not perform the task in the second scenario. The Applicant did not provide additional risk mitigations to address these use errors.	second scenario, citing a lapse in memory (they forgot). One participant skimmed the IFU and did not notice this task. We note that the IFU contains instructions and images pertaining to folding the patch prior to disposal, including why it is necessary to do so. **We provide a recommendation to further mitigate this use error in Table A**. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

3.1 ANALYSIS OF NON-CRITICAL TASKS

The HF validation study showed use errors, (e.g., failures, difficulties, and close calls) with the following non-critical tasks. Based on our review of the available participants' subjective feedback, and the Applicant's root cause analysis, we determined that the residual risk is acceptable without further need for risk mitigation strategies at this time to address the use errors related to the following non-critical use tasks:

Remove patch from pouch

Apply half of the patch to application site

Apply other half of the patch

Can you wear the patch in the shower or when exercising?

3.2 LABELS AND LABELING

Tables 4 and A below includes the identified medication error issues with the submitted labels and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 4: Identified Issues and Recommendations for Division of Psychiatry			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Full Prescribing Information- Section 2 Dosage and Administration			
1.	We note that Section 2.3 includes the statement: (b) (4)	In the HF validation study, some participants did not fold the patch before disposal. We are concerned that surplus drug in a used transdermal system may cause accidental exposure.	Consider including that the transdermal system should be folded and discarded. For example "advise patients/caregivers that the transdermal system should be folded in half and discarded." in Section 2.3.
2.	In section 2.3 (b) (4) the limitations to	The instructions for use indicate other limitations to adherence that may need to be addressed in this section.	Consider adding other limitations such as use of lotions, oils, and gels to this section.

	transdermal system adherence are limited (b) (4)		

Table A: Identified Issues and Recommendations for Noven Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Carton and Container Labeling			
1.	As currently presented, the format for the expiration date is not defined.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.
2.	The back panel statement (b) (4) can be improved.	We are concerned (b) (4)	Replace this statement with "Fold used patch and discard according to instructions for use".
3.	We note that there are overlaps in colors used for the	The use of the same color font for the proprietary name, and the product's strength	Revise the font color of the strength so that they appear in unique colors and the colors do not overlap with the color of the proprietary name.

	proprietary name, and the 4.5 mg/9 hour strength statement.	minimizes the difference between the strengths, which may lead to wrong strength selection errors.	

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrate that representative users experienced use errors with critical tasks. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 for the Division and Table A for the Applicant. We ask that the Division convey Table A in its entirety to the Applicant. We have determined that, in this particular case, the proposed changes can be made without submitting an additional HF validation study.

4.1 RECOMMENDATIONS FOR NOVEN PHARMACEUTICALS, INC.

Our evaluation of the proposed user interface, proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Please see table A that contains our recommendations that should be implemented for the product user interface and labels and labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Xelstrym that Noven submitted on 12/6/2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Central Nervous System Stimulant
Active Ingredient (Drug or Biologic)	dextroamphetamine
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Route of Administration	Transdermal
Dosage Form	Transdermal system
Strength	5, 10, 15, and 20 mg per transdermal system
Dose and Frequency	Recommended starting dose is 5 mg, can be titrated to effect. The maximum daily dose is (b) (4) mg/day.
How Supplied	Carton containing 30 individually packaged transdermal systems
Storage	Room temperature (68 to 77 F°)
Intended Users	Pediatric to adult users (6 to over 18 years of age)
Intended Use Environment	Non-healthcare environments

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On January 19, 2022, we searched the L:drive and AIMS using the terms, “215401” and “073862” to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified two previous reviews[a,b] , and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the Usability Engineering Report below.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

Validation Study	\\CDSESUB1\evsprod\nda215401\0044\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\hfe-ue-rpt\human-factors-engineering-validation-study-report.pdf
Usability Engineering	\\CDSESUB1\evsprod\nda215401\0044\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\hfe-ue-rpt\hfe-ue-rpt.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Xelstrym labels and labeling submitted by Noven.

IFU	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\proposed-standalone-ifu.pdf
PI	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\proposed.pdf
Carton 4.5 mg Inside	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-carton-4-5mg-inside-9hrs.pdf
Carton 4.5 mg Outside	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-carton-4-5mg-outside-9hrs.pdf
Pouch 4.5 mg	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-pouch-4-5mg-9hrs.pdf

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Back-lay 4.5 mg	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-back-lay-4-5mg-9hrs.pdf
Carton 9 mg Inside	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-carton-9mg-inside-9hrs.pdf
Carton 9 mg Outside	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-carton-9mg-outside-9hrs.pdf
Pouch 9 mg	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-pouch-9mg-9hrs.pdf
Back-lay 9 mg	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-back-lay-9mg-9hrs.pdf
Carton 13.5 mg Inside	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-carton-13-5mg-inside-9hrs.pdf
Carton 13.5 mg Outside	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-carton-13-5mg-outside-9hrs.pdf
Pouch 13.5 mg	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-pouch-13-5mg-9hrs.pdf
Back-lay 13.5 mg	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-back-lay-13-5-mg-9hrs.pdf
Carton 18 mg Inside	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-carton-18mg-inside-9hrs.pdf
Carton 18 mg Outside	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-carton-18mg-outside-9hrs.pdf
Pouch 18 mg	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-pouch-placebo-9hrs.pdf
Back-lay 18 mg	\\CDSESUB1\evsprod\nda215401\0044\m1\us\114-label\1141-draft-label\carton-desc-back-lay-18-mg-9hrs.pdf

F.2 Label and Labeling Images for 4.5 mg strength

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Clinical Inspection Summary

Date	11/12/2021
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Shin-Ye Sandy Chang, Pharm.D. Regulatory Project Manager Cathy Southammakosane, M.D., Clinical Reviewer Bernard Fischer, M.D., Clinical Team Leader
NDA #	215401
Applicant	Noven Pharmaceuticals, Inc.
Drug	Xelstrym (Dextroamphetamine Transdermal System)
NME	No
Therapeutic Classification	Central Nervous System (CNS) Stimulant
Proposed Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Consultation Request Date	04/01/2021
Initial Summary Goal Date	11/15/2021
Action Goal Date	12/22/2021
PDUFA Date	12/22/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators (CIs) Drs. Waxmonsky and Wigal were inspected in support of NDA 215401 for Xelstrym (Dextroamphetamine Transdermal System, d-ATS) for the treatment of attention deficit hyperactivity disorder in children and adolescents. Based on the results of these inspections, the study (Protocol N25-006) appears to have been conducted adequately, and the data generated by these sites appear to be acceptable in support of the respective indication.

II. BACKGROUND

Xelstrym (dextroamphetamine transdermal system, d-ATS) patch has been developed by Noven Pharmaceuticals, Inc. (sponsor) for transdermal use for the treatment of ADHD in children and adolescents. The d-ATS patch contains the active ingredient dextroamphetamine base in a multi-polymeric adhesive matrix designed to release dextroamphetamine upon application to intact skin. It contains about 1 mg of dextroamphetamine base per cm2 of surface area. The development of d-ATS patch relies on nonclinical safety, clinical pharmacology, efficacy, and safety data of Adderall (amphetamine capsules, NDA 021303) and Vyvanse (lisdexamfetamine dimesylate capsules, NDA 021977). Dextroamphetamine, a central nervous system (CNS) stimulant, is a well-established treatment for ADHD.

The sponsor conducted a randomized, double-blind, placebo-controlled, cross-over, laboratory classroom study to assess the safety and efficacy in children and adolescents with ADHD (Protocol N25-006). Clinical inspections were conducted for this protocol.

Protocol N25-006

Title: "A Randomized, Double-Blind, Placebo-Controlled, Cross-Over, Laboratory, Classroom Study to Evaluate the Safety and Efficacy of d-Amphetamine Transdermal Drug Delivery (d-ATS) Compared to Placebo in Children and Adolescents with ADHD"

Subjects: 110 subjects were enrolled in the study

Study Sites: 3 US sites

Study Initiation and Completion Dates: 28 September 2012 and 23 March 2013

The primary study objective was to assess efficacy and safety of d-ATS compared to placebo, as measured by the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) total score.

This was a randomized, double-blind, cross-over, placebo-controlled study to evaluate the safety and efficacy of d-ATS in children and adolescents 6 to 17 years of age with ADHD. The study consisted of the following 5 periods:

- a 4-week Screening Period: Day -28 to Day -4,
- a 72-hour Washout Period: Day -3 to Day -1,
- a 5-week, open-label, stepwise Dose Optimization Period: Day 1 to Day 35,
- a 2-week, randomized, cross-over Double-Blind Treatment Period (analog classroom sessions in the laboratory school setting): Day 36 to Day 49,
- Safety Follow-Up Period (7 days after last dose of study drug): Day 56.

The study drug, d-ATS, had the following 4 dose strengths: 5mg/4.76cm^2, 10mg/9.52cm^2, 15mg/14.29cm^2, and 20mg/19.05cm^2. During the open-label Dose Optimization Period, treatment with d-ATS was initiated on Day 1 after the baseline visit at 5 mg/ 4.76 cm2. d-ATS was then adjusted to the next available dose at weekly intervals, until optimal dose was reached. Optimal dose was defined as the dose that would produce a reduction in ADHD RS-IV score ≥ 30% and the Clinical Global Impressions- Improvement Scale, (CGI-I) score of 1 or 2; and had tolerable side effects. Tolerability would be determined by the investigator, based on review of adverse events and clinical judgment.

During the crossover Double-Blind Treatment Period, eligible subjects were randomized to one of two treatment sequences: 1) d-ATS (optimized dose) followed by placebo, each for one week, or 2) placebo followed by d-ATS (optimized dose), each for one week. For the first six days of each week, study drug would be administered by the subject/parent/caregiver. On the last day of each week (analog classroom days), the patches would be applied in the clinic by study staff at the start of the laboratory classroom assessment. The patch of d-ATS or placebo were placed daily in the morning for 9 hours, and then removed. The SKAMP assessments were administered at pre-dose (-0.5 hours) and at 1, 2, 3, 4.5, 6, 7, 9, 10, and 12 hours post-dose.

The primary efficacy endpoint was the change in the mean SKAMP total score from baseline to the end of study.

Rationale for Site Selection

The clinical sites were chosen using a risk-based approach primarily based on numbers of enrolled subjects, treatment effect, protocol deviations, and prior inspection history.

III. RESULTS

1. James Waxmonsky, M.D
Site # 01
SW 8th Street
Miami, FL 33199
Inspection dates: September 27-October 19, 2021

At this site for Protocol N25-006, 55 subjects were screened, 41 were enrolled, and 38 completed the study. Three subjects discontinued the study. One subject withdrew consent. Two subjects discontinued the study in the open-label stepwise Dose Optimization Period prior to randomization due to adverse events: 1) Subject #(b) (6) had irritability, appetite loss, and insomnia; and 2) Subject #(b) (6) had appetite loss and insomnia. These adverse events were reported to FDA.

The inspection reviewed all 41 enrolled subjects' SKAMP Individual items and the Total Score Items from Baseline to the study endpoint (efficacy data). The inspection also reviewed 14 out of 41 enrolled subjects' other source records. These source records reviewed included, but were not limited to, informed consent; inclusion/exclusion criteria; randomization, blinding, dosing, and study drug administration; adverse event reporting; and protocol compliance. The administrative files such as study monitoring, ethics committee approval and communications, financial disclosures, FDA 1572s, study staff background and training were also reviewed during the inspection.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

2. Tim Wigal, M.D.
Site # 02
19722 MacArthur Blvd
Irvine, CA 02612
Inspection dates: July 15-22, 2021

At this site for Protocol N25-006, 52 subjects were screened, 39 were enrolled, and 35 subjects completed the study. Four subjects were discontinued. The subjects and the reasons for discontinuations were verifiable, i.e., there were no discrepancies between the source records and the line listings submitted by the sponsor for discontinuations.

The inspection reviewed all 35 study completers' SKAMP Individual items and the Total Score Items from Baseline to the study endpoint (efficacy data); this was per the inspection summary email sent to Dr. Sellers at the close of the inspection. The inspection also reviewed 12 subjects' source records including medical history, adverse events/serious adverse events, concomitant medications, and protocol deviations against the data listings provided by the sponsor in order to ensure that data were completely and accurately reported. Other records were reviewed included, but were not limited to, Independent Review Board (IRB) approvals, training records, delegation of authority logs, financial disclosures, drug accountability, informed consent forms, and study eligibility criteria.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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cc:
DARRTS: NDA 215401
DPP /Project Manager/Shin-Ye Sandy Chang
DPP/Division Director/Tiffany Farchione
DPP/Medical Officer/Cathy Southammakosane
DPP/Clinical Team Leader/Bernard Fischer
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief (acting)/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENN W SELLERS
11/12/2021 11:09:45 AM

PHILLIP D KRONSTEIN
11/12/2021 11:22:42 AM

KASSA AYALEW
11/12/2021 12:04:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research
Food and Drug Administration
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MEMORANDUM of CONSULTATION

Date: November 5, 2021

From: Shera Schreiber, MD, Medical Officer, DDD

Through: David Kettl, MD, Clinical Team Leader, DDD

To: Cathy Southammakosane, MD Medical Reviewer, DP
Pamela Horn, MD, Clinical Team Leader, DP

CC: Barbara Gould, CPMS, DDD

Re: Division of Dermatology and Dentistry Consult
Subject of Consult: Request for collaborative review of NDA 215401 for XELSTRYM™ (Dextroamphetamine Transdermal System (d-ATS)) from DP:

"Noven Pharmaceuticals submitted an original NDA, proposing the use of d-Amphetamine Transdermal System (d-ATS) for the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) (b) (4)

DDDP was consulted during the IND phase to provide input on clinical trial design (consult review dated 12/10/2019) and to provide input on the overall dermal safety profile of d-ATS in the internal and Sponsor pre-NDA meeting held on September 3, 2020.

The Applicant primarily relies on Study N25-006 (a randomized, double-blind, placebo-controlled, cross-over laboratory classroom study to evaluate the efficacy and safety of the d-ATS patch in children and adolescents with ADHD) and Study N25-015 (Group A) (A Multiple Dose, Open-label, 4-Week, Phase 1 Study to Characterize the Pharmacokinetics, Safety, and Tolerability of d-Amphetamine Transdermal System (d-ATS) in Adult Subjects Diagnosed with ADHD) to assess systemic and dermal safety. Additional dermal studies include N25-018 (skin sensitivity and irritation study), N25-

012 (heat effect and skin irritation study), N25-013 (adhesion and skin irritation study), and N25-007 (adhesion and skin irritation study).

DP is requesting for DDDP to review these studies and to assist in assessment of dermal safety."

Materials Reviewed:

- Study N25-018: A Randomized, Evaluator-blinded Study to Evaluate Skin Irritation and Sensitization of d-Amphetamine Transdermal System in Healthy Adults
- Summary of Clinical Safety (including ISS)
- XELSTRYM™ Draft Labeling
- Pre-NDA Meeting Minutes for IND 73862: Type B meeting held September 3, 2020
- DDDP Consult #2016 by Dr. Patricia C. Brown for IND 73862, dated December 10, 2019

Conclusions:

The primary evaluations for local safety of topically applied products occur in the actual clinical trials which utilize the to be marketed product under the proposed conditions of use. Dermal safety studies can supplement those assessments as well as assist sponsors in the process of formulation development.

For the purposes of this application, the dermal safety study (N25-018) is adequate, noting that much is already known regarding the safety of amphetamine products from historical clinical use as well as trials previously reviewed to support existing labeling of similar products (i.e., methylphenidate transdermal system).

Should the application be approved, labeling will be based in part on the results from the dermal safety study, and in part on the safety information in precedent amphetamine labeling.

The results of the dermal safety study submitted by the applicant, indicates that XELSTRYM™ (Dextroamphetamine Transdermal System (d-ATS)) has the potential for irritation and sensitization, and thus should be adequately conveyed in the labeling.

The referenced products, Adderall XR® and Vyvanse® include language for hypersensitivity which should also be included for this transdermal product.

While precedent labeling from the Adderall XR® and Vyvanse® prescribing information may serve as a guide for this transdermal product, the language for section 6 should be based on the clinical experience from the actual clinical trials reviewed for this

application as opposed to patch studies in healthy subjects. Typically, detailed data from these studies are not included in labeling.

Background:

The Division of Psychiatry (DP) requested that the Division of Dermatology and Dentistry (DDD) evaluate the dermal safety study submitted by Noven Pharmaceuticals, Inc. to support the overall safety evaluation for XELSTRYM™ (Dextroamphetamine Transdermal System (d-ATS)). On February 22, 2021, the applicant submitted a 505(b)(2) application for XELSTRYM™ (Dextroamphetamine Transdermal System (d-ATS)) for the indication of treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older. The 505(b)(2) relies on the Agency's previous findings of efficacy and systemic safety for the listed drugs (LDs), Adderall XR® (mixed salts of single-entity amphetamine capsules; NDA 021303) and Vyvanse® (lisdexamfetamine dimesylate capsules; NDA 021977). Adderall XR® was approved on October 11, 2001 for the treatment of ADHD, and Vyvanse® February 23, 2007 for the same indication in children 6 to 12 years of age. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The mode of therapeutic action in ADHD is not known.

The XELSTRYM™ patch contains approximately 1 mg/cm^2 dextroamphetamine base that delivers d-amphetamine upon application to intact skin. Each patch is composed of the following consecutive layers: (1) an oversized protective silicone-coated polyester release liner, (2) a proprietary acrylic adhesive formulation containing dextroamphetamine, and (3) a polyester and polyurethane laminate film. The applicant has developed 4 dosage strengths (4.5 mg/9 hrs, 9.0 mg/9 hrs, 13.5 mg/9 hrs, and 18.0 mg/9 hrs) of XELSTRYM™ for a 9-hr wear time within 24 hrs. The patches are compositionally equivalent, and the difference in dose is affected through a proportional increase in the surface area (cm^2) of the patches.

The development program for XELSTRYM™ included 13 clinical studies. The applicant conducted a pivotal efficacy/safety study (N25-006) to evaluate the safety and efficacy of XELSTRYM™ in children and adolescents with ADHD and 2 relative bioavailability studies (N25-004 and N25-012 Part 2) to establish a PK bridge with Adderall XR® and Vyvanse®. Additionally, the applicant completed four Phase 1 studies (N25-002, N25-005, N25-010, and N25-015), a human factors package (including 2 usability studies [N25-007 and N25-013], a pre-summative study [N25-017A], a validation study [N25-017B], a label comprehension study [N37-001]), and 3 transdermal safety studies (adhesion [N25-013], irritation/sensitization [N25-018], and effects of heat [N25-012 Part 1]) to support this 505(b)(2) NDA application. Of the 3 transdermal safety studies, DDD had previously been consulted regarding the protocol for Study N25-018.

As a 505 (b)(2) application, labeling for the proposed transdermal product will be impacted by the labeling and prior safety experience for related amphetamine products.

In Dr. Patricia Brown's clinical consult memo (consult #2016), dated December 10, 2019, the following comments were provided regarding the protocol for Study N25-018, entitled "A Randomized, Evaluator-blinded Study to Evaluate Skin Irritation and Sensitization of d-Amphetamine Transdermal System in Healthy Adults":

> *Dermal safety studies to assess local safety for topical drug products are recommended but are not required. The potential of a proposed drug product to induce irritation and sensitization may be evaluated during well-controlled (e.g., Phase 3) trials using appropriate scales.*
>
> *In general, regarding Noven Clinical Study Protocol # N25-018, elements of study design including duration of patch placement, methods of assessment of irritability and sensitization, inclusion and exclusion criteria, and stopping criteria are acceptable. Safety assessment in this protocol will be addressed by the review division.*
>
> *DDDP, however, has the following comments/recommendations:*
>
> *1) In general, dermal safety studies should be performed with the final-to-be-marketed formulation.*
> *2) For cumulative irritation, the sponsor proposes application of d-ATS [5 mg] patch, 0 mg d-ATS (placebo), and Saline Patch (0.9% physiological saline) patch (low irritancy control. Recommended study design also includes a high irritancy control (e.g,. sodium laurel sulfate 0.1%).*
> *3) During the trial, if test articles are reinforced with tape, skin irritation from the tape should be reported separately from the skin irritation associated with the test article application area.*
> *4) Descriptive irritation score data should be submitted in a frequency table illustrating the number and proportion of each test article with each combination of the dermal response numerical score and "other effects" letter score at each evaluation time point.*

In the meeting minutes of the pre-NDA meeting held with the applicant on September 3, 2020, the following response was provided regarding the overall dermal safety profile for XELSTRYM™:

FDA Response to Question 6:

> *We cannot agree that the local safety profile has been fully characterized prior to reviewing the data in the NDA. However, although the study report is not complete, the information from the irritation/sensitization study N25-018 appears adequate for filing, the number of subjects is acceptable, and additional provocative dermal safety studies in healthy subjects for your proposed transdermal system are not necessary.*

Review of Dermal Safety Studies:
Study N25-018

Title:
"A Randomized, Evaluator-blinded Study to Evaluate Skin Irritation and Sensitization of d-Amphetamine Transdermal System (d-ATS) in Healthy Adults"

Principal Investigator/Study Center:
Jonathan S. Dosik, MD
TKL Research, Inc.
One Promenade Blvd., Suite 1101/1201
Fair Lawn, NJ 07410

Study Phase: 1

Study Dates:
December 2, 2019 – May 12, 2020

Study Objectives:

- To evaluate skin sensitization potential after repeated exposure of d-ATS, placebo, and saline patches in healthy adults.
- To evaluate skin irritation after repeated exposure to d-ATS, placebo, and saline patches in healthy adults.

Study Design:
This was a single center, randomized, evaluator-blinded skin irritation and sensitization study.

Inclusion Criteria:

1) Subject provided written informed consent prior to entering the study or undergoing any study procedures;
2) Healthy male and female (non-pregnant, non-lactating) 18 - 65 years of age, inclusive;
3) Subject was considered by the Principal Investigator/Sponsor to be healthy on the basis of medical history, physical examination, vital signs, ECG and clinical laboratory test results; deviations or excursions considered to be non-clinically significant as per the Principal Investigator were acceptable;
4) Subject had a normal screening ECG; non-specific ST-T wave changes or other changes deemed by the Principal Investigator as not clinically significant were acceptable;
5) Female subject was (i) a woman physiologically incapable of becoming pregnant [confirmed to be post-menopausal (having amenorrhea for > 12 months), had a hysterectomy with or without bilateral oophorectomy at least 6 months prior to the Screening Visit] or (ii) a woman of childbearing potential (WOCBP) with a negative pregnancy test at the Screening Visit and agreed to either abstain from

sexual intercourse or use 2 forms of reliable barrier method of contraception (e.g., condom with spermicide, diaphragm, intrauterine device (IUD), contraceptive sponge) for at least 14 days before and throughout the duration of study (from Screening Visit through the Follow-up Visit) or used a hormonal method of contraception for at least 30 days before the study and agreed to continue to use the same type of hormonal contraceptive during the study. Acceptable forms of birth control included (i) surgical sterilization (such as a tubal ligation), which occurred more than 3 months prior to the Screening Visit (ii) approved hormonal contraceptives (such as birth control pills, implants or injections), (iii) an intrauterine device, (iv) barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository), (v) Vasectomy in male partner, which occurred more than 3 months prior to the Screening Visit; bilateral oophorectomy have been enrolled. If the female subject agreed to use an occlusive cap/vault caps with spermicidal foam/gel/film/cream/suppository and her male partner agreed to use a condom with spermicidal foam/gel/film/cream/suppository, this constituted as two methods of birth control;

6) Subject had a body mass index (BMI) between 18 kg/m^2 and 35 kg/m^2, inclusive;
7) Subject had liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin, ≤ 1.5x upper limit of normal (ULN) (isolated bilirubin >1.5xULN was acceptable if bilirubin was fractionated and direct bilirubin <35%);
8) Subject was capable of understanding and complying with the protocol and signed the ICF.

Exclusion Criteria:

1) Subject was pregnant or lactating, or females planning a pregnancy during the course of the trial;
2) Subject with a history or presence of clinically significant disease (glaucoma, cardiovascular, hepatic, renal, gastrointestinal, neurologic, psychiatric, dermatologic, pulmonary, hematological, musculoskeletal, genitourinary, thromboembolic, advanced arteriosclerosis, hyperthyroidism, moderate to severe hypertension, asthma, urticaria, angioedema, edema, bronchospasm or immunologic disease or any other disorder). Conditions deemed not-clinically significant according to the Principal Investigator's discretion were acceptable;
3) Subject with a sitting blood pressure (BP) <90/50 or >139/89 mmHg and a sitting heart rate (HR) <45 or >90 beats/min;
4) Subject had a clinically significant ECG finding or QTcF interval >450 msec for males and >470 msec for females;
5) Subject had evidence of orthostatic hypotension (decrease of >20 mmHg systolic or >10 mmHg diastolic or both at supine for 5 minutes and again after assuming an upright position for 2 minutes) accompanied by symptoms (faintness, lightheadedness, dizziness, confusion);
6) Subject had a history of narcotic abuse, drug abuse, and alcoholism;

7) Subject had a clinically significant abnormal laboratory test result. Deviations considered to be non-clinically significant as per the Principal Investigator were acceptable;
8) Subject had a history of allergy or sensitivity to amphetamine or components in the patch;
9) Subject had a history or presence of significant skin disorder such as atopy, psoriasis, vitiligo, chronic cutaneous lupus erythematosus (CCLE), or conditions known to alter skin appearance (e.g., rash, infection, abnormally dry skin, abrasions), presence of tissue scar (e.g., tattoo) or excessive hair, body piercing, presence of open sores at the potential site of patch application or skin type that could have, in any way, confound interpretation of the trial results (i.e., skin type VI on the Fitzpatrick scale);
10) Subject had a lifetime history of significant dermatologic cancers (e.g., melanoma, squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the application sites;
11) Subject with any dermatologic diseases that might have interfered with the evaluation of the test site reactions;
12) Subject had a history of any allergy to soaps, lotions, cosmetics, adhesives, or adhesive dressings;
13) Subject had a history of significant allergies (including food or drug allergies; minor seasonal allergies were allowed);
14) Subject with a history of a condition that would have significantly influenced the immune response (e.g., primary or acquired immunodeficiencies such as human immunodeficiency virus (HIV) positive or acquired immunodeficiency syndrome (AIDS), allergic diseases such as anaphylaxis, asthma or generalized drug reaction, neoplasms such as lymphoma or leukemia, or rheumatoid arthritis);
15) Subject with a history of severe depression, psychoses, bipolar disorder, mania, aggression, marked anxiety, agitation, tension, seizures, Tourette's Syndrome, motor tics, glaucoma, migraines, or unexplained syncope;
16) Subject was on medications or treatments that would have significantly influenced or exaggerated responses to the test product or that would have altered inflammatory or immune response to the product (e.g., cyclosporine, tacrolimus, systemic or topical corticosteroids, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy) within 3 weeks prior to dosing;
17) Subject used any excluded over the counter medications (including herbal remedies) that would have interfered with the objectives of the study or were contraindicated with the study drug for at least 7 days or 4-5 five half–lives, whichever was longer, prior to the first dose;
18) Subject used monoamine oxidase inhibitors within 14 days of dosing;
19) Subject used systemic or topical drugs and analgesics at the patch application site or antihistamines within 72 hours prior to dosing or systemic or topical corticosteroids within 3 weeks of study enrollment;
20) Subject with symptoms of significant acute illness at screening or prior to dosing;
21) Subject with positive screen for hepatitis B and C;

22) Subject was sunbathing, used a tanning bed within 7 days of the Screening Visit or Admission, or had sunburn in the test area that could have interfered with skin evaluation;
23) Subject who could foresee an intensive solar exposure during trial participation (ultraviolet [UV] radiation etc.) within 7 to 14 days of the Screening Visit;
24) Subject was a Study Investigator, Sub-Investigator, Study Coordinator or was employed by the site or the Sponsor, or was an immediate family member (e.g., spouse, parent, child or sibling, whether biological or legally adopted) of an employee of the site, participating Investigator, CRO or Sponsor;
25) Subject received any investigational product or therapy within 30 days prior to study drug administration;
26) Any subject not able to meet study requirements in the opinion of the Principal Investigator.

Study Drugs:

1) **Investigational Drug**: d-Amphetamine Transdermal System (d-ATS) (5 mg d-amphetamine /4.76 cm^2) patch.
2) **Placebo**: Placebo (0 mg d-ATS/ 4.76 cm^2) patch.
3) **Negative Control**: Saline (0.9% physiological saline) patch.

Reviewer's Comment: *The study design did not implement a high irritancy control (e.g., sodium lauryl sulfate 0.1%), as recommended by the Agency in dermatology consult #2016 on December 10, 2019.*

Study Plan:

This was a single center, randomized, evaluator-blinded skin irritation and sensitization study.

A total of 229 healthy, adult subjects were enrolled and randomized in the study, and 201 subjects (87.8%) completed the study.

The Treatment Phase of the study consisted of 4 periods: Induction Period, Rest Period, Challenge Period, and Re-challenge Period, described as follows:

Induction Period (Day 1 – 22):

The Induction Period lasted 3 weeks (21 days). The Induction Period utilized the Jordan-King modification of the Draize procedure and consisted of repetitive patch applications of three (3) test articles (one d-ATS [5 mg] patch, one placebo [0 mg] patch, and one saline patch) to the same respective application sites on the left side of the back (Left, Center, and Right) daily (every 24 hours) for a total of 21 consecutive days.

During the Induction Period, each of the test articles was applied to the skin on the left side of the back daily for a minimum of 18 and maximum of 21 applications over a 21-day period distributed as 7 applications per week. The patches remained in place for 24 hours (±3 hours) every day. Subjects that required missing a visit were allowed up to 3

non-consecutive visits and required patches remaining in place. Patches were applied to the same skin sites throughout the Induction Period, such that the active treatment was applied to the active drug site, the placebo patch was applied to the placebo site, and the saline patch was applied to the saline site.

An assessment of the skin was conducted on each clinic day during the 3-week study period and the last week of the study. Each of the application sites was evaluated for irritation prior to patch application (i.e., Induction Day 1) using the Dermal Response Scale. The application sites were examined, evaluated, and graded by a trained evaluator/rater approximately 30 minutes to 1 hour following removal of the patch according to irritation assessments. Meaningful or excessive degree of irritation was defined if combined irritation score was equal to 3 or greater.

Patches were applied continuously to the same respective application sites during the Induction Period. If a subject experienced irritation with a combined score of ≥3 at any patch application site or experienced symptomatic intolerable irritation at the patch application site, the patch may have been moved to a new treatment naïve site (N-1 site) on the back. Subjects received subsequent patch applications on the N-1 site. A second change of site (treatment naïve site, on the back) (N-2) was made if a combined score of ≥3 or intolerable irritation occurred at the N-1 site. At the Principal Investigator's discretion and in the event of a third combined score of ≥3 or intolerable irritation, the patch application site was discontinued, and no further applications were made. The use of the first and second adjacent sites was recorded in the source documents to clearly indicate that the patch application sites were moved from the original application site.

Adhesion of the patches to the skin was evaluated immediately prior to patch removal at 24 hours post Day 1. Adhesion was monitored throughout the entire study period, which was necessary for a suitably provocative induction of Irritation/Sensitization.

Hypoallergenic adhesive tape was applied to reinforce adhesion of the d-ATS, placebo and saline patches on Day 2 in order to ensure that patches remained in contact with the skin for the entire wear period. Any skin irritation associated with the tape was documented and reported separately from that of the patch application area.

Rest Period (Day 23 - 37):
Following the Induction Period, the subject did not receive any treatment for approximately 2 weeks (15 ± 2 days).

Challenge Period (Day 38 - 43):
During the Challenge Period, there was a single 48-hour application of test articles (d-ATS, placebo, and saline patches) to a treatment-naïve skin site on the right side of the back (Left, Center, and Right) to further evaluate reactions suggestive of skin sensitization with application sites scored for irritation prior to patch application (i.e., Challenge Day 1). Each of the application sites was evaluated for irritation prior to patch application (i.e., Challenge Day 1) using the Dermal Response Scale. The application sites were examined and evaluated by a trained evaluator/rater following removal of the

patch according to irritation assessments. Subjects with a combined score of 2 or greater at 48 or 72 hours after patch removal during the Challenge Period were individually evaluated for potential sensitization.

Subjects returned to the Clinical Site after 48 hours for irritation and adhesion assessments and patch removal and at the following time points:

- 30 minutes to 1-hour post-removal (+/- 5 minutes)
- 24 hours post-removal (± 1 hour)
- 48 hours post-removal (± 4 hours)
- 72 hours post-removal (± 8 hours)

The opinion of the investigator on whether the skin reaction(s) were indicative of a contact sensitization was documented (positive, negative, or equivocal).

Subjects were considered potentially sensitized if all the following criteria were met:

- The subject had at least one assessment occurring at more than 24 hours (i.e., at 48 or 72 hours) after the removal of the Challenge Period patch, AND
- The subject had a combined "Dermal Response" and "Other Effects" numeric score ≥2 at their last assessment during the Challenge Period, AND
- The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Period was higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Period

Re-challenge Period (Day 72 – 77):

If required, subjects who experienced a potential sensitization reaction during the Challenge Period and were judged equivocal or positive after challenge on Day 43 would have been rechallenged on Day 72 (4 weeks after the Challenge Period) with additional patch applications (d-ATS, placebo, and saline) in the same way as at Challenge Period.

During the Re-challenge Period, test articles (one 5 mg d-ATS patch, one placebo patch, and saline patch) were applied to treatment-naïve skin sites on the right side of the back for 48 hours under the same conditions as for the Challenge Period (Day 38).

Subjects returned to the Clinical Site after 48 hours for irritation and adhesion assessments and patch removal. Irritation was assessed prior to patch application i.e., Re-challenge Day 1 and at the following time points:

- 30 minutes to 1-hour post-removal (+/- 5 minutes)
- 24 hours post-removal (± 1 hour)
- 48 hours post-removal (± 4 hours)
- 72 hours post-removal (± 8 hours)

A subject was considered sensitized if the following criteria were met:

- The subject had at least one assessment occurring more than 24 hours (i.e., at 48 or 72 hours) after the removal of the Re-challenge Test article AND
- The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last assessment during the Re-challenge Period AND

- The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Period and the Induction Period AND
- The subject met all these criteria at both the Challenge Period as well as the Rechallenge Period.

An end of treatment (EOT) or early termination (ET) visit was performed for all subjects (Induction Day 22, Challenge Day 43 or Re-challenge Day 77). For subjects who did not experience reactions suggestive of sensitization, the EOT Visit was performed at the end of the Challenge Period. For subjects who experienced reactions suggestive of sensitization and were assigned to the Re-challenge Period, the EOT Visit was performed the last day of irritation evaluation after removal of the re-challenge patch.

Dermal Evaluations:

Irritation

The application site was examined for signs of skin irritation at time points after patch removal. All subjects were evaluated by a trained-skin evaluator using the Berger and Bowman scale. Half grades were not assigned; if reactions fell between the unit grades, the more severe of the two grades was assigned. Photographs of the application site were taken at the time of irritation assessments prior to patch application on Day 1. Additionally, photographs were taken of any irritation reaction(s) scored ≥3. Findings were graded using the following two scales:

Scale 1: Dermal Response Scale

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

Scale 2: 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 exudate covering all or part of the application site
H (3) = small petechial erosions and/or scabs

Adhesion

During the Induction Period, subjects had the first patch placed on Day 1 and returned to the Clinical Site daily as scheduled for adhesion and visibility scoring prior to patch removal. After wearing the challenge and/or re-challenge patch for 48 hours (or until removal due to intolerable reaction), subjects returned for adhesion scoring. Adhesion scores were recorded immediately prior to patch removal at 24 hours post patch

application during induction, at 48 hours post application during challenge and rechallenge using the 5-point adhesion scale, depicted below:

Adhesion Scale
0 = ≥ 90% adhered (essentially no lift off the skin)
1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)
3 = > 0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
4 = 0% adhered - patch detached (patch completely off the skin)

Safety Evaluations:
Safety was monitored throughout the study by repeated clinical and laboratory evaluations according to the following schedule of events:

Table 1: Schedule of Events

Phase	Screening	Treatment																			
Period		Induction[a]			Rest[b]	Challenge Days						Re-challenge Days						End of Treatment/ Early Termination	Follow up Visit
		Clinic Days																			
Days	Approx.-28 to -1	1	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21	22	23-37	38	39	40	41	42	43	72	73	74	75	76	77		
Procedures/Assessments																			
Demography	X																		
Informed Consent	X																		
Assign Subject Screening Number	X																		
Inclusion/Exclusion Criteria	X	X[c]				X[c]						X[c]							
Medical History/Current Medical Conditions	X	X																	
Prior/Current Medications	X																		
Fitzpatrick Skin Type	X																		
Physical Examination	X																	X	
Vitals Signs	X[d]	X[e]	X[e]	X[e]		X[e]						X[e]						X[e]	
Body Temperature	X																	X	
Height, Weight, BMI	X																		
12 Lead ECG[f]	X																	X	
Alcohol Screen	X																		
C-SSRS	X	X		X		X						X						X	
Blood Chemistry, Hematology and Urinalysis	X																		
Urinalysis	X																	X	
Urine Drug Test	X[g]	X[g]																	
HBV, HCV and HIV tests	X																		
Pregnancy Screen (WOCBP)[h]	X	X				X						X						X	
Assign Subject Enrollment Number		X																	
Patch Application[i]		X	X			X						X							
Patch Removal			X	X				X						X					
Adhesion Assessment[j]			X	X			X						X						
Irritation Assessment[k,l]		X	X	X		X		X	X	X	X[m]	X		X	X	X	X[n]		
Adverse Events		X	X	X	X	X	X	X	X	X	X[m]	X	X	X	X	X	X[n]	X	X[p]
Concomitant Medications		X	X	X	X	X	X	X	X	X	X[m]	X	X	X	X	X	X[n]	X	
Subject Contact					X[o]														
Text visibility assessment[q]		X[q]	X[q]																

EOT: End of Treatment; ET: Early Termination; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; WOCBP: Women of childbearing potential;
ECG: Electrocardiograph
Footnotes:
a During the Induction Period, applications of the test articles were made to the same skin sites daily for 21 consecutive days, for a total of 21 applications Each patch
remained in place for 24 hours (± 3 hours)
b During the Rest Period, subjects were contacted at least twice to confirm reporting of AEs or concomitant medications
c Inclusion/Exclusion Criteria was reconfirmed on Day 1 of the Induction, Challenge and on Day 1 of the Re-Challenge Periods (if required)
d Screening vital signs consisted of sitting BP, HR and RR, oral body temperature, and supine BP for orthostatic hypotension
e Vital signs consisting of sitting BP, HR and RR were measured only on Day 1, Day 8, Day 15, and Day 22 of the Induction Period, Day 1 of Challenge and Re-challenge
(if required), as well as at EOT/ ET In addition, oral body temperature was recorded at EOT/ ET
f Any ECG which demonstrated a clinically significant abnormality at Screening was exclusionary and the subject was not enrolled in the trial

g Urine drug screen was done at Screening and Day 1 of the Induction Period
h Serum pregnancy test was done at Screening only All other pregnancy tests were urine and were done prior to patch application at Day 1 of Induction, Challenge and
Re-challenge Periods, if required, and at EOT/ET Clinical Site may have performed pregnancy tests on all females if it was their standard procedure
i After confirmation of eligibility, the first set of three patches was applied
j Subjects returned to the Clinical Site post patch application for adhesion of the patches to the skin immediately prior to patch removal at 24 hours post application Day
1 assessments, and daily for patch removal and irritation assessments
k Subjects returned to the Clinical Site daily post patch application for adhesion assessments, patch removal and irritation assessments
l Irritation was assessed prior to patch application on Day 1, and 30 minutes to 1 h post-removal during Induction Period During Challenge/Re-challenge Periods,
irritation was assessed prior to patch application on Day 1 and 30 minutes to 1 h, 24h, 48h and 72h post-removal A photograph of the application site was taken at the
time of irritation assessment prior to patch application on Day 1 Additionally, photographs were taken of any irritation reaction(s) scored ≥2
m All EOT procedures were performed on the last Challenge visit if there was no Re-challenge
n All EOT procedures were performed at the last Re-challenge visit, if required
o Subjects had a safety visit approximately 7 days (± 1 day) after EOT/ET Visit The Principal Investigator or qualified study staff contacted all subjects by phone for
continued safety monitoring of AEs At the discretion of the Principal Investigator, subjects may have been required to return to the Clinical Site for their Follow-up
Safety Visit
p Subjects had a safety visit approximately 7 days (± 1 day) after EOT/ET Visit The Principal Investigator or qualified study staff contacted all subjects by phone for
continued safety monitoring of AEs At the discretion of the Principal Investigator, subjects may have been required to return to the Clinical Site for their Follow-up
Safety Visit
q Patch backing text visibility was evaluated 30 ± 5 minutes after patch application on Day 1 and prior to patch removal (from 30 minutes before patch removal until
patch removal) on Day 2

Reviewer's Comments:

- *The sample size and study population as defined by the inclusion and exclusion criteria were acceptable.*
- *The application of the study product 7 times per week (i.e., every 24 hours) was adequate to elicit an irritancy response.*
- *The scales used to grade the findings of irritation and sensitization were acceptable.*

Results

Study Population

Disposition:

- Investigators enrolled and randomized 229 subjects, and 201 subjects completed the study
    - 20 subjects (8.7%) voluntarily withdrew from the study
    - 5 subjects (2.2%) were discontinued due to an adverse event (AE)
    - 2 subjects (0.9%) were lost to follow-up
    - 1 subject (0.4%) was discontinued for taking exclusionary medication

The following table provides a summary of the reasons for subject discontinuation:

Table 2: Summary of Disposition for Study N25-018

Characteristics	Overall	Population		
		Safety	PPI	PPS
Subjects Screened	522			
Screen failures				
Did Not Meet Inclusion/Exclusion Criteria, n (%) [1]	293 (56.1)			
Subjects Randomized [2]	229			
Qualified per Population, n (%)	229 (100.0)	229 (100.0)	206 (90.0)	200 (87.3)
Number of Subjects Completing the Study, n (%) [3]	201 (87.8)	201 (87.8)	200 (87.3)	200 (87.3)
Number of Subjects Discontinued the Study, n (%)	28 (12.2)	28 (12.2)	6 (2.6)	0
Reason for Early Discontinuation				
Withdrawal By Subject, n (%)	20 (8.7)	20 (8.7)	6 (2.6)	0
Adverse Event, n (%)	5 (2.2)	5 (2.2)	0	0
Lost To Follow-Up, n (%)	2 (0.9)	2 (0.9)	0	0
Other, n (%)	1 (0.4)	1 (0.4)	0	0

Notes: **Safety Population** includes all subjects who have received at least one administration of the investigational product.
Per-protocol Cumulative Irritation (PPI) Population includes all subjects who have all patches applied sequentially to the same site for the entire 21-day Induction Period (without any period of detachment longer than 24 hours). If a test article is moved or removed due to excessive irritation, it should be included in the PP population using Last (Worst) Observation Carried Forward (LOCF) from the original application site.
Per-protocol Sensitization (PPS) Population includes all subjects who have All patches worn (without any period of detachment longer than 24 hours) for the full 21-day Induction Period AND for the entire 48 hours during Challenge and Re-challenge Periods. Each subject will return for at least one of the scheduled evaluations at 24, 48 and 72 hours after removal of the Challenge/ Re-challenge patch.If a test patch is moved or removed due to excessive irritation,it should be included using LOCF.
[1] Percentage is relative to total number screened.
[2] Percentages in this section are relative to total number randomized, unless otherwise noted (see footnote 3).
[3] Percent of subjects completing the study is relative to randomized in the corresponding column.

Demographics:

- The majority of subjects were female (79%), White, (68.1%) and had a mean age of 41.3 years (range 18 to 64 years).

Table 3: Summary of Subject Demographic for Study N25-018 – Safety Population (N=229)

Characteristics/ Statistics	
Age (years)	
N	229
Mean (SD)	41.3 (12.24)
Median	41.0
Min, Max	18, 64
Sex, n(%)	
Male	48 (21.0)
Female	181 (79.0)
Race, n(%)	
White	156 (68.1)
Black or African American	68 (29.7)
Asian	5 (2.2)
Ethnicity, n(%)	
Hispanic or Latino	100 (43.7)
Not Hispanic or Latino	129 (56.3)
Height (cm)	
N	229
Mean (SD)	164.4 (8.78)
Median	164.0
Min, Max	147, 192
Weight (kg)	
N	229
Mean (SD)	74.3 (13.07)
Median	72.6
Min, Max	48, 113
BMI (kg/m2)	
N	229
Mean (SD)	27.4 (3.78)
Median	27.2
Min, Max	19, 35
Fitzpatrick Skin Type, n (%) [1]	
II	85 (37.1)
III	75 (32.8)
IV	43 (18.8)
V	26 (11.4)

Notes: [1] I = Always burns easily, never tans; II = Always burns easily, tans minimally; III = Burns moderately, tans gradually; IV = Burns minimally, always tans well; V = Rarely burns, tans very well.

Sensitization Potential

As per investigator, 8 subjects (4%) displayed positive sensitization to d-ATS, and none per control patches tested in this study (see Table 4 below). Based on the definition of potential sensitization, 10 subjects (5%) and 1 subject (0.5%) were potentially sensitized to the d-ATS and saline patches, respectively.

Table 4: Sensitization Potential – PPS Population (N=200)

Sensitization	d-ATS patch	Placebo	Saline patch
Investigator Interpretation [1]			
Subjects with Negative Sensitization, n (%)	189 (94.5)	200 (100.0)	200 (100.0)
95% Confidence Limit on Incidence (%)	90.37, 97.22	98.17, 100.0	98.17, 100.0
Subjects with Equivocal Sensitization, n (%)	3 (1.5)	0	0
95% Confidence Limit on Incidence (%)	0.31, 4.32	0.00, 1.83	0.00, 1.83
Subjects with Positive Sensitization, n (%)	8 (4.0)	0	0
95% Confidence Limit on Incidence (%)	1.74, 7.73	0.00, 1.83	0.00, 1.83
Potential Sensitization derived as per Protocol [2]			
Subjects with Potential Sensitization, n (%)	10 (5.0)	0	1 (0.5)
95% Confidence Limit on Incidence (%)	2.42, 9.00	0.00, 1.83	0.01, 2.75

Notes: PPS Population is the Per-protocol population for the sensitization analysis.
95% confidence limits are calculated using exact binomial distribution (Clopper-Pearson).
[1]Investigator Interpretation: Positive – Investigator has deemed that subject has been sensitized during Challenge and Re-challenge Periods, if subject was available for Re-challenge Period.
Negative – Investigator has deemed that subject has not been sensitized either during Challenge or Re-challenge Periods, if subject was available for Re-challenge Period.
Equivocal – Investigator has determined that a conclusion concerning sensitization cannot be made during Challenge and Re-challenge Periods, if subject was available for Re-challenge Period.
[2] Potential Sensitization derived as per Protocol: A subject was potentially sensitized if all the following criteria are met: a. The subject has at least one evaluation time point occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Period TDS; b. The subject has a combined irritation score of at least 2 at their last evaluation during Challenge Period; c. The above two criteria were met during both the Challenge Period and the Re-challenge Period, if the subject completed a Re-challenge Period.

Of note, re-challenge was not performed in 6 of the 8 subjects deemed sensitized due to social distancing restrictions associated with the COVID-19 pandemic. The 2 subjects (Subjects (b) (6)) who were able to return demonstrated positive sensitization results based on re-challenge.

Reviewer's Comments:

- *This study was adequate in design and conduct for evaluation of contact sensitization potential of the test product.*
- *Despite the re-challenge limitations posed by the COVID-19 pandemic, the study results indicate that XELSTRYM ™ has the potential for contact sensitization and thus should be adequately conveyed in labeling.*

Irritation:

Irritation scores were recorded throughout the Induction Period. The mean and total cumulative irritation scores for the Induction Period are presented in the table below.

Table 5: Mean and Total Cumulative Irritation Scores, Induction Period, PPI Population (N=206)

		MEAN IRRITATION SCORE	TOTAL IRRITATION SCORE
	Number of Subjects	Mean (SD)	Mean (SD)
A. d-ATS patch	206	2.10 (0.73)	43.69 (15.25)
B. Placebo patch	206	1.30 (0.69)	26.91 (14.29)
C. Saline patch	206	0.21 (0.41)	4.28 (8.35)

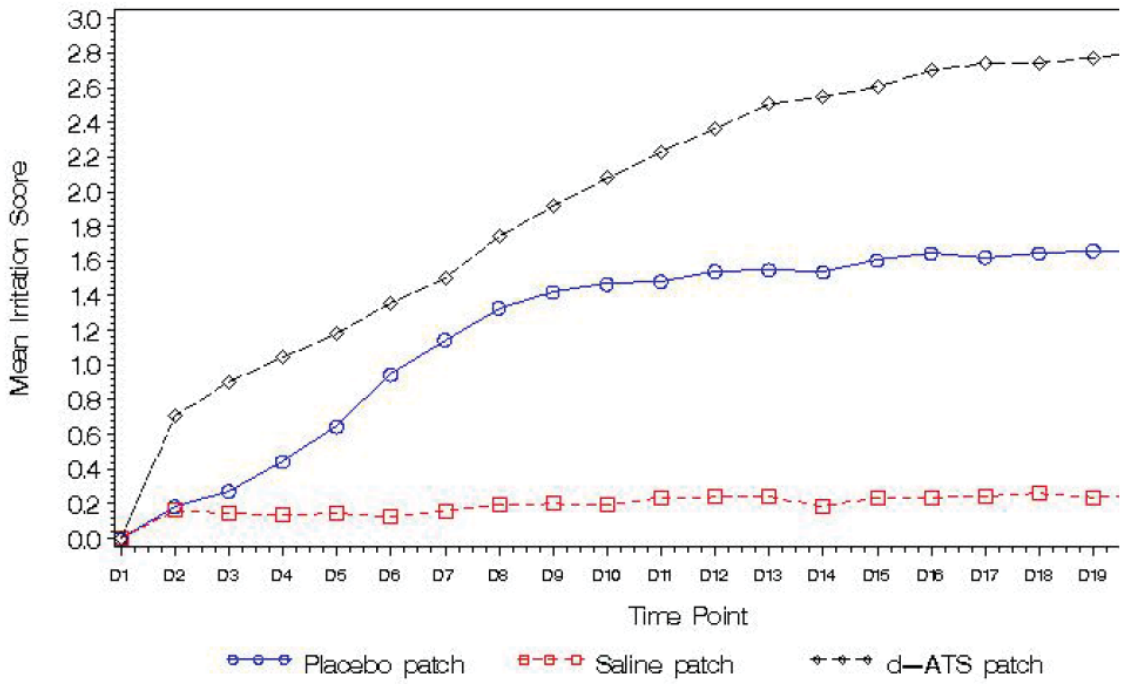
Notes: Mean Irritation Score will be calculated as the sum of the combined irritation scores over the assessment time points divided by the total number of assessments.
Total Irritation Score will be calculated as the sum of the combined irritation scores over the assessment time points.

Among subjects in the PPI Population for the primary analysis, d-ATS had a mean (SD) irritation score of 2.10 (0.73), Placebo had a mean (SD) irritation score of 1.30 (0.69) and 0.9% Saline had a mean (SD) irritation score of 0.21 (0.41). The mean irritation score of d-ATS was higher than Placebo and 0.9% Saline. The mean irritation score of Placebo was lower than d-ATS but higher than 0.9% Saline.

d-ATS had a total (SD) irritation score of 43.69 (15.25), Placebo had a total (SD) irritation score of 26.91 (14.29) and 0.9% Saline had a total (SD) irritation score of 4.28 (8.35). The total irritation score of d-ATS was higher than Placebo and 0.9% Saline. The mean irritation score of Placebo was lower than d-ATS but higher than 0.9% Saline.

Additionally, mean irritation scores increased over time, as depicted in Figure 1, below.

Figure 1: Mean Irritation Scores per Timepoint in Induction Period by Treatment – PPI Population (N=206)



Reviewer's Comment: *The normalized total irritation score was 437 for d-ATS, 269 for Placebo, and 43 for saline (a normalized total score can be calculated by summing the total irritation scores for each subject, dividing by the number of subjects and multiplying by a factor of 10). Scores ranging from 0 to 49 suggest no significant irritation, 50 to 199 suggest a product is slightly irritating, scores 200 to 449 indicate a product is moderately irritating, and scores ranging from 450 to 630 indicate a product is highly irritating. Therefore, d-ATS was moderately irritating, Placebo was moderately irritating but less so than d-ATS, and saline demonstrated no significant irritation. Therefore, the labeling for XELSTRYM™ should adequately convey its potential for irritation.*

Safety Findings:
There were no deaths or serious adverse events (SAEs) reported during this study.

Five subjects (2.2%) experienced AEs leading to study treatment discontinuation during the Induction Period. One subject experienced hypertension. The AE was mild in severity, possibly related, and recovered/resolved. One subject experienced cellulitis (on gluteal muscles); the AE was moderate in severity, unrelated, and recovered/resolved. One subject experienced tape reaction at the application Sites 1, 2, and 3; the AE was mild in severity, unrelated, and recovered/resolved. One subject experienced abnormal heart rate; the AE was moderate in severity, possibly related, and recovered/resolved. One subject experienced 3 AEs; headache, nausea and vomiting. All 3 AEs were mild in severity, possibly related, and recovered/resolved.

Overall, 44 AEs were observed among 32 subjects (14%) in this study. Thirty-one (31) subjects (13.5%) reported 43 AEs during the Induction Period and one subject (0.4%). Twenty-eight (28) subjects (12.2%) experienced 39 treatment-related AEs (TEAEs) during the Induction Period only. The most common AEs belonged to the system organ class (SOC) of nervous system disorders; 17 subjects (7.4%) with 18 mild related AEs (1 (0.4%) dizziness, 1 (0.4%) dysgeusia, and 16 (7.0%) headache), 2 subjects (0.9%) with 2 moderate related AEs (2 (0.9%) headache), and one subject (0.4%) with one severe related AE (1 (0.4%) headache).

Additional safety measurements included vital signs, ECGs, C-SSRS: Suicidal Ideation questionnaires, C-SSRS: Suicidal Behavior questionnaires and adhesion assessments. All these results were within the normal limits or deemed not clinically significant by the Investigator.

Reviewer's Comment: Overall, the rate of TEAEs was relatively low, and the reported AEs are consistent with those reported for other stimulant medications.

Conclusion: The Applicant conducted a cumulative skin irritation and sensitization study in 201 subjects; this meets the minimum requirement of 200 evaluable subjects generally recommended by DDD for such studies. The results showed that the investigational product was moderately irritating and demonstrated the potential for contact sensitization, and thus should be adequately conveyed in labeling.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERA C SCHREIBER
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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	August 31, 2021
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 215401
Product Type:	Combination Product
Drug Constituent Name and Strength	Xelstrym (d-amphetamine transdermal system) 5 mg, 10 mg, 15 mg, 20 mg
Device Constituent:	Transdermal system
Rx or OTC:	Rx
Applicant/Sponsor Name:	Noven Pharmaceuticals, Inc. (Noven)
Submission Date:	02/22/2021
OSE RCM #:	2021-373
DMEPA 1 Safety Evaluator:	Jason Flint, MBA, PMP
DMEPA 1 Team Leader (Acting):	Murewa Oguntimein, PhD, MHS, CHES, CPH
DMEPA 1 Division Director (Acting):	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 215401 for Xelstrym (d-amphetamine transdermal system).

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed transdermal system device constituent part that is intended to treat Attention Deficit Hyperactivity Disorder (ADHD).

(b) (4)	
Xelstrym Patches	Xelstrym Pouch, Carton, and IFU

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

We previously reviewed a human factors validation study protocol[1] for this product, however, we note that the Applicant did not implement all of our recommendations. We address the issues with the study methodology in section 3.1.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D

[1] Flint J. Human Factors Validation Study Protocol Review for Xelstrym (d-amphetamine transdermal system) (IND 073862). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020MAR27. RCM No.: 2020-246

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Information Requests Issued During the Review	E
Labels and Labeling	F

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	Adult Patients with ADHD – 18 (10 experienced) (8 naïve) Pediatric Patients with ADHD – 16 (1 experienced) (15 naïve) Lay Caregivers – 16 (4 experienced) (12 naïve)
Training	No training
Test Environment	(b) (4)

Characteristic	Use Environment	Influence on Product Use	Study Environment
Lighting	Well-lit; users are expected to be able to apply the Product in a location of their choosing	Lighting conditions may affect users' ability to read the IFU and labeling	Well-lit
Noise and Stress	Ambient background noise with occasional loud periods	Background noise and distractions may reduce users' ability to focus	Same; will include a background soundtrack simulating typical home noises (e.g., music, household appliances, etc.)
Temperature and Humidity	Ambient temperature	The impact of extreme temperatures while wearing patch is unknown.	Temperature and humidity controlled environment in a building
Work Surface	May have comfortable seating, may include tables of varying heights	No potential use related impact on the Product	Same; will include comfortable seating, tables, and a sink

Sequence of Study	• Simulated Use • Knowledge Tasks • Subjective Feedback • Root Cause Analysis

3 DISCUSSION

3.1 METHODOLOGY

We note that the Applicant did not include an equal number of naive and experienced transdermal system users as originally described in the HF Validation Study Protocol. The Applicant stated that they experienced difficulty recruiting participants with transdermal system experience, particularly in the pediatric population. Furthermore, the Applicant widened their recruitment criteria for caregivers to include caregivers who supervised medication administration within the past 2 years, and guardians of children of any age, instead of those aged 6 to 10 years. We reviewed the Applicant's rationale for these deviations and find their rationale acceptable.

Additionally, we note that the Applicant did not use the intend-to-market presentation during the HF validation study, despite the recommendation in our review of the HF validation study protocol. This raises serious concerns since the Applicant ultimately did not validate the intend-to-market user interface. Additionally, the Applicant made changes to the labels and labelling in an attempt to mitigate the use errors identified during the HF validation study, however, these changes were also not validated.

4 RESULTS AND ANALYSES

Table 3 describes the identified issues and DMEPA's analyses and recommendations for critical tasks.

Table 3. Identified Issues for Critical Tasks and Recommendations for Applicant

	Identified Issue	DMEPA Analysis and Recommendations
1.	For the tasks associated with **Select patch for application** there were: • 4 use errors - participants selected more than one patch for a single administration • 3 use errors – participants did not apply only one patch at a time • 11 use errors - participants did not know to apply a patch on the next day • 18 use errors - participants did not know to apply a new patch in a new location • 24 use errors - participants did not select a new location for a new patch The root cause analysis and subjective feedback for these use errors indicated that there was confusion with elements of the instructions for use (IFU), including: • Step 1 in the IFU identified 5 application sites, which corresponded to the 5 patches in the carton • Participants did not know there was an IFU. • Participants interpreted phrases "worn for 9 hours" and "apply immediately" on the pouch label as indicating, in conjunction, to re-apply patch every 9 hours. • Dosing with current ADHD medication is every 6-8 hours when effect is needed so participant assumed Product dosing would be similar. • Participants skimmed IFU and did not read carefully because it looked overall similar to other patches. The Applicant provided plans to implement risk mitigation steps by changing the location and contents of the IFU and adding content to the carton.	According to the URRA, the use errors identified in the study could lead to skin irritation and overdose resulting in injury, poisoning, gastrointestinal disorders, nervous system disorders, psychiatric disorders, metabolism, and nutrition disorders. Our review of the subjective feedback and root cause analysis indicate that the user interface played a role in these use errors. The Applicant proposed mitigation strategies but did not provide data or information to show that the proposed mitigations will be effective. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant regarding validating their proposed changes by conducting another human factors validation study.
2.	For the tasks associated with **Check expiration date** there were**:**	According to the URRA, the use errors identified in the HF study could lead to in

	• 19 use errors - participants did not know to check the expiration date • 1 use error - participants did not know to not use an expired patch • 6 use errors - could not locate and understand the expiration date The root cause analysis and subjective feedback for these use errors indicated that the participants had difficulty understanding the expiration date, would not waste the product for financial reasons, or expected to find the expiration date in a different location, such as the top left corner of the pouch, or on the bottom of the carton. No additional risk mitigation steps were proposed.	injury, poisoning, gastrointestinal disorders, and psychiatric disorders. Our review of the subjective feedback indicates that participants had difficulty locating and interpreting the expiration date. Our review indicates that the carton and pouch labels submitted to the NDA do not include an expiration date format, and that these labels were not tested in the HF validation study. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant. We recommend that this task be re-valuated in an additional HF validation study.
3.	For the critical tasks associated with **Select application site** there were**:** • 21 use errors - participants selected the wrong patch location • 8 use errors - participants did not know to avoid placing the patch on skin that would be covered by tight clothing • 3 use errors - participants did not know to avoid placing the patch over skin that has cuts, scrapes, burns, rashes, or any other skin problems • 5 use errors - participants did not know to avoid placing the patch on areas with excessive hair The root cause analysis and subjective feedback for these use errors indicated that there was confusion with elements of the IFU, including: • Participants did not know there was an IFU • Participants chose the application location based on what was accessible (participants chose the hand, forearm, thigh, and calf). The Applicant provided plans to implement risk mitigation steps by changing the location of the IFU in the carton to make it easier to locate.	According to the URRA, the use errors identified in the study could lead to skin irritation and overdose resulting in injury, poisoning, gastrointestinal disorders, nervous system disorders, psychiatric disorders, metabolism, and nutrition disorders. Our review of the subjective feedback and root cause analyses indicate that participants had difficulty locating the IFU in the carton and relied on their own judgement to choose the application location. The Applicant proposed a mitigation strategy but did not provide data or information to show that the proposed mitigations will be effective. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant regarding validating their proposed changes by conducting another human factors validation study.
4.	For the tasks associated with **Prepare application site** there were:	According to the URRA, the use errors identified in the study could lead to skin irritation and overdose resulting in injury,

	4 use errors - participants did not know to check that the skin was dry 9 use errors - participants did not know to check that the skin was free of powder, oil, lotion, or gel 30 use errors - participants did not know to use scissors to clip hair close to the skin instead of shaving the application site The root cause analysis and subjective feedback for these use errors indicated that: • Participants did not know there was an IFU • Participants chose not to read (or would not read) the IFU • The leaflet had a crease through the information in the IFU, so did not notice the text. The Applicant provided plans to implement risk mitigation strategies by changing the location of the IFU to make it easier to locate.	poisoning, gastrointestinal disorders, nervous system disorders, psychiatric disorders, metabolism, and nutrition disorders. Our review of the subjective feedback and root cause analysis indicate that the location of the IFU led participants to believe that there was no IFU. Additionally, some participants noted that there was a crease through some text in the IFU that made them overlook the text. The Applicant proposed a mitigation strategy, but the proposed mitigation will not address all of the root causes identified. Additionally, the Applicant did not provide data or information to show that the proposed mitigations will be effective. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant regarding validating their proposed changes by conducting another human factors validation study.
5.	For the tasks associated with **Open pouch and Remove patch** there were**:** • 12 use errors - participants damaged the patch while opening the pouch and removing the patch in the first trial The root cause analysis and subjective feedback for these use errors indicated that: • Opening at top of pouch was not large enough to reach in and grasp patch, so participants had to widen it. • Pouch sides remained stuck together after cutting along dotted line. • Assumed dotted lines on pouch indicated a tear-off perforation. • Only slip liner came out of pouch at first, so participants did not realize there was more inside. The Applicant did not propose any risk mitigation steps.	According to the URRA, the use errors identified in the study could lead to underdose resulting in gastrointestinal disorders, nervous system disorders, psychiatric disorders, metabolism, and nutrition disorders. Our review of the subjective feedback and root cause analyses indicated that the pouch design contributed to these use errors. We note that the participants indicated that the pouch opening was too small, and the pouch was sticking together, making it difficult to remove the transdermal system without damaging it. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant.
6.	For the tasks associated with **Apply patch to application site** there were**:**	According to the URRA, the use errors identified in the study could lead to a missed

	• 7 use errors - participants did not remove the slip liners from the patch • 51 use errors – participants did not peel away 2 protective release liners and did not wash hands when the adhesive drug layer was touched • 14 use errors – participants did not apply the entire adhesive side of patch to skin at the application site • 15 use errors – participants did not apply the patch right away after the slip liners were removed • 5 use errors – participants did not know that the patch should be applied right away after removing the slip liners • 11 use errors – participants did not smooth or press down on patch to ensure it sticks to skin The root cause analysis and subjective feedback for these use errors indicated that: • The slip liners were difficult to see • Participants did not know there was an IFU • Insufficient adhesion/tension to remove the second slip liner • Figure A was faint and hard to see The Applicant proposed several changes to the location and contents of the IFU to address these use errors.	dose or unintentional exposure to a non-user, resulting in injury, poisoning, gastrointestinal disorders, nervous system disorders, and psychiatric disorders. Our assessment of the subjective feedback and root cause analyses indicate that the location and content of the IFU and the design of the slip liners contributed to these use errors. While the Applicant proposed mitigation strategies for the IFU, they do not propose any mitigations to address the use errors related to adhesion or the slip liners. Additionally, the Applicant did not provide data or information to show that the proposed mitigations will be effective. We provide recommendations in Table 4: Identified Issues and Recommendations for Applicant regarding additional risk mitigations and validating the proposed changes by conducting another human factors validation study.
7.	For the tasks associated with **Determine when to remove patch from skin** there were: • 14 use errors – participants did not report removal time 9 hours from application time. The root cause analysis and subjective feedback for these use errors indicated that participants did not know there was an IFU or relied on previous experience with other ADHD medications (once per day administration) or other transdermal systems that last for 24 hours. The Applicant provided plans to implement risk mitigation strategies by changing the location of the IFU to make it easier to locate.	According to the URRA, these use errors identified could lead to overdose resulting in injury, poisoning, gastrointestinal disorders, nervous system disorders, psychiatric disorders, metabolism, and nutrition disorders. Our assessment of the subjective feedback and root cause analyses indicated that the location of the IFU and negative transfer of participants' experience with other ADHD medications or transdermal systems played a role in these use errors. The Applicant proposed a mitigation strategy but did not provide data or information to show that the proposed mitigations will be effective. While the Applicant proposed

		mitigation strategies for the IFU, they do not propose any mitigations to address the use errors related to negative transfer. Negative transfer should have been considered during the HFE design process for this product to ensure adequate mitigations are in place to overcome the negative transfer. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant regarding validating their proposed changes by conducting another human factors validation study.
8.	For the tasks associated with **Wear patch** there were: • 28 use errors – participants did not know to check the patch regularly throughout the day • 4 use errors – participants did not know to not reapply a detached patch • 9 use errors – participants did not know to avoid exposing the patch to external heat sources • 17 use errors – participants did not know to check the patch after bathing, swimming, or showering The root cause analysis and subjective feedback for these use errors indicated that: • Participants did not know there was an IFU • Participants expected that the "patch" would stay on all day • Step 4 in the IFU contained a lot of "dense" looking text, so participants did not read it • Participants focused on numbered steps instead of bullets at top of IFU because the information at the top looked like technical information from the USPI, not patient-oriented information. The Applicant provided plans to implement risk mitigation strategies by changing the location of the IFU to make it easier to locate.	According to the URRA, these use errors identified could lead to a missed dose or unintentional exposure to a non-user, resulting in injury, poisoning, gastrointestinal disorders, nervous system disorders, and psychiatric disorders. Our assessment of the subjective feedback and root cause analyses indicated that the location and content of the IFU played a role in these use errors. While the Applicant proposed mitigation strategies, changing the IFU location will not address some of the root causes identified. For example, it will not address the root causes of the IFU containing dense text. Additionally, the Applicant did not provide data or information to show that the proposed mitigations will be effective. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant regarding validating their proposed changes by conducting another human factors validation study.
9.	For the tasks associated with **Remove patch from skin** there were: • 5 use errors – participants did not know to remove patch before applying a new patch	According to the URRA, these use errors identified could lead to overdose resulting in injury, poisoning, gastrointestinal disorders, nervous system disorders, psychiatric disorders, metabolism, and nutrition disorders.

	• 17 use errors – participants did not know to apply oil-based product or soap and water to remove glue if needed The root cause analysis and subjective feedback for these use errors indicated that participants: • Patch adhered tightly enough that it was hard to get hold on an edge to remove it • Relied on previous experience that alcohol-based products are effective at removing glue residue. • Did not know there was an IFU. The Applicant provided plans to implement risk mitigation strategies by changing the location of the IFU to make it easier to locate.	We note that the Applicant's root cause analysis is incomplete because it did not address what elements of the user interface may have contributed to these use errors. Our assessment of the subjective feedback and root cause analyses indicated that the location of the IFU and negative transfer of participants' experience with other products played a role in these use errors. While the Applicant's proposed a mitigation strategy of changing the location of the IFU, this mitigation will not address the root causes related to patch adherence. Additionally, the Applicant did not provide data or information to show that the proposed mitigations will be effective. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant regarding validating their proposed changes by conducting another human factors validation study.
10.	For the tasks associated with **Dispose of patch** there were: • 14 use errors – Participants did not fold patch in half with sticky sides together or cover the adhesive side of the patch • 30 use errors – Participants did not know to discard folded patch by flushing down toilet or placing in a trash container with a lid • 20 use errors – Participants did not know to wash hands after discarding the patch The root cause analysis and subjective feedback for these use errors indicated that participants: • Did not know there was an IFU • Saw Figure K, but did not read all associated text, and Figure K did not communicate that the lid was important. • Did not notice Step 7 because it was at the bottom of the leaflet. • Knew to clean hands but assumed either hand sanitizer or soap and water would be acceptable (i.e., they chose to use hand sanitizer instead of soap and water) • Did not notice phrase "with a lid" in IFU text.	According to the URRA, these use errors identified could lead to overdose resulting in injury, poisoning, gastrointestinal disorders, nervous system disorders, psychiatric disorders, and accidental exposure to the product. Furthermore, we note that errors associated with disposal for this amphetamine product also presents a public health concern due to risk for accidental exposure to others in the household as well as pets. Our assessment of the subjective feedback and root cause analyses indicated that the location and contents of the IFU contributed to these use errors. The Applicant proposed mitigation strategies but did not provide data or information to show that the proposed mitigations will be effective. We provide a recommendation in Table 4: Identified Issues and Recommendations for Applicant regarding validating their proposed

	The Applicant provided plans to implement risk mitigation strategies by changing the location of the IFU to make it easier to locate and changing steps in the IFU to address the use errors identified in the HF validation study.	changes by conducting another human factors validation study.
11.	For the tasks associated with **Store Patch** there were**:** • 4 use errors – Participants did not know to store at room temperature. The root cause analysis and subjective feedback for these use errors indicated that the participants did not know there was an IFU or did not notice relevant text in the IFU. The applicant did not identify any risk mitigations to address these use errors.	According to the URRA, these use errors identified could lead to overdose resulting in injury, poisoning, gastrointestinal disorders, nervous system disorders, and psychiatric disorders. We note that the Applicant's root cause analysis is incomplete because it did not address what elements of the user interface may have contributed to these use errors. Additionally, we note that in some cases the Applicant indicated that they were unable to complete a full root cause analysis due to time constraints. We identified that the IFU and Carton contain information on the required storage conditions, however the carton only contains the temperature range, not an indication that the temperature range is "room temperature". We provide a recommendation in the labeling section of this review.

4.1 LABELS AND LABELING

Tables 4 and 5 below include the identified medication error issues with the submitted labels and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 4: Identified Issues and Recommendations for Division of Psychiatry

	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information: Section 2 Dosing and Administration			
1.	The dosing statements include terminal zeroes, for example 9.0 mg/9 hours.	Use of terminal zeros can be error prone.	Remove the trailing zeros throughout this section (e.g., change 9.0 mg to 9 mg)
2.	The (b) (4) limitations to transdermal system	The instructions for use indicate other limitations to adherence that may need to be addressed in this section.	Consider adding other limitations such as use of lotions, oils, and gels to this section.

	adherence are limited (b) (4)		

Table 5: Identified Issues and Recommendations for Applicant (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Product Design			
1.	Your root cause analysis indicates that participants damaged the transdermal system when trying to remove it from the pouch because the pouch was not large enough for users to reach in and grasp the patch, and the pouch was sticking together, making it difficult to remove the transdermal system.	We note that you did not provide any risk mitigations for these use errors.	We recommend you use a human factors engineering process to update your user interface and address the use errors and use difficulties seen in your HF validation study. When the user interface has been updated, conduct another HF validation study to ensure that the user interface supports the safe and effective use of your product by the intended users and in the intended use environments.
2.	Your root cause analysis indicates that several users were not able to remove the slip liners from the patch because the slip liners were difficult to see.	We note that you did not provide any risk mitigations for these use errors.	
Instructions for Use (IFU)			
1.	Your root cause analysis indicated that participants in your HF validation study were unable to locate the IFU, or that they did not know there was an IFU.	We note that you intend to change the location of the IFU in your carton to make it easier for users to locate it, however, you did not provide any data or information to show that this proposed mitigation is effective.	We recommend you use a human factors engineering process to update your user interface and address the use errors and use difficulties seen in your HF validation study. When the user interface has been updated, conduct another HF validation study to ensure that the user interface supports the safe and effective use of your product by the intended users and in the intended use environments.
2.	Your root cause analysis indicated	We note that you proposed several changes to your user	

	that several elements of the user interface contributed to use errors with the use of your product.	interface as mitigation steps to the observed use errors, however, your proposed mitigations do not appear to address all the root causes. For example, for the use error of participants not removing the slip liner, you provided a root cause of "slip liner difficult to see" but did not provide a risk mitigation to address that particular root cause. Another example is that negative transfer was cited by participants as a contributor to use error, yet no mitigations were provided to try to overcome the negative transfer. Additionally, you did not provide any data or information to show that the proposed mitigations are effective.	
Carton Labeling and Container Label (Pouch Labeling)			
1.	The strengths for the 9 mg/9 hour and 18 mg/9-hour doses contain terminal zeroes.	Use of terminal zeros can be error prone.	Remove the terminal zero (e.g., 9.0 mg) to avoid a ten-fold misinterpretation of the dose.
2.	The product user interface can be improved.	We note that several participants in your human factors validation study did not know to remove the transdermal system after 9 hours. Additionally, we note that the statement (b) (4) may be interpreted as a suggestion.	We recommend you make the instruction to remove the patch after nine hours more prominent and more directive in nature. For example, consider a statement similar to "Wear patch for no more than 9 hours".
3.	The terminology, "Dosage and Administration: See package insert" is not consistent with the Prescribing Information (PI).	We generally expect terminology to be consistent throughout labels and labeling to minimize confusion.	Revise the statement, "Dosage and Administration: See package insert" to "Recommended Dosage: See prescribing information."
4.	As currently presented, the	To minimize confusion and reduce the risk for deteriorated drug	FDA recommends that the human-readable expiration date on the drug

	format for the expiration date is not defined.	medication errors, identify the format you intend to use. We note that confusion regarding the expiration date was also seen in the human factors validation study.	package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.
5.	The principal display panel (PDP) does not contain the statement "For Transdermal Use Only"	The PDP should contain the route of administration if the product is not for oral use, per 21 CFR 201.100(b)(3) to minimize the risk of wrong route of administration errors.	Add the statement, "For Transdermal Use Only" to the principal display panel.
6.	The back panel contains the statement (b) (4) which can be improved.	We are concerned (b) (4)	Replace this statement with "Fold used patch and discard according to instructions for use".
7.	The storage temperature statement can be improved.	We note that several participants in your HF validation study did not know to store the product at room temperature, and that the storage temperature information on the pouch and carton labeling does not state "room temperature".	We recommend adding the statement "Store at room temperature" to the labeling.

5 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors with critical tasks that may result in harm. This is particularly concerning due to the potential for significant adverse events associated with overdose of the product, or inadvertent exposure/poisoning if the transdermal system does not stay adhered due to improper application. The Applicant proposed several revisions to the product user interface to mitigate the risk for use errors, however, the proposed risk mitigations do not address all of the root causes for the use errors identified in the HF validation study. We note that in several cases the Applicant focused only on placement of the IFU without consideration of the need for additional mitigation strategies. Additionally, the Applicant did not provide data or information (for example, from another HF validation study) to demonstrate that the proposed risk mitigations will be successful. Furthermore, our evaluation of the proposed user interface, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 for the Division and Table 5 for the Applicant. We ask that the Division convey Table 5 in its entirety to the Applicant. In addition, we provide our recommendations for the Applicant related to the HF validation study in section 4.1 below. We recommend that the Applicant consider additional design modifications, implement our recommendations, and conduct another HF validation study to demonstrate that the product is designed for safe and effective use by the intended users, for the intended use, and in the intended environment.

5.1 RECOMMENDATIONS FOR NOVEN PHARMACEUTICALS, INC.

The results of the human factors (HF) validation study demonstrated several use errors with critical tasks that may result in harm to the patient. This is particularly concerning due to the potential for significant adverse events associated with overdose of the product, or inadvertent exposure/poisoning if the transdermal system does not stay adhered due to improper application. We note that in several cases you focused only on placement of the IFU without consideration of the need for additional mitigation strategies. However, while you proposed changes to the user interface to address some of the use errors identified, the proposed risk mitigations do not address all of the root causes for the use errors identified in the HF validation study. Additionally, you did not provide data or information to show that the proposed risk mitigation strategies will be effective. Our review indicates that additional risk mitigations are necessary, and therefore, you should further analyze the root causes and residual risks seen your HF validation study and redesign your user interface accordingly. Another HF validation study should be conducted to demonstrate that the product is designed for safe and effective use by the intended users, for the intended use, and in the intended environment.

In addition, our evaluation of the proposed user interface, proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in table 5 and we recommend that you implement these recommendations prior to conducting another HF validation study.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Xelstrym that Noven Pharmaceuticals, Inc. submitted on 02/22/2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Central Nervous System Stimulant
Active Ingredient (Drug or Biologic)	dextroamphetamine
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Route of Administration	Transdermal
Dosage Form	Transdermal system
Strength	5, 10, 15, and 20 mg per transdermal system
Dose and Frequency	Recommended starting dose is 5 mg, can be titrated to effect. The maximum daily dose is (b) (4) mg/day.
How Supplied	Carton containing 30 individually packaged transdermal systems
Storage	Room temperature (68 to 77 F)
Intended Users	Pediatric to adult users (6 to over 18 years of age)
Intended Use Environment	Non-healthcare environments

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On 08/18/2021, we searched the L: drive and AIMS using the terms, ”dextroamphetamine” to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[1], and we identified that the Applicant did not implement all of our recommendations.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

HF Study	\\CDSESUB1\evsprod\nda215401\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\n25-017b\n25-017b.pdf
UE Report	\\CDSESUB1\evsprod\nda215401\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\hfe-ue-rpt\hfe-ue-rpt.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Xelstrym labels and labeling submitted by Noven Pharmaceuticals, Inc on 02/22/2021.

Carton 4.5 mg	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\carton-4-5mg-9hrs.pdf
Carton 9 mg	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\carton-9mg-9hrs.pdf
Carton 13.5 mg	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\carton-13-5-9hrs.pdf
Carton 18 mg	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\carton-18mg-9hrs.pdf
Pouch 4.5 mg	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\pouch-4-5mg-9hrs.pdf
Pouch 9 mg	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\pouch-9mg-9hrs.pdf

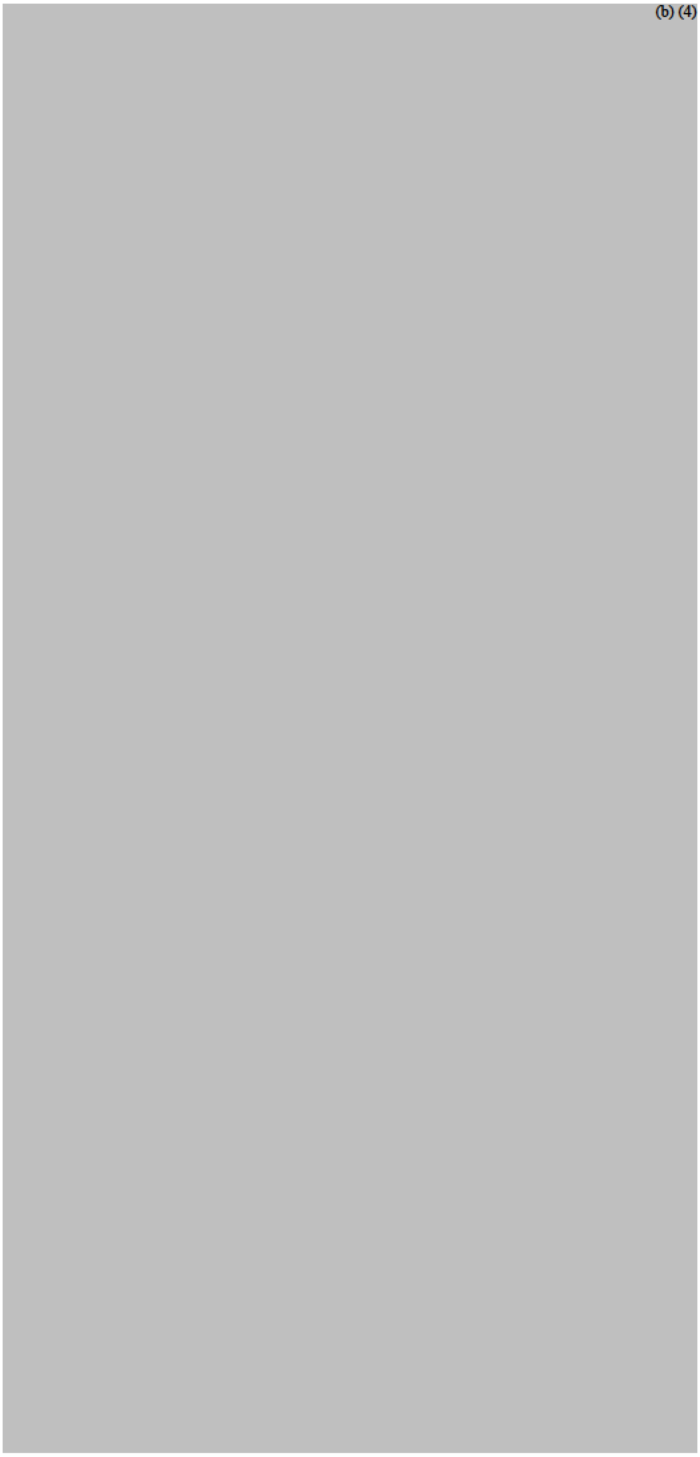
[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Pouch 13.5 mg	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\pouch-13-5mg-9hrs.pdf
Pouch 18 mg	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\pouch-18mg-9hrs.pdf
Prescribing Information	\\CDSESUB1\evsprod\nda215401\0001\m1\us\114-label\1141-draft-label\proposed.docx

E.2 Label and Labeling Images

4.5mg External Carton

(b) (4)



7 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JASON A FLINT
09/01/2021 11:13:52 AM

OLUWAMUREWA OGUNTIMEIN
09/01/2021 11:20:16 AM

IRENE Z CHAN
09/01/2021 01:30:31 PM