CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215401Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215401
Assessment 1

Drug Product Name	Dextroamphetamine Transdermal System (d-ATS)
Dosage Form	Transdermal System
Strength	5, 10, 15, 20 mg
Route of Administration	Transdermal System
Rx/OTC Dispensed	Rx
Applicant	Noven Pharmaceuticals, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	22 Feb 21	All, original submission
Supporting document 4; eCTD 0004	10 May 21	Drug product
Supporting document 6; eCTD 0006	17 May 21	Drug product, method verification materials
Supporting document 8; eCTD 0008	25 May 21	Drug product, method verification materials
Supporting document 9; eCTD 0009	11 Jun 21	Drug product, biopharm
Supporting document 10; eCTD 0010	2 Jul 21	Drug product
Supporting document 15; eCTD 0015	19 Jul 21	Drug substance
Supporting document 19; eCTD 0019	5 Aug 21	Drug product, process
Supporting document 21; eCTD 0021	18 Aug 21	Biopharm
Supporting document 28; eCTD 0028	30 Sep 21	Process

Reference ID: 4897953

Supporting document 29; eCTD 0029	1 Oct 21	Drug product
Supporting document 30; eCTD 0030	8 Oct 21	Drug product, biopharm
Supporting document 31; eCTD 0031	12 Oct 21	Drug product
Supporting document 32; eCTD 0032	14 Oct 21	Drug substance
Supporting document 33; eCTD 0033	27 Oct 21	Drug product
Supporting document 34; eCTD 0034	29 Oct 21	Drug product
Supporting document 35; eCTD 0035	3 Nov 21	Drug product
Supporting document 38; eCTD 0038	10 Nov 21	Process
Supporting document 39; eCTD 0039	12 Nov 21	Drug product
Supporting document 40; eCTD 0040	19 Nov 21	Drug product
Supporting document 41; eCTD 0041	23 Nov 21	Drug product
Supporting document 43; eCTD 0043	1 Dec 21	Drug product - additional data provided to supplement the response provided on 8 Oct 21; the original response dated 8 Oct 21 was sufficient and this additional data will not be reviewed.

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Katie Duncan	Donna Christner
Drug Product	Andrei Ponta	Julia Pinto
Manufacturing	Mesfin Abdi	Vaikunth Prabhu
Microbiology	N/A	N/A
Biopharmaceutics	Kaushalkumar Dave	Tapash Ghosh
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	Anna Wokovich and Bethel Asmelash	Cynthia Sommers
Environmental	Andrei Ponta	Julia Pinto

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	1	5 Oct 21	Reviewed by Katie Duncan
	IV			4		
	IV			4		
	III			4		
	III			4		

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

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
073862	IND	
021303	NDA	RLD - Adderall XR
021977	NDA	RLD - Vyvanse

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this application.

A shelf-life of 18 months is acceptable when stored at controlled room temperature 20°–25°C (68°–77° F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

d-ATS contains approximately 1 mg/cm^2 dextroamphetamine base that delivers d-amphetamine upon application to intact skin. Each d-ATS system 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.
Noven 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 d-ATS for a 9-hr wear time within 24 hrs. The patches are compositionally equivalent, and the difference in dose is effected through a proportional increase in the surface area (cm^2) of the patches.

A shelf-life of 18 months is acceptable when stored at controlled room temperature 20°–25°C (68°–77° F).

Proposed Indication(s) including Intended Patient Population	treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older
Duration of Treatment	chronic
Maximum Daily Dose	20 mg

Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The CMC information for the dextroamphetamine base drug substance is cross-referenced to DMF (b) (4) DMF (b) (4) was reviewed by Katharine Duncan, Ph.D. on 05-Oct-2021 (Panorama) in support of this NDA and found adequate. The applicant provides a brief description of the general properties of the drug substance and organic impurities. The drug substance specification is adequate to ensure the quality, strength, and purity of the drug substance. Adequate descriptions of the non-compendial analytical methods are provided and sufficient validation data are provided in the NDA. The drug substance manufacturer and applicant have set a retest period of (b) (4) months when stored at (b) (4) °C, which may be granted. The NDA is recommended for approval from the perspective of drug substance quality.

Drug Product: Adequate

The drug product is a rounded rectangle dextroamphetamine drug-in-adhesive transdermal system available in four sizes (4.76 cm^2, 9.52 cm^2, 14.29 cm^2, and 19.05 cm^2) corresponding to four dose proportional strengths: 4.5 mg/9 hours, 9.0 mg/9 hours, 13.5 mg/9 hours, and 18.0 mg/9 hours. Each system is comprised of three layers: (1) a translucent flexible backing film; (2) an adhesive formulation containing amphetamine; and (3) an oversized release liner. Two protective slip liners are packaged on each side of the system. Note that only one system is to be used per day (24 hours).

The drug product contains the drug substance and the following inactive ingredients and components: acrylic adhesive (b) (4) (b) (4) polyester release liner, PET/polyurethane backing, and (b) (4) Green Ink (b) (4) are present in the drug product at lower levels then the currently approved transdermal drug products. This is acceptable.

The Applicant has provided release results for eight registration batches, all of which met the proposed specifications.

The primary packaging for Dextroamphetamine Transdermal System is a (b) (4) pouch. There are two different pouch sizes that are used for the four strengths. Pouches are placed into cartons. Each carton contains 30 pouches containing one transdermal system.

Stability studies are being conducted per ICH guidelines on multiple drug product batches (three 4.5 mg/9 hours batches, one 9.0 mg/9 hours batch, one 13.5 mg/9 hours, and seven 18 mg/9 hours batches). These batches are representative of the proposed commercial product in the commercial container closure system. The stability studies are currently

ongoing; however, 20 months of long-term storage conditions (25°C/60% RH) results are available as well as 6 months of accelerated storage conditions (40°C/75% RH) results. Based on current data, the Applicant is requesting and has been granted an 18–month shelf-life for the proposed drug product.

The Applicant has also developed a placebo (9.52 cm^2), equivalent to the lowest 9 mg / 9-hour strength in size, for use as demonstration material. The excipients, manufacturing process, and packaging material are the same as the proposed commercial drug product. (b) (4) The Applicant has provided release results for two placebo batches, both of which met all proposed specifications including confirmation of the absence of the drug substance. Stability results support a 24-month expiry for the placebo.

The sponsor submitted two comparability protocols in the NDA. (b) (4)

After discussion, the sponsor has withdrawn both protocols, the approval recommendation for this NDA does not apply to either of these protocols.

Quality In Vivo Adhesion Assessment

Xelstrym (dextroamphetamine) Transdermal System is recommended for approval from the in vivo adhesion assessment perspective. The results from inpatient studies N25-010, N25-013 (Day 2 data) support the probability that a (dextroamphetamine) transdermal system maintains ≥75% surface area adhesion during the entire wear period (i.e. a lower confidence limit ≥0.80). Further the relatively low failure (<75% surface area adhered) rate observed in the outpatient setting (Day 1 of N25-013) further provides a robust demonstration of adhesion performance for 9 hours of wear in the real world setting.

Labeling: Adequate

Manufacturing: Adequate

The manufacturing process for Dextroamphetamine Transdermal System 4.5 mg, 9.0 mg, 13.5 mg, 18.0 mg/unit consists of the following (b) (4)

The drug product, Dextroamphetamine transdermal pouch, is designed as a three-layer product: a polyester/ polyurethane backing layer, drug-in-adhesive matrix containing dextroamphetamine base, (b) (4) acrylic, (b) (4) and a (b) (4) release liner that is removed prior to system application.
Based on submission contents, process review recommendation is adequate.

DS manufacturer, (b) (4) is acceptable based on compliance history, acceptable profile codes and experience in the proposed responsibilities.

DP manufacturer, Noven Pharmaceuticals, Inc, has acceptable profile codes and experience in the proposed responsibilities. Even though the facility appears acceptable for drug product manufacturing responsibilities to support this NDA, due to previous compliance history and significant number of FARs/recalls related to profile code since previous inspection, it was recommended to conduct PAI to assess the firm's recall status, and identification and resolution of root causes associated with quality defects. PAI inspection was conducted between 11/01/2021 – 11/17/2021 and the facility is approved for the proposed responsibilities outlined in the application on 11/19/2021 by ORA.

Biopharmaceutics: Adequate

To support the 505(b)(2) NDA, the Applicant conducted PK bridging studies [relative bioavailability (BA) studies] between the proposed TDS and the listed drug product(s), Vyvanse (NDA 021977) and Adderall XR (NDA 021303). Under clinical study N25-005, the Applicant studied amphetamine exposure (Cmax and AUC) across the range of proposed commercial dosage strengths (5 to 20 mg loaded dose) and claimed dose proportionality in exposure across these strengths.

IVRT Method: The Applicant conducted various studies and provided justifications for selection of the suitable IVRT testing conditions. The proposed IVRT method for the proposed drug product is as follows: 500 mL (4.5 mg/9 Hrs and 9 mg/9 Hrs) or 900 mL (13.5 mg/9 Hrs and 18 mg/9 Hrs) of 0.05 M Potassium Phosphate Buffer at 32°C at a pH of 6.8 using USP Apparatus 6 (cylinder) at 50 rpm. The provided IVRT data show that the proposed IVRT method is discriminating towards (b) (4) critical manufacturing variables for the proposed TDS. Based on the provided information/data and justifications, as well as the demonstrated discriminating ability, the proposed IVRT method is deemed acceptable for quality control testing of the proposed drug product.

Formulation Bridging: In-vitro or in-vivo bridging study is not needed for the proposed product, as there were no changes made in (i) composition for the clinical batches, exhibit batches, and proposed commercial drug product, (ii) product manufacturing site, and (iii) manufacturing process in the scale-up.

Biowaiver: There are four strengths of Dextroamphetamine Transdermal System as indicated in Table 1. These strengths are cut from the same laminate and vary only in their area, and human PK study was conducted on each of the strengths. Therefore, a biowaiver request is neither submitted nor required in the current submission.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/ equipments • Site	L	Controlled by specification	Acceptable	
In Vitro Release	-Formulation -Stability -Salt/Base conversion -Migration	L	Controlled by specification	Acceptable	
Crystals	-Formulation, -Salt/Base conversion -solubility in matrix -Stability -Excipient migration	L	Controlled by specification	Acceptable	

Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/ equipments • Site	L	Controlled by specification	Acceptable	
Adhesion (contact adhesive, border adhesive)	-Formulation -Raw materials -Process -Stability	L	Controlled by specification	Acceptable	
Release Liner Removal (contact adhesive, border adhesive)	-Formulation -Raw materials -Process -Stability	L	Controlled by specification	Acceptable	
Probe Tack (contact adhesive, border adhesive)	-Formulation -Raw materials -Process -Stability	L	Controlled by specification	Acceptable	
Dynamic Shear	-Formulation -Raw materials -Process -Stability	L	Controlled by specification	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/ equipments • Site	L	Controlled by specification	Acceptable	
Leachables	• Formulation • Raw materials • Container closure • Process parameters • Scale/ equipments • Site	M	Controlled by specification	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

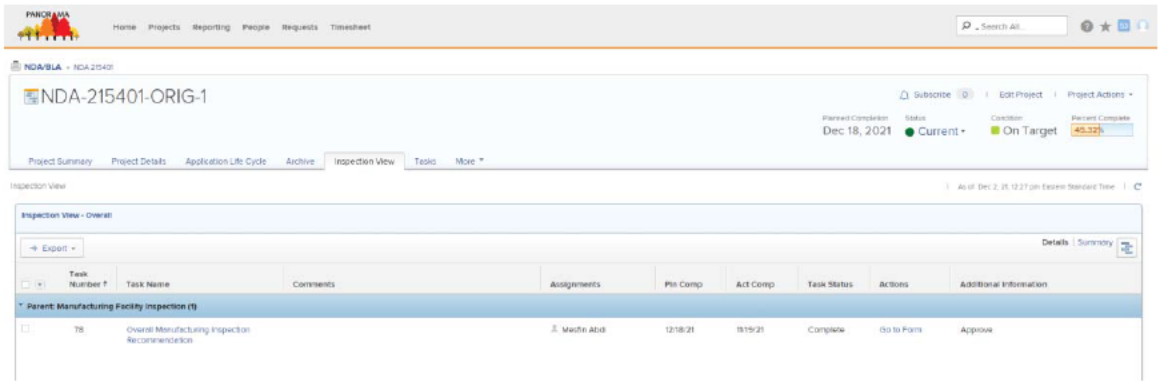
5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies *(Specify discipline, such as Environmental)*

Screenshot from Panorama showing approval of facilities taken on 2 Dec 21



Valerie Amspacher
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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

(b) (4)

[redacted]

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	XELSTRYMTM (dextroamphetamine) transdermal system
Dosage form, route of administration	Transdermal system
Controlled drug substance symbol	Present
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Transdermal System: 4.5 mg/9 hours, 9.0 mg/9 hours, 13.5 mg/9 hours, 18.0 mg/9 hours

Reference ID: 4897953

Is the information accurate? ☒ Yes ☐ No.

2. ***Section 2 Dosage and Administration***

(b) (4)

[redacted]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	XELSTRYM can be applied to one of the following application sites: hip, upper arm, chest, upper back, or flank. Instruct patients to select a different application site from the previous application site to reduce dermal reactions

Reference ID: 4897953

Is the information accurate? ☒ Yes ☐ No

3. *Section 3 Dosage Forms and Strengths*

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Transdermal System
Strengths: in metric system	Transdermal System: 4.5 mg/9 hours, 9.0 mg/9 hours, 13.5 mg/9 hours, 18.0 mg/9 hours
Active moiety expression of strength with equivalence statement	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not present

Is the information accurate? ☒ Yes ☐ No

Revisions identified (e.g., (b) (4) replaced with bullets, description of the TDS should be included) and will be communicated to the Applicant as part of labeling negotiations. The PI is adequate assuming Applicant accepts edits.

4. *Section 11 Description*

(b) (4)

Reference ID: 4897953

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	XELSTRYMTM (dextroamphetamine) transdermal system
Dosage form and route of administration	Transdermal System: 4.5 mg/9 hours, 9.0 mg/9 hours, 13.5 mg/9 hours, 18.0 mg/9 hours
Active moiety expression of strength with equivalence statement (if applicable)	Not Applicable
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Present
Statement of being sterile (if applicable)	Not Applicable
Pharmacological/ therapeutic class	Not Present
Chemical name, structural formula, molecular weight	Present

Reference ID: 4897953

If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Not Applicable

Is the information accurate? ☒ Yes ☐ No

Revisions identified and will be communicated to the Applicant as part of labeling negotiations. The PI is adequate assuming Applicant accepts edits.

The Applicant will be asked to include the pharmacological class, include a table with TDS characteristics, and remove everything below the TDS component heading.

5. ***Section 16 How Supplied/Storage and Handling***

(b) (4)

Reference ID: 4897953

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Transdermal System: 4.5 mg/9 hours, 9.0 mg/9 hours, 13.5 mg/9 hours, 18.0 mg/9 hours
Available units (e.g., bottles of 100 tablets)	Cartons containing 30 systems
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A translucent product with a printed backing on one side and a release liner on the other packaged in an individual pouch
Special handling (e.g., protect from light)	Protect from light
Storage conditions	Controlled Room Temperature (b) (4)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Noven Pharmaceuticals

Is the information accurate? ☒ Yes ☐ No

Revisions (replacement (b) (4) with bullet format, include description of the systems, include protect from light) identified and will be communicated to the Applicant as part of labeling negotiations. The PI is adequate assuming Applicant accepts edits.

Reviewer's Assessment of Package Insert: ***Inadequate, deficiencies communicated to OND PM***

Prescribing Information complies with regulatory requirements from a CMC perspective; however, some information is absent. Revisions identified and will be communicated to the Applicant as part of labeling negotiations.

II. Labels:

1. ***Container Labels***

(b) (4)

Reference ID: 4897953

2. *Carton Label*

(b) (4)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Present	Present
Dosage strength	Present	Present
Net contents	Present	Present
"Rx only" displayed prominently on the main panel	Present	Present
NDC number (21 CFR 207.35(b)(3)(i))	Present	Present
Lot number and expiration date (21 CFR 201.17)	Present	Present
Storage conditions	Present	Present
Bar code (21CFR 201.25)	Present	Present
Name of manufacturer/distributor	Present	Present
And others if space is available	NA	NA

Reviewer's Assessment of Labels: ***Adequate***

The carton/container label complies with regulatory requirements from a CMC perspective. This is acceptable.

Overall Assessment and Recommendation: Adequate pending corrections during labeling negotiations.

Reference ID: 4897953

Andrei Ponta

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Julia Pinto

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BIOPHARMACEUTICS

Application No: NDA 215401; 505(b)(2)
Drug Product Name/Strengths: Xelstrym™ (Dextroamphetamine) Transdermal System; 4.5 mg/9 hours, 9.0 mg/9 hours, 13.5 mg/9 hours and 18.0 mg/9 hours
Route of Administration: Transdermal
Indication: Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older
Applicant Name: Noven Pharmaceuticals, Inc.
Date of Submission: 02/22/2022 (Original)

Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Tapash Ghosh, PhD

REVIEW SUMMARY

Submission: The Applicant submitted this NDA for Xelstrym™ (Dextroamphetamine) Transdermal System (TDS); 4.5 mg, 9.0 mg, 13.5 mg, 18.0 mg/unit, under the 505(b)(2) pathway with its reliance on the prior safety and efficacy findings of the Agency for the Listed Drugs (LD) ADDERALL XR (approved under NDA 021303) and VYVANSE (approved under NDA 021977). To support the 505(b)(2) NDA, the Applicant conducted PK bridging studies [relative bioavailability (BA) studies] between the proposed TDS and the listed drug product(s), Vyvanse (NDA 021977) and Adderall XR (NDA 021303). Under clinical study N25-005, the Applicant studied amphetamine exposure (Cmax and AUC) across the range of proposed commercial dosage strengths (5 to 20 mg loaded dose) and claimed dose proportionality in exposure across these strengths. A biowaiver request is neither submitted nor required in the current submission.

Review Objective: This Biopharmaceutics review is focused on the evaluation of (1) the proposed in vitro drug release testing (IVRT) method and acceptance criteria, and (2) formulation bridging.

IVRT Method: The Applicant conducted various studies and provided justifications for selection of the suitable IVRT testing conditions. The proposed IVRT method for the proposed drug product is as follows: *500 mL (4.5 mg/9 Hrs and 9 mg/9 Hrs) or 900 mL (13.5 mg/9 Hrs and 18 mg/9 Hrs) of 0.05 M Potassium Phosphate Buffer at 32°C at a pH of 6.8 using USP Apparatus 6 (cylinder) at 50 rpm*. The provided IVRT data show that the proposed IVRT method is discriminating towards (b) (4) (b) (4) critical manufacturing variables for the proposed TDS. Based on the provided information/data and justifications, as well as the demonstrated discriminating ability, the proposed IVRT method is deemed acceptable for quality control testing of the proposed drug product.

IVRT Acceptance Criteria: Based on the IVRT data for the clinical and registration batches collected for all strengths at the time of batch release and the additional IVRT data collected at the current (24 months) stability testing time-point, the FDA recommended same IVRT acceptance criteria for the all strengths of the proposed drug product.

Reference ID: 4897953

The final and approved IVRT method and agreed-upon IVRT acceptance criteria for the quality control testing of the proposed drug product at batch release and during stability testing are as follows:

FDA approved IVRT method and acceptance criteria for the proposed drug product

Apparatus	USP Apparatus 6 (Cylinder)
Paddle Speed	50 rpm
Volume	500 mL (4.5 mg/9 Hrs and 9 mg/9 Hrs) 900 mL (13.5 mg/9 Hrs and 18 mg/9 Hrs)
Medium	0.05 M Potassium Phosphate Buffer at a pH of 6.8
Temperature	32.0 ± 0.5°C
Acceptance Criteria	0.25 Hour: (b) (4)% 1 Hour: (b) (4)% 6 Hours: NLT (b) (4)%

Formulation Bridging: In-vitro or in-vivo bridging study is not needed for the proposed product, as there were no changes made in (i) composition for the clinical batches, exhibit batches, and proposed commercial drug product, (ii) product manufacturing site, and (iii) manufacturing process in the scale-up.

Biowaiver: There are four strengths of Dextroamphetamine Transdermal System as indicated in Table 1. These strengths are cut from the same laminate and vary only in their area, and human PK study was conducted on each of the strengths. Therefore, a biowaiver request is neither submitted nor required in the current submission.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 215401 for Xelstrym™ (Dextroamphetamine) Transdermal System; 4.5 mg, 9.0 mg, 13.5 mg, 18.0 mg/unit, is adequate and recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	02/22/2021	Original NDA Submission
0009	06/11/2021	Quality/Response to Information Request
0021	08/18/2020	Quality/Response to Information Request
0030	10/08/2021	Quality/Response to Information Request
0032	10/14/2021	Quality/Response to Information Request

BACKGROUND

Noven's Dextroamphetamine Transdermal System (referred by the Applicant as d-ATS or ATS) is developed for daily application as a treatment for attention deficit hyperactivity disorder (ADHD). The proposed drug product is a drug-in-adhesive matrix type system. The drug product is a rounded rectangle dextroamphetamine drug-in-adhesive transdermal patch available in four sizes (4.76 cm2, 9.52 cm2, 14.29 cm2, and 19.05 cm2). Dextroamphetamine Transdermal System (d-ATS) contains approximately 1 mg/cm2 dextroamphetamine base in an adhesive that delivers drug upon application to intact skin. Each system is comprised of 3 layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are: (1) A translucent flexible backing film; (2) an adhesive formulation containing amphetamine; and (3) an oversized release liner, which is attached to the adhesive surface and must be removed before the patch can be used. Two additional protective slip liners are packaged on each side of the patch and are also disposed-off prior to application. The patch has target coat weight of (b) (4) mg/cm2. There are four strengths of Dextroamphetamine Transdermal System as indicated in Table 1. These strengths are cut from the same laminate and vary only in their area.

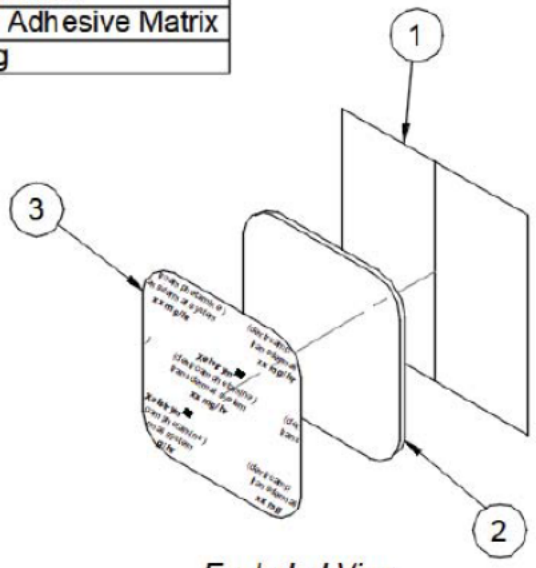
Table 1: Dosage Strengths of Dextroamphetamine Transdermal System

Dextroamphetamine Content per Patch (mg)	Dosage Strength (mg/9 hrs)[a]	Patch Size (cm^2)
5.0	4.5	4.76
10.0	9.0	9.52
15.0	13.5	14.29
20.0	18.0	19.05

Reference ID: 4897953

Figure 1: Diagram of Dextroamphetamine Transdermal System

TDS	
Item No.	Description
1	Release Liner
2	Drug in Adhesive Matrix
3	Backing



Exploded View

The composition of the four strengths is proportional. The unit composition of each strength is presented in Table 2.

Table 2: Unit Composition of Dextroamphetamine Transdermal Systems

Ingredient	Reference to Quality Standard	Function	Theoretical Weight (mg) per Patch			
			4.76 cm^2	9.52 cm^2	14.29 cm^2	19.05 cm^2
Dextroamphetamine Base	In-house standard	Active	5.0	10.0	15.0	20.0
Acrylic Adhesive (b) (4)	In-house standard	Adhesive	(b) (4)			
Acrylic Adhesive (b) (4)	In-house standard	Adhesive				
Polyester Release Liner	In-house standard	Release liner				
PET/ Polyurethane Backing	In-house standard	Patch backing				
(b) (4) Green Ink (b) (4)	N/A	(b) (4)				
(b) (4)	USP					

Reference ID: 4897953

To support the 505(b)(2) NDA, the Applicant conducted PK bridging studies [relative bioavailability (BA) studies] between the proposed TDS and the listed drug product(s), Vyvanse (NDA 021977) and Adderall XR (NDA 021303) under studies N25-002, N25-012, and N25-004. Study N25-002 compared the amphetamine PK between 2 formulations of d-ATS in healthy adults. Study N25-012 assessed the comparative bioavailability of d-ATS against both Vyvanse and Adderall XR in healthy adults, and Study N25-004 assessed the comparative bioavailability of d-ATS against Adderall XR in children, 6 to 12 years of age, with ADHD. Under clinical study N25-005, the Applicant studied amphetamine exposure (Cmax and AUC) across the range of proposed commercial dosage strengths (5 to 20 mg loaded dose) and claimed dose proportionality in exposure across these strengths. A biowaiver request is neither submitted nor required in the current submission.

The Applicant stated that the composition of the drug product tested in clinical studies is same as that of the to-be-marketed drug product. There are no other changes (such as process or manufacturing related) between the clinical and to-be-marketed drug products. Therefore, a formulation bridging is not required.

The Biopharmaceutics review is focused on the evaluation of the proposed in vitro drug release testing (IVRT) method and acceptance criteria.

The proposed IVRT method and acceptance criteria are as follows:

Table 3: IVRT method and acceptance criteria originally proposed by the Applicant

Apparatus	USP Apparatus 6 (Cylinder)
Paddle Speed	50 rpm
Volume	500 mL (4.5 mg/9 Hrs and 9 mg/9 Hrs) 900 mL (13.5 mg/9 Hrs and 18 mg/9 Hrs)
Medium	0.05 M Potassium Phosphate Buffer at a pH of 6.8
Temperature	32.0 ± 0.5°C
Acceptance Criteria	0.25 Hour: (b) (4)% 1 Hour: (b) (4)% 6 Hours: NLT (b) (4)%

SOLUBILITY OF DEXTROAMPHETAMINE

In the original submission, the Applicant did not provide drug substance solubility data across the physiological pH range. The Applicant provided these data on 10/14/2021, in response to an IR. The solubility of dextroamphetamine base across the physiological pH range is as follows:

Buffer pH	Avg Solubility (mg/mL)	Avg Solubility (w/w)
1.2	21.90	45
4.5	21.83	45
6.8	22.09	44

Reference ID: 4897953

The provided solubility data indicate that dextroamphetamine is highly soluble across the pH range of 1.2-6.8.

IVRT METHOD DEVELOPMENT

(b) (4)

[redacted]

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Discriminating ability of the IVRT method

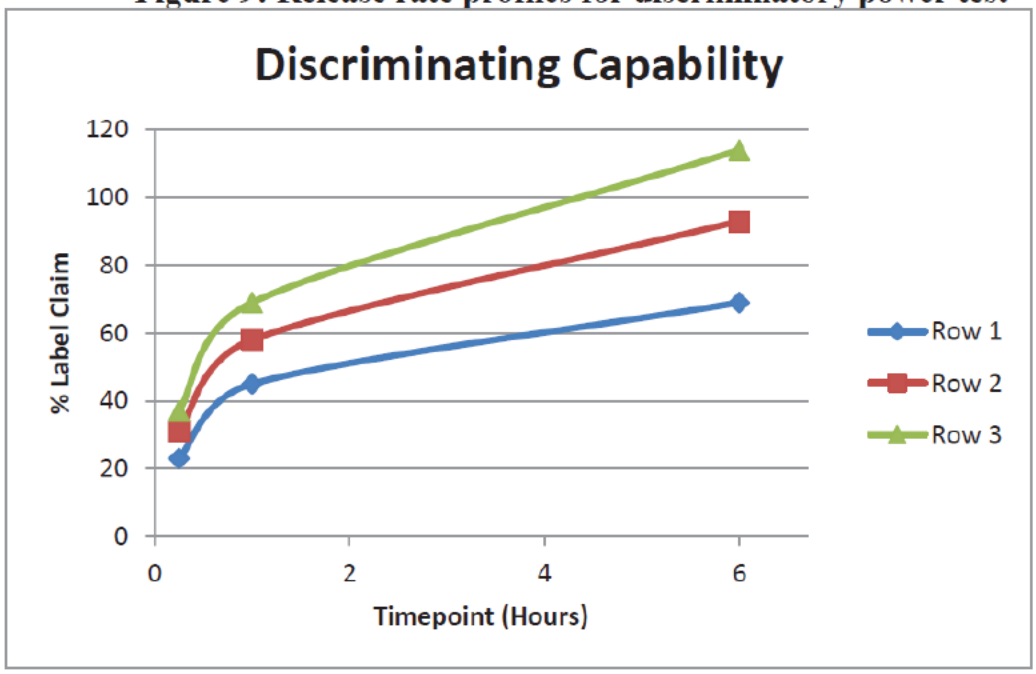
The discriminating ability of the proposed IVRT method was evaluated by obtaining drug release profiles of samples intentionally manufactured with meaningful variations for the most critical manufacturing variable. For d-Amphetamine Transdermal system (d-ATS), (b) (4) is the manufacturing variable that is critical to the quality of the product and was varied. Pilot scale lots of d-Amphetamine transdermal systems were produced (b) (4) Sample description is detailed in table 6.

Table 6: Sample description for discriminatory power test

(b) (4)	

The drug release profiles shown in figure 9 show the drug release profiles. Samples prepared (b) (4) (b) (4) (row 2) serve as the control of the product. The release profile of the control was compared to the other two manipulated conditions and the similarity factor (*f2*) and dissimilarity factor (*f1*) were calculated for both profiles. Table 7 shows the results obtained for the comparison of the release profiles generated from the control (b) (4) and (b) (4) samples. Table 8 shows the results obtained for the comparison of the release profiles generated from the control (b) (4) and (b) (4) samples. In both cases, the *f*1 values are more than 15 and the *f*2 values are less than 50 which indicate dissimilarity between the profiles.

Figure 9: Release rate profiles for discriminatory power test



Reference ID: 4897953

Table 7: Dissolution Profile Comparison row 1 [redacted] versus row 2 [redacted]

	Time Point (hours)		
	0.25	**1**	**6**
row 2 [redacted]	31	58	93
row 1 [redacted]	23	45	69
(R-T)^2	64	169	576
R-T abs	8	13	24
f1	33		
f2	39		

Table 8: Dissolution Profile Comparison row 2 [redacted] versus row 3 [redacted]

	Time Point (hours)		
	0.25	**1**	**6**
row 2 [redacted]	31	58	93
row 3 [redacted]	37	69	114
(R-T)^2	36	121	441
R-T abs	6	11	21
f1	17		
f2	42		

In the original submission, the Applicant had provided limited data for discriminating ability of the proposed IVRT method. Via an IR, the Applicant was recommended to provide additional data to support/demonstrate discriminating ability of the proposed IVRT method. The Applicant provided additional data on 06/11/2021 where [redacted] was tested.

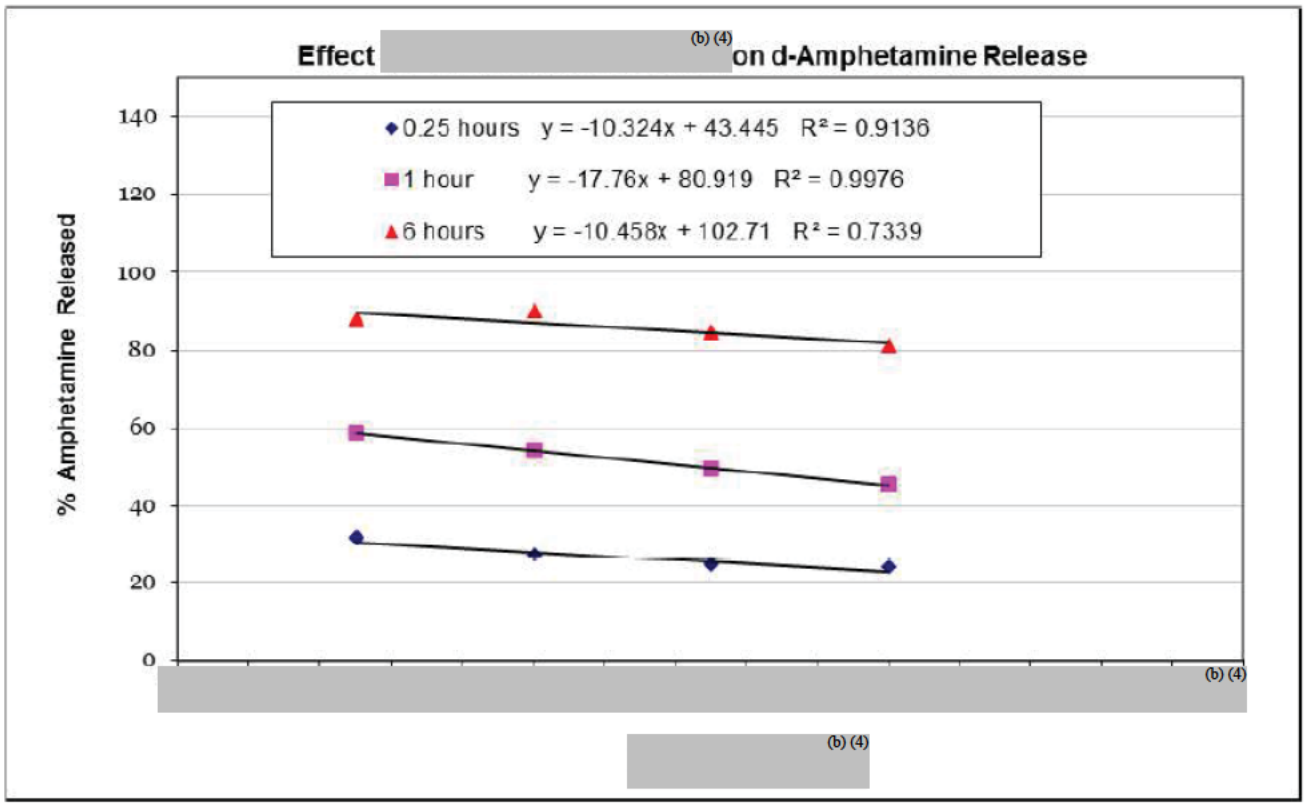
[redacted]

The [redacted] has been characterized in terms of the response of IVRT. The current proposed [redacted] specification [redacted] The IVRT method was used to test units from each lot for IVRT and the time points were taken at 0.25 hour, 1 hour, and 6 hours. The average data are summarized in Table 9 and Figure 10 for evaluating the relationship between the [redacted] and release rate at 0.25-hour, 1-hour, and 6-hour time points.

Table 9. IVRT results for varying [redacted]

Finished Product Lot Number	RDN029-7-1P9.52 (C)	RDN029-7-1P9.52 (D)	RDN029-7-1P9.52 (B)	RDN029-7-1P9.52 (A)
[redacted]				
0.25-hour Average Release Rate (%)	31.4	27.1	24.4	23.7
1-hour Average Release Rate (%)	58.7	54.5	49.4	45.6
6-hour Average Release Rate (%)	87.8	89.8	84.4	80.8

Figure 10. [redacted] versus IVRT



The provided data show no significant difference in release profiles between the studied groups. However, the provided data show a trend/correlation between the [redacted] and drug release rate where the rate of drug release decreases with increasing [redacted] The provide data show that the proposed IVRT method has the potential to exhibit discriminating ability [redacted]

The design of the proposed drug product is relatively simple where there are only three layers in the system and the drug is dispersed in the adhesive layer. Due to the simplicity of the design of the TDS, there are limited variables that can be altered to test the discriminating ability of the proposed IVRT method. The Applicant has adequately demonstrated discriminating ability of the proposed IVRT

method toward relevant critical attributes/variables. Based on the provided data, the proposed IVRT method is deemed adequate for QC testing of the proposed drug product.

IVRT Acceptance Criteria

IVRT acceptance criteria are set based on data from clinical and registration batches. Full-profile of IVRT data (n=12) collected at the time of batch release for (pivotal) clinical and registration batches could not be located in the original submission. Therefore, the Applicant was recommended to provide these data (individual, mean and % RSD) in tabular format (Excel or .xpt) and in graphical presentation. On 06/11/2021, the Applicant provided IVRT data for (pivotal) clinical and registration batches collected only at 15 minutes (0.25 hours), 60 minutes (1 hour) and 360 minutes (6 hours). The Applicant was recommended to provide full profile data for these batches for the time-points of 5, 10, 15, 30, 45, 60, 120, 180, 240, 300 and 360 minutes. The Applicant was informed that if the data for these time-points were not collected at the time of batch release, it should collect these full-profile data at the current stability testing time-period and submit the requested data (individual, mean and % RSD) in tabular format (Excel or .xpt) and in graphical presentation.

On 08/18/2021, the Applicant stated that full IVRT profile (n=12), at the requested sampling times was not collected at the time of batch release. The Applicant newly collected data from registration batches at 24-months time-point and provided these data (Appendix 1). The Applicant stated that the clinical batches were beyond expiry and therefore the data were not collected. Upon reviewing the provided IVRT data, this Reviewer determined that there are no trends during stability testing period and the provided IVRT data are adequate to setup IVRT acceptance criteria. Based on the provided data (including the data from registration lots[1] as shown in Tables 2-3 of Appendix 1), the Applicant was recommended (via IR dated 10/01/2021) to implement the following IVRT acceptance criteria for QC testing of the proposed drug product:

0.25 Hour: (b) (4)%
1 Hour: (b) (4)%
6 Hours: NLT (b) (4)%

In response (dated 10/08/2021), the Applicant accepted the FDA recommendation and accordingly revised the acceptance criteria. The Applicant's response is adequate. The following IVRT method and acceptance criteria are deemed adequate for QC testing of the proposed drug product:

FDA approved IVRT method and acceptance criteria for the proposed drug product

Apparatus	USP Apparatus 6 (Cylinder)
Paddle Speed	50 rpm
Volume	500 mL (4.5 mg/9 Hrs and 9 mg/9 Hrs) 900 mL (13.5 mg/9 Hrs and 18 mg/9 Hrs)
Medium	0.05 M Potassium Phosphate Buffer at a pH of 6.8
Temperature	32.0 ± 0.5°C
Acceptance Criteria	0.25 Hour: (b) (4)% 1 Hour: (b) (4)% 6 Hours: NLT (b) (4)%

[1] \\CDSESUB1\evsprod\nda215401\0021\m3\32-body-data\32p-drug-prod\xelstrym-d-ats\32p2-pharm-dev\ivrt-profile-registration-24-month-excel.xlsx

Appendix 1

Table 1: Clinical Lots of the proposed drug product

Clinical Study Number First Subject Enrolled/Last Subject Completed	Study Type	Finished Product Lot Number (dose)	Date of (b) (4) Manufacture	Mfg Site	Drug Product Composition	Container Closure System	Manufacturing Process+	Assay Results mg/unit / %LC
N25-002 November 3, 2009/ November 11, 2009	Phase I PK Study in Healthy Adults	R907231-A1 (9.38 mg/ 9.38 cm^2)	07/24/09	(b) (4)	Commercial formulation; (b) (4)	Pilot	Pilot A	10.2 / 109%
		R907232-A1 (9.85 mg/ 9.38 cm^2)	07/27/09					10.7 / 109%
N25-004 November 6, 2010/ November 27, 2010	Phase I PK Study in Children with ADHD	R1005181-A2 (8.40 mg/ 8.0 cm^2)	05/20/10		Commercial formulation	Pilot	Pilot	8.14 / 97%
N25-005 September 26, 2011/ November 9, 2011	Phase I Dose Ranging PK Study in Children with ADHD	R1108031-A1 (5.00 mg/ 4.76 cm^2)	08/08/11		Commercial formulation	Pilot	Pilot	5.07 / 101%
		R1108031-A2 (10.0 mg/ 9.52 cm^2)						10.7 / 107%
		R1108031-A3 (20.0 mg/ 19.05 cm^2)						20.9 / 105%
N25-006 September 28, 2012/ March 23, 2013	Phase II Classroom Study in Children and Adolescents with ADHD	R1204231-A1 (15.0 mg/ 14.29 cm^2)	04/24/12		Commercial formulation	Pilot	Pilot	14.6 / 97%
		R1204232-A1 (10.0 mg/ 9.52 cm^2)	04/25/12					9.44 / 94%
		R1204233-A1 (5.00 mg/ 4.76 cm^2)	04/26/12					4.83 / 97%
		R1204234-A1 (20.0 mg/ 19.05cm^2)	04/27/12					19.6 / 98%
		R1204171-A1 (0.0 mg/unit/ 4.76 cm^2)	04/19/12					0 Placebo
		R1204171-A2 (0.0 mg/unit/ 9.52 cm^2)	04/19/12					0 Placebo
		R1204171-A3 (0.0 mg/unit/ 14.29 cm^2)	04/19/12					0 Placebo
		R1204171-A4 (0.0 mg/unit/ 19.05 cm^2)	04/19/12					0 Placebo
N25-007	Usability Study in Children,	R1204231-A1 (15.0 mg/ 14.29 cm^2)	04/24/12		Commercial formulation	Pilot	Pilot	14.6 / 97%

Reference ID: 4897953

Clinical Study Number First Subject Enrolled/Last Subject Completed	Study Type	Finished Product Lot Number (dose)	Date of (b) (4) Manufacture	Mfg Site	Drug Product Composition	Container Closure System	Manufacturing Process+	Assay Results mg/unit / %LC
May 16, 2013/ July 10, 2013	Adolescents and Adults with ADHD	R1204232-A1 (10.0 mg/ 9.52 cm^2)	04/25/12					9.44 / 94%
		R1204233-A1 (5.00 mg/ 4.76 cm^2)	04/26/12					4.83 / 97%
		R1204234-A1 (20.0 mg/ 19.05cm^2)	04/27/12					19.6 / 98%
N25-010 March 29, 2014/ May 2, 2014	Multiple Application Site Study in Healthy Adults	R1402031-A1 (20.0 mg/ 19.05 cm^2)	02/04/14	(b) (4)	Commercial formulation	Pilot	Pilot	20.6 / 103%
N25-012 July 23, 2019/ August 30, 2019	Heat PK and Bioavailability Study in Healthy Adults	86997 (5.00 mg/ 4.76 cm^2)	05/16/19		Commercial formulation	Commercial*	Commercial	5.09 / 102%
		86998 (20.0 mg/ 19.05 cm^2)						19.7 / 99%
N25-013 October 18, 2014/ December 30, 2014	Usability and Adhesion Study in Children, Adolescents and Adults with ADHD	76397 (20.0 mg/ 19.05 cm^2)	7/9/2014		Commercial formulation	Pilot	(b) (4)	20.8 / 104%
		76033 (5.00 mg/ 4.76 cm^2)	7/9/2014					5.09 / 102%
N25-015 November 13, 2019/ March 17, 2020	Multi-Dose Study in Adults with ADHD	86998 (20.0 mg/ 19.05 cm^2)	05/16/19		Commercial formulation	Commercial*	Commercial	19.7 / 99%
N25-018 December 2, 2019/ May 12, 2020	Irritation and Sensitization Study in Healthy Adults	86997 (5.00 mg/ 4.76 cm^2)	05/16/19		Commercial formulation	Commercial*	Commercial	5.09 / 102%
		87458 (0.0 mg/unit/ 4.76 cm^2)	08/08/19					0 Placebo

Table 2: Registration Lots of the proposed drug product

Drug Product Strength (mg/9 Hrs)	Registration Lot Number
4.5	86997
	87222
	87224
9	87225
13.5	87221
18	86998
	87220
	87226

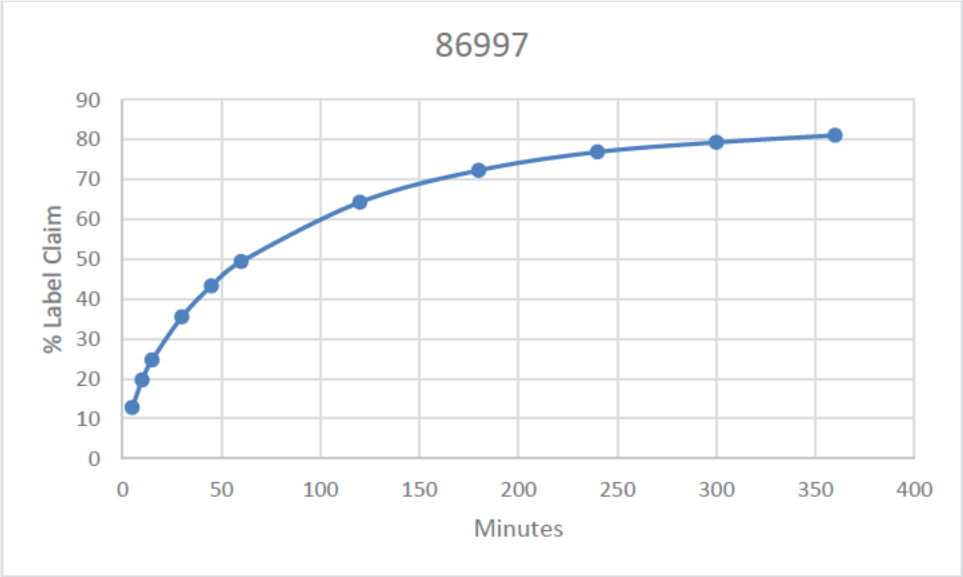
Table 3. Drug release data (Mean and RSD) for the registration lots of the proposed drug product

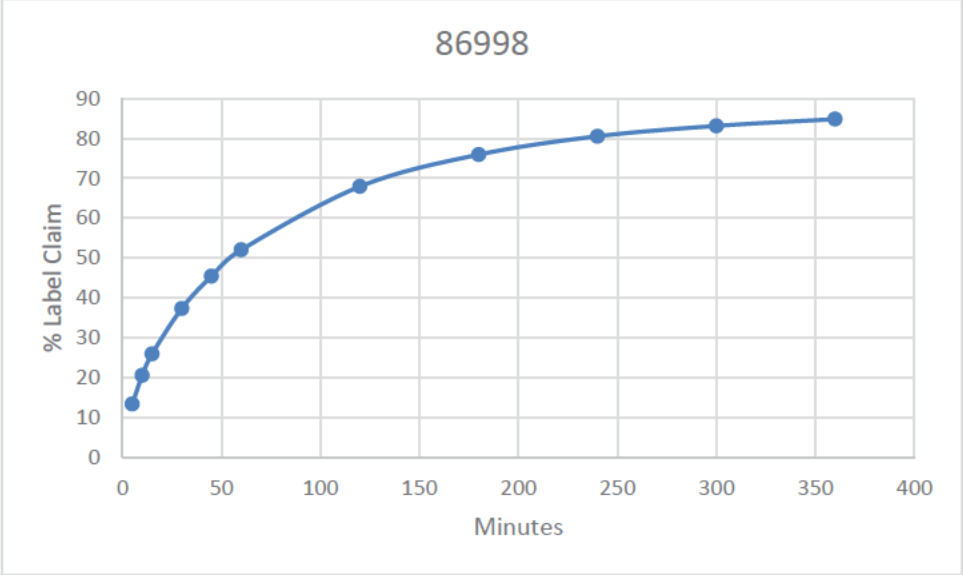
Time (Minutes)	Batch 86997 (4.5 mg/9 Hrs)		Batch 87222 (4.5 mg/9 Hrs)		Batch 87224 (4.5 mg/9 Hrs)		Batch 87225 (9 mg/9 Hrs)		Batch 87221 (13.5 mg/9 Hrs)		Batch 86998 (18 mg/9 Hrs)		Batch 87220 (18 mg/9 Hrs)		Batch 87226 (18 mg/9 Hrs)	
0	**Mean**	**RSD**	**Mean**	**RSD**	**Mean**	**RSD**	**Mean**	**RSD**	**Mean**	**RSD**	**Mean**	**RSD**	**Mean**	**RSD**	**Mean**	**RSD**
5	12.8	3.4	14.1	2.0	14.8	6.3	14.4	3.4	13.4	3.7	13.3	3.3	14.7	3.2	14.6	4.4
10	19.7	3.2	22.0	1.9	22.6	4.9	22.3	2.7	20.8	4.5	20.5	3.7	22.8	3.0	22.5	2.9
15 (0.25 Hrs*) (b) (4) %	24.7	2.5	27.5	1.8	28.3	4.4	28.2	2.0	25.9	5.3	25.9	4.0	28.8	2.5	28.2	2.8
30	35.5	2.2	39.3	1.2	40.5	4.1	40.3	1.8	37.7	4.1	37.3	3.2	41.3	2.6	40.7	3.2
45	43.3	1.7	47.7	1.6	48.8	3.9	48.9	2.1	45.9	3.6	45.4	2.6	49.7	2.6	49.4	2.9
60 (1 Hrs*) (b) (4) %	49.4	1.5	54.3	1.3	55.5	3.2	55.7	1.5	52.3	3.6	52.0	2.5	56.7	2.3	56.3	3.2
120	64.3	1.2	69.8	1.1	70.7	2.3	72.3	1.3	68.2	2.1	67.9	1.9	72.6	1.8	73.0	3.3
180	72.3	1.0	77.7	1.4	78.3	1.4	80.5	1.3	76.2	1.6	75.9	1.9	80.1	1.6	81.6	3.2
240	76.9	1.0	81.8	1.2	82.6	1.2	85.2	1.2	80.7	1.2	80.5	1.7	84.3	1.7	86.2	3.3
300	79.3	0.9	84.3	1.1	85.0	1.0	88.1	1.2	83.5	0.9	83.1	1.9	87.0	1.5	89.1	3.6
360 (6 Hrs*) NLT (b) (4) %	81.1	0.9	85.8	1.3	86.8	1.1	90.2	1.1	85.2	0.8	84.8	1.8	88.0	1.5	89.9	0.7

*Time-point for QC Acceptance Criteria

Reference ID: 4897953

IVRT profiles of registration batches collected at 24 months time-point





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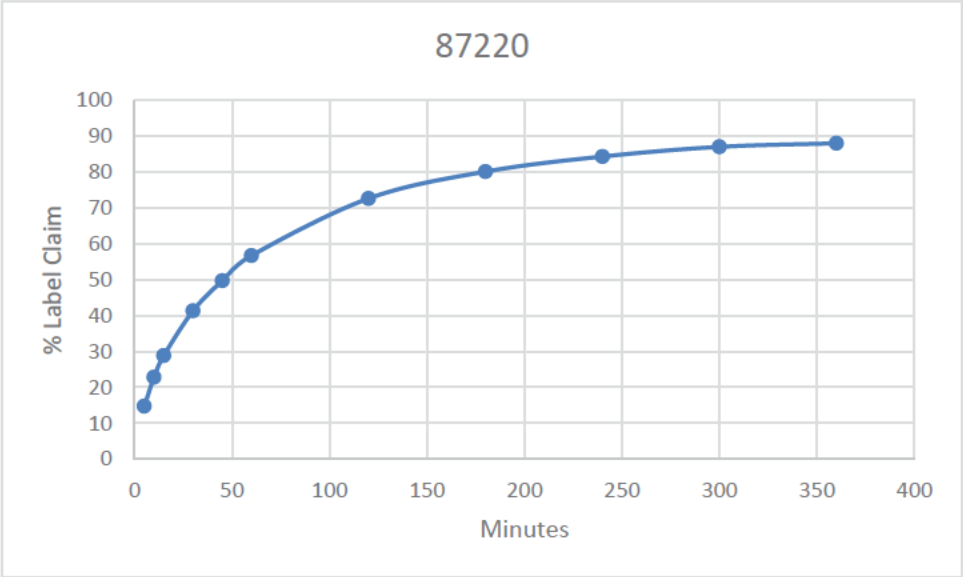

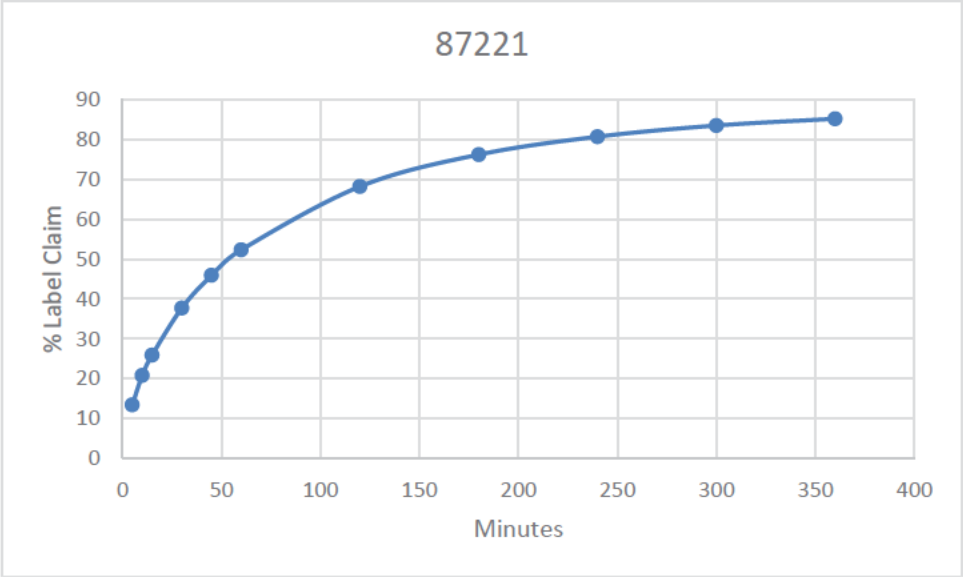

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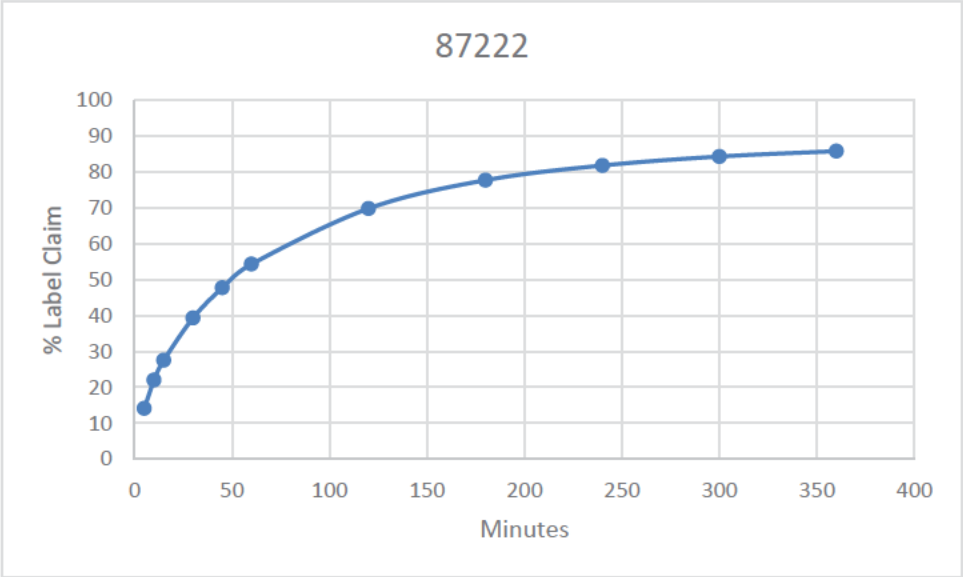

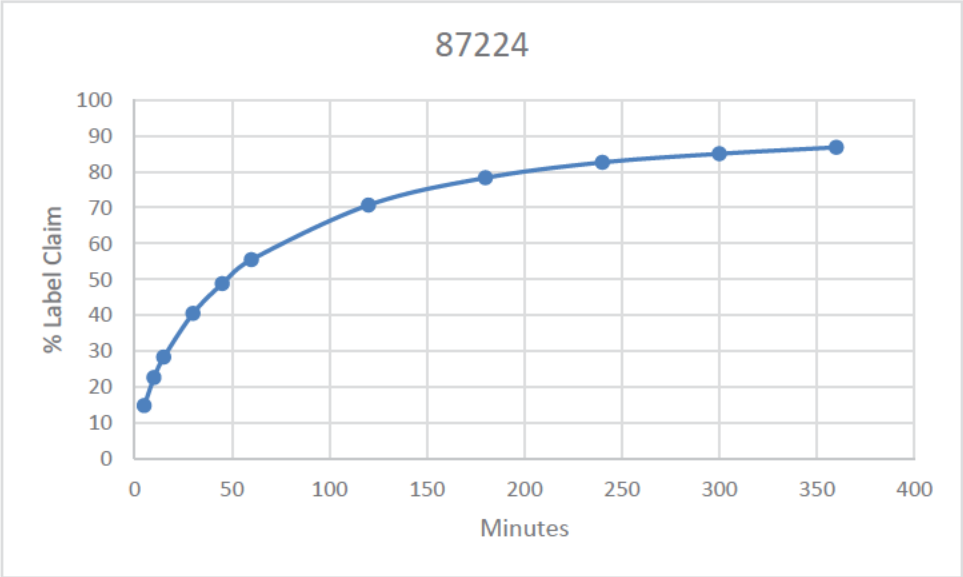

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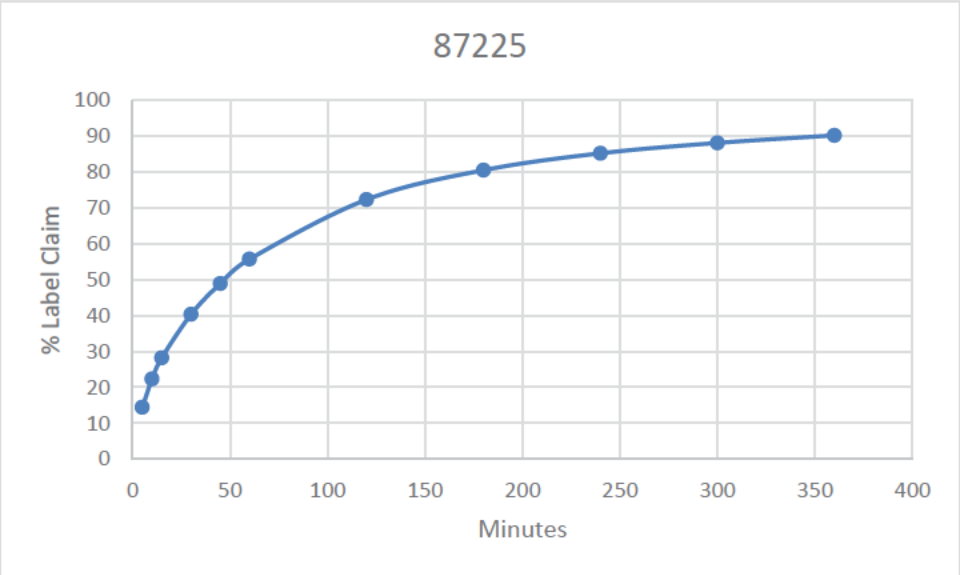

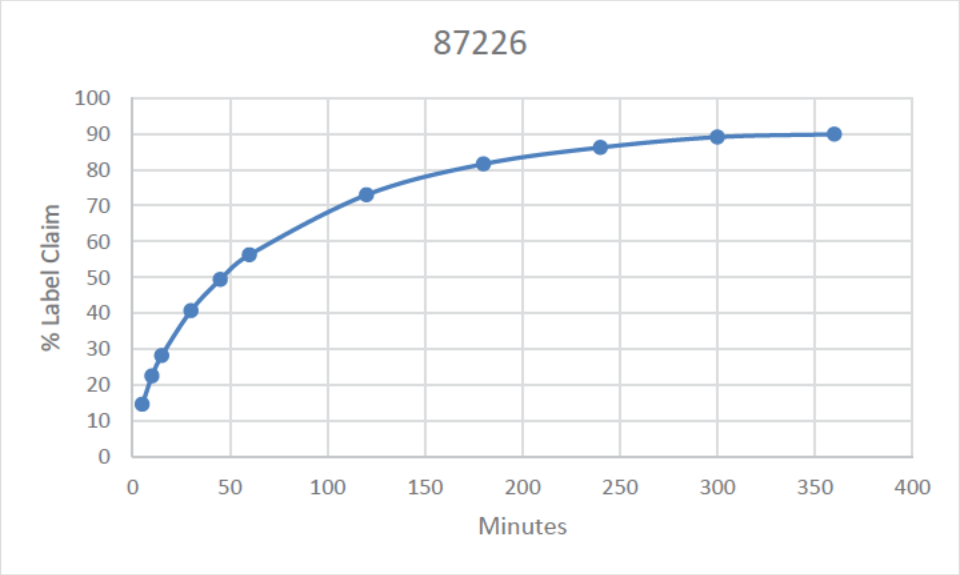

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