

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208510Orig1s000**

**CHEMISTRY REVIEW(S)**

**Recommendation: APPROVAL**

**NDA 208510  
Review #1**

Drug Name/Dosage Form	Vyvanse (lisdexamfetamine) Chewable Tablets
Strength	10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Shire Development LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment (SD 14)	04-NOV-2016	DP
Amendment (SD 13)	19-OCT-2016	DP
Amendment (SD 12)	15-SEP-2016	DP, Biopharm, Process
Amendment (SD 11)	18-AUG2016	DP, Process
Amendment (SD 8)	24-JUN-2016	Biopharm, Facilities
Amendment (SD 6)	24-MAY-2016	DP
Original (SD 4)	31-MAR-2016	All

**Quality Review Team**

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Mariappan Chelliah	Branch 1/DNDP 1/ONDP
Drug Product	Mariappan Chelliah	Branch 1/DNDP 1/ONDP
Process	Arwa ElHagrasy	Branch 3/DPA 1/OPF
Microbiology	Arwa ElHagrasy	Branch 3/DPA 1/OPF
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Biopharmaceutics	Gerlie Gieser	Branch 1/DB/ONDP
Regulatory Business Process Manager	Grafton Adams	Branch 1/DRBP1/OPRO
Application Technical Lead	Wendy Wilson-Lee	Branch 1/DNDP1/ONDP
Environmental Analysis (EA)	Mariappan Chelliah	Branch 1/DNDP1/ONDP

## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS**

**A. DMFs:**

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type IV	(b) (4)	(b) (4)	Adequate	02-NOV-2016	
	Type IV			Not reviewed		Sufficient information provided in NDA

**B. Other Documents: *IND, RLD, or sister applications***

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21977	Vyvanse Capsules
IND	67482	Vyvanse Capsules

**2. CONSULTS**

None.

## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 208510 for commercialization of Vyvanse (lisdexamfetamine) Chewable Tablets 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg.

### II. Summary of Quality Assessments

#### A. Product Overview

Lisdexamfetamine dimesylate is a Class II scheduled drug. Lisdexamfetamine dimesylate chewable tablet is formulated in strengths of 10, 20, 30, 40, 50, and 60mg. It is a central nervous system stimulant and indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and moderate to severe Binge Eating Disorder (BED). The Applicant already markets lisdexamfetamine dimesylate in capsule form in strengths of 10, 20, 30, 40, 50, 60, and 70 mg. The chewable tablet formulation offers ease of administration for patients who may experience difficulty swallowing. The chewable tablet eliminates the need to further manipulate the approved capsule to provide ease of dosing for these patients (i.e. open and sprinkle contents on food) and may offer more complete administration of dose. It is anticipated that children will be the major patient population utilizing this formulation.

<b>Proposed Indication(s) including Intended Patient Population</b>	Attention Deficit Hyperactivity Disorder (ADHD) in Pediatrics and Adults Moderate to Severe Binge Eating Disorder in Adults
<b>Duration of Treatment</b>	Chronic administration, once daily
<b>Maximum Daily Dose</b>	70 mg
<b>Alternative Methods of Administration</b>	No alternative methods for chewable tablets

<b>Patient-Based Product Quality Analysis</b>		
	<b>Key Evidence/Uncertainties</b>	<b>Conclusions/Reasons</b>
<b>Performance As Intended</b>		
<ul style="list-style-type: none"> <li>• Chewability</li> <li>• Palatability</li> </ul>	Chewable tablets should be easy to chew, palatable, appropriately size and shaped to minimize choking and obstruction, and able to readily disintegrate to minimize potential aspiration	Based on our assessment of the information provided in the submission, Vyvanse Chewable Tablets possess the necessary attributes to ensure that the product

	<p>and facilitate dissolution of the dosage form.<sup>1</sup> Two sensory studies conducted during development identified the preferred sweetener and flavor combination. These sensory studies also confirmed that the commercial formulation provides sufficient taste masking and provides favorable palatability for all strengths.</p>	<p>meets the quality target product profile of being easy to chew, palatable, and appropriately sized while exhibiting fast disintegration.</p>
<p><b>Additional Safety Concerns</b></p> <ul style="list-style-type: none"> <li>• Lack of 70 mg strength chewable tablet</li> <li>• Tablet size/shape</li> </ul>	<p><b><u>70 mg Strength</u></b></p> <p>The current Vyvanse label lists 70 mg as the maximum daily dose for both the ADHD and BED indications. However, the applicant chose not to develop a 70 mg strength chewable tablet (b) (4)</p> <p>However, DPP indicated that it is expected that patients, including pediatric patients, will benefit from the maximum daily dose of 70 mg for both indications. The lack of a 70 mg chewable tablet presents a potential safety risk as patients will have to utilize combinations of lower strength tablets to reach the prescribed 70 mg dose. The lack of a 70 mg strength presents a risk of both under dosing and overdosing as patients may mix up tablets when combining (i.e. taking two-10 mg or two-60 mg</p>	<p>For this case, the Agency does not have a basis to compel the Applicant to develop and commercialize a 70 mg strength chewable tablet despite the maximum labeled dose. We recommend that prescribers be advised that patients requiring the 70 mg dose should be prescribed the approved Vyvanse capsule product.</p> <p>Based on the tablet diameters and the lack of reports of adverse events related to choking and obstruction clinical studies, we consider the proposed tablet sizes and shapes to be low risk with respect to patient safety.</p>

<sup>1</sup> Draft FDA Guidance for Industry Quality Attribute Considerations for Chewable Tablets, 2016

	<p>chewable tablets instead of one-10 mg and one-60 mg chewable tablet). It is unclear if the potential safety risks rise to a level sufficient to enable the Agency to compel the applicant to develop a 70 mg chewable tablet.</p> <p><b><u>Tablet Size/Shape</u></b> The intended method of administration for the drug product is chewing. Although chewing is the intended route of administration, the potential exists for patients to swallow the tablets whole without chewing. This could result in either choking while swallowing or bowel obstruction. The need to understand the potential safety risks associated with choking is especially important given that the expected majority of patients who will be prescribed Vyvanse chewable tablets are pediatric.</p> <p>The review team was uncertain about the choking hazard potential, especially for younger pediatric patients. Both tablet shape and size are contributing factors that could lead to choking. Tablets 8 mm in diameter or smaller and oval-shaped tablets are considered easy to swallow for adults.<sup>2</sup></p>	
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<sup>2</sup> Channer, K. Virjee, JP. 1986, The Effect of Size and Shape of Tablets on their Esophageal Transit. Journal of Clinical Pharmacology, 26, 141-146.

	<p>Vyvanse chewable tablets range from (b) (4) based on the longest dimension for each tablet shape. Current FDA guidance indicates that the largest dimension of tablet intended to be swallowed whole should not exceed 22 mm.<sup>3</sup> Although not explicitly stated in the guidance, we assume that the size and shape criteria applies to teenage and adult patients. We also assume that for patients on the younger end of the pediatric age spectrum, the maximum diameter is smaller. However, using the 22 mm diameter as a standard for comparison, all proposed tablet diameters for Vyvanse chewable tablets are within a range considered low risk for choking and obstruction. Similarly, using the oval shape as a comparison standard, the Vyvanse chewable tablet shapes (round, capsule, hexagonal, square, triangle, diamond) would not be considered easy to swallow. The adverse events reported for the pivotal clinical trials did not include any reports of choking or obstruction. The main gastrointestinal adverse event reported was dry mouth.</p>	
<p><b>Manufacturing</b></p> <ul style="list-style-type: none"> <li>• Compliance with cGMP</li> </ul>	<p>All associated manufacturing, testing, and</p>	<p>There are no issues concerning facilities or</p>

<sup>3</sup> FDA Guidance for Industry Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules, 2016.

<ul style="list-style-type: none"> <li>• Availability Issues</li> </ul>	<p>packaging facilities were deemed acceptable. At launch, manufacturing will be at (b) (4) of the planned commercial scale. However, formal process validation of the commercial process has not been performed. Based on the information provided in the submission, we consider all unit operations to be low risk at commercial scale. We presume that process validation at commercial scale will be successful.</p>	<p>commercial availability based on the assessment of the information provided in the submission.</p>
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**B. Quality Assessment Overview**

**Drug Substance**

Lisdexamfetamine dimesylate is an L-lysine amide pro-drug of dextroamphetamine. It was previously approved for use as a drug substance for lisdexamfetamine dimesylate capsules under NDA 021977. The Sponsor has cross-referenced NDA 021977 for all the drug substance related CMC information. This review relies on the adequacy of the CMC information that was reviewed under NDA 021977.

**Drug Product**

Lisdexamfetamine dimesylate chewable tablets are formulated in strengths of 10, 20, 30, 40, 50, and 60 mg. The maximum daily dosage recommended by the labeling is 70 mg for lisdexamfetamine dimesylate. While the capsule form is available at the 70 mg dose strength, for (b) (4), Shire proposes to market the chewable tablets with the maximum dose strength of 60 mg. The chewable formulation contains excipients that are commonly used in oral formulations. It also contains artificial strawberry flavor and sucralose (b) (4) lisdexamfetamine.

All the dose strengths of the chewable tablets have unique size, shape, and debossing, which assures the visual differentiation among different dose strengths of the tablets. The tablets are packaged in counts of 100 in 120cc HDPE bottles. However, because lisdexamfetamine is a class II controlled drug substance, (b) (4)

The proposed specification for the chewable tablets resembles the specification of the capsule form that was approved under NDA 021977. The proposed specification for the drug product is adequate to ensure that the critical quality attributes of a chewable tablet formulation are well controlled. The Sponsor has manufactured three registration/stability

batches of the chewable tablets corresponding to each dose strength. The stability batches and the proposed commercial batches will have identical formulations. However, the proposed commercial manufacturing process will have minor differences compared to the registration/stability batches. In order to support these minor changes, Shire manufactured two batches that use the proposed commercial manufacturing process. The available batch and stability data meet the proposed specification for the lisdexamfetamine chewable tablets.

The Sponsor studied the stability of these tablets using a bracketing approach. Up to 12 months of long-term stability data for the registration/stability batches are available. The available stability data supports the proposed shelf-life of 24 months when the tablets are stored at 20-25°C (68-77°F); excursion permitted to 15-30°C (59-86°F).

### **Biopharmaceutics**

Lisdexamfetamine mesylate exhibits high solubility and high permeability. The proposed Vyvanse® chewable tablets exhibit ‘very rapid dissolution’ (b) (4) % dissolves in 15 min) in various dissolution media across the physiologic pH range. The 60 mg chewable tablet was evaluated in the pivotal BE study. The Applicant’s biowaiver request for the 5 lower strengths of the chewable tablets is granted based on the proportional similarity and comparable *in vitro* dissolution profiles of these lower strengths to the bio-strength (60 mg). If a maximum daily dose of 70 mg is needed, it is reasonable to combine lower strengths (e.g., 60 + 10 mg). Should the Applicant decide to market the higher 70 mg strength of the Vyvanse® chewable tablet, the submission of a biowaiver request is deemed feasible since 70 mg is already covered by the available PK data, the recommended dose range, and the commercially available strengths of Vyvanse® capsules.

The proposed commercial manufacturing process is adequately bridged to the process that was used to manufacture the clinical and registration batches. The Applicant’s proposal to use disintegration (in lieu of dissolution) for routine QC testing of the Vyvanse® chewable tablets is acceptable. The data provided support a disintegration time of ‘NMT (b) (4) over the proposed acceptance criterion of ‘NMT (b) (4). To support biowaiver requests and post-approval CMC changes of Vyvanse® chewable tablets, the dissolution method approved for Vyvanse capsules is acceptable, with a slight modification (i.e., (b) (4)).

### **Process**

The manufacturing process for this drug product is adequate for NDA approval. The process involves manufacturing of chewable tablets using a (b) (4).

### **Facilities**

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on the firm inspectional history, inspection report reviews, and district office recommendation, the manufacturing facilities listed for NDA 208510 are found to be acceptable.

### **C. Special Product Quality Labeling Recommendations**

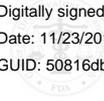
All statements regarding administration instructions in the prescribing information and medication guide should indicate that the drug product **must be chewed** prior to swallowing.

### **D. Final Risk Assessment (see Attachment)**



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Wilson- Lee

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### ***Environmental Analysis***

The Sponsor is requesting categorical exclusion from environmental analysis in accordance with 21 CFR 25.31(b). In addition, they state that no extraordinary circumstances exist under 21 CFR 25.15(d) that would warrant the preparation of an environmental assessment.

#### **Reviewer's Assessment: Adequate**

Shire considers NDA 021977 as the controlling NDA for CMC information related to the lisdexamphetamine dimesylate drug substance. They project combined annual consumption of (b) (4) of lisdexamphetamine dimesylate because of current marketing under NDA 021977 and the approval of this NDA.

As per the "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications," the expected introduction concentration (EIC) of an active moiety into the aquatic environment is calculated as follows:

$EIC\text{-Aquatic (ppb)} = A \times B \times C \times D$  where

A = kg/year produced for direct use (as active moiety)

B =  $1 / 1.214 \times 10^{11}$  liters per day entering publicly owned treatment works

C = year/365 days

D = 10  $\mu\text{g}/\text{kg}$  (conversion factor)

EIC = (b) (4)

The projected EIC is far below the 1 ppb threshold that would trigger the environmental assessment per 21 CFR 25.31(b). Therefore, the Sponsor's request of categorical exclusion from environmental assessment is acceptable.

### ***Methods Verification Package***

**Reviewer's Assessment: Not Applicable.**

### ***Comparability Protocols***

**Reviewer's Assessment: Not Applicable.**

***Post-Approval Commitments***

**Reviewer's Assessment: Not Applicable**

***Lifecycle Management Considerations***

**Reviewer's Assessment: Not Applicable**

*No issue was identified for lifecycle management considerations.*

***List of Deficiencies: None***

***Primary Reviewer: Mariappan Chelliah (see below for date)***

***Secondary Reviewer: Wendy Wilson-Lee (see below for date)***



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**LABELING**

**Review Summary:** The proposed container labels meet all regulatory requirements from a CMC perspective. The applicant did not propose any carton labels. Review and revision of the prescribing information, MedGuide, and any other associated patient labeling will be conducted in collaboration with the clinical division.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	eCTD Seq.#	DOCUMENT DATE
Initial NDA filing	003	31-Mar-2016
Amendment	012	19-Oct-2016

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

**R Regional Information**

**1.14 Labeling**

*Immediate Container Label*

As a representative example, the container label for the 10mg lisdexamfetamine dimesylate chewable tablet is shown below:



**Reviewer's Assessment: Adequate**



## QUALITY ASSESSMENT



The container labels of the lisdexamfetamine chewable tablets are very similar to that of the container labels of the lisdexamfetamine dimesylate capsules approved under NDA 021977. The only outstanding deficiency that needs to be resolved is that the NDC# as printed on the container label does not match with the NDC# as printed in the prescribing information. This will be resolved as we continue to work with the labeling review team. Other than the NDC#, the container label is adequate and meets all regulatory requirements from a CMC perspective.

### ***Carton Labeling***

The packaging system does not include carton. Accordingly, the Sponsor did not provide carton labeling.

**Reviewer's Assessment: Not Applicable**

***List of Deficiencies: None***

***Primary Reviewer: Mariappan Chelliah (see below for date)***

***Secondary Reviewer: Wendy Wilson-Lee (see below for date)***



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**BIOPHARMACEUTICS**

**Product Background:**

**NDA:** 208510 (505)(b)(1)

**Drug Product Name / Strength:** Vyvanse® (lisdexamfetamine dimesylate) Chewable Tablets/ 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg

**Route of Administration:** Oral

**Proposed Dosage** for ADHD and BED (6 years and older): same as Vyvanse® oral capsules (start 30 mg QD, then titrate up to 70 mg QD)

**Applicant Name:** Shire Development LLC

**Review Summary:**

- Lisdexamfetamine mesylate exhibits high solubility and high permeability. The proposed Vyvanse® chewable tablets exhibit ‘very rapid dissolution’ (b)(4)% dissolves in 15 min) in various dissolution media across the physiologic pH range.
- The 60 mg chewable tablet was evaluated in the pivotal BE study. The Applicant’s biowaiver request for the 5 lower strengths of the chewable tablets is granted based on the proportional similarity and comparable *in vitro* dissolution profiles of these lower strengths to the bio-strength (60 mg). If a maximum daily dose of 70 mg is needed, it is reasonable to combine lower strengths (e.g., 60 + 10 mg). Should the Applicant decide to market the higher 70 mg strength of the Vyvanse® chewable tablet, the submission of a biowaiver request is deemed feasible (b)(4) Vyvanse® capsules.
- The proposed commercial manufacturing process is adequately bridged to the process that was used to manufacture the clinical and registration batches.
- The Applicant’s proposal to use disintegration (in lieu of dissolution) for routine QC testing of the Vyvanse® chewable tablets is acceptable. The data provided support a disintegration time of ‘NMT (b)(4) over the proposed acceptance criterion of ‘NMT (b)(4)
- To support biowaiver requests and post-approval CMC changes of Vyvanse® chewable tablets, the dissolution method approved for Vyvanse capsules is acceptable, with a slight modification (i.e., (b)(4)).

Disintegration Acceptance Criterion Agreed to with the Applicant: “NMT (b)(4)

Dissolution method and acceptance criterion for potential biowaiver requests and post-approval changes (the same as Vyvanse Capsules):

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
2 (paddles)	50 rpm (without sinker)	0.1 N HCl	900 mL	Q (b)(4)% at 15 min

From a Biopharmaceutics perspective, NDA 208510 for Vyvanse® Chewable Tablets is recommended for APPROVAL.

**List Submissions being reviewed :**

SDN-4: Original – 3/31/2016

SDN-6: Stability Update – 5/24/2016

SDN-9: Response to Information Request -6/24/2016

SDN-11: Response to Information Requests (Effect of desiccant on dissolution) 8/18/2016

SDN-12: Response to Information Requests (Disintegration Specification) – 9/15/2016

**Highlight Key Outstanding Issues from Last Cycle:**

None: First Review Cycle

**Concise Description of Outstanding Issues:**

None.

**BCS Designation**

**Reviewer's Assessment:** Note that there was no formal request for BCS-1 designation of Vyvanse® chewable tablets. Lisdexamfetamine mesylate exhibits characteristics consistent with a high solubility/high permeability drug substance. The rate and extent of drug dissolution from the product was media-dependent. As explained by the Applicant, the lower dissolution of the drug product (b) (4)

**Solubility:** The drug substance lisdexamphetamine dimesylate is an (b) (4) white powder that exhibits high solubility [solubility at 37 °C across the physiologic pH range (including water) is ≥ 790 mg/mL].

**Permeability:** The drug substance is likely to exhibit high permeability. In a mass balance study, 96% of the radiolabelled 70 mg oral dose appeared within 48 hours in the urine of humans as metabolites (mainly, d-amphetamine and hippuric acid), and 2.2% of the dose appeared in the urine as the prodrug lisdexamphetamine.

**Dissolution:** The drug product is very rapidly dissolving, i.e., at least (b) (4)% of the drug is released within 15 min in various pH media (pH 1.2, 4.5, 6.5, 7.5). However, it is noted that dissolution in (b) (4) is incomplete (plateaus at (b) (4)% starting at (b) (4) min); per the Applicant such phenomenon is related (b) (4)

such as those present in buffer systems.

***Disintegration and Dissolution Method and Acceptance Criteria***

Note that Disintegration Time of 'NMT (b) (4)' and Tablet Breaking Force (but not Dissolution) are included in the proposed release and shelf-life specifications of the Chewable Tablets.

**Reviewer's Assessment:****Disintegration (in lieu of Dissolution) for Routine QC Testing - ACCEPTABLE**

The Applicant's proposal to substitute Disintegration Testing for Dissolution Testing in the Finished Product QC Specifications of Vyvanse® Chewable Tablets is acceptable for the following reasons: (1) The immediate release tablets are intended to be chewed rather than orally ingested as intact tablets. (2) All proposed strengths of the chewable tablets exhibited 'very rapid dissolution' (at least (b) (4) % in 15 min) in 0.1 N HCl as well as in higher pH media so there is very low risk that the tablets would not dissolve completely within a reasonable timeframe in case the tablet is inadvertently swallowed without chewing. Similarly, in a DOE study, chewable tablets intentionally manufactured with a wide range of disintegrant levels, hardness levels, (b) (4) all showed 'very rapid dissolution'. (3) There is an apparent correlation between the Applicant's DOE model-estimated maximum disintegration time and observed mean dissolution at (b) (4) min (but not at (b) (4) min); see Figure 1. Limited data from the registration batches suggest that this correlation could probably be better at the earlier (i.e., (b) (4)) dissolution time point. [Note however that this correlation was not evident using the disintegration and dissolution data of the registration and proposed commercial batches, likely due to the use of more controlled manufacturing process parameters (as opposed to those studied in DOE)]. (4) Since the drug substance is highly soluble, the discriminating power of dissolution testing could conceivably be lower than disintegration testing as evidenced by the better correlation observed between the latter and tablet hardness (a critical attribute for chewable tablets; see Table 10 of 3.2.P.2.2 Drug Product; see also Figure 1A of this review). Additionally, it is known that the API exists only as (b) (4), and thus, drug substance polymorphic changes would not be expected to alter the dissolution profile of the drug product. (5) In SDN-11 dated 08/18/2016, the Applicant reported that in developmental studies, the disintegration time of the 20 and 40 mg chewable tablets packaged (b) (4) suggesting that disintegration testing is a stability-indicating test. Of note, dissolution also decreased under the same conditions but not without a commensurate decrease in assay and an increase in total impurities. (6) Per the Applicant, the developed and validated dissolution method will be retained as a reference method (b) (4)



**Disintegration Method and Acceptance Criterion: ACCEPTABLE**

Disintegration Testing follows the USP <701> method. The proposed disintegration acceptance criterion (NMT (b) (4)) for all six strengths of the proposed commercial chewable tablets should be optimized to 'NMT (b) (4)) for the following reasons: (1) Although the Applicant states that the proposed disintegration specification of 'NMT (b) (4)) is stricter than the interim acceptance criterion (NMT (b) (4)) used for the release and stability testing of the registration batches, the reported disintegration time of the bio-batch is (b) (4) min (range (b) (4) min) at the initial (Month 0) stability time point; see Figure 2. (2) The available 12-month long-term and 3-month accelerated stability data show that all strengths of the registration and the proposed commercial (optimized process) batches would comply with a recommended disintegration acceptance criterion of 'NMT (b) (4)) the individual tablet values for all strengths ranged from (b) (4) min. (3) A lower than (b) (4) cut-off for disintegration time for the proposed tablets is not deemed necessary because the product labeling will state that the tablets must (or should) be chewed, and additionally there are other QC tests for the finished product, i.e., tablet crushing strength that would control for the chewability of the tablet. (4) Based on the linear correlation between 'cumulative dissolution at (b) (4))' and 'max disintegration time' in the DOE study (see Figure 1), a disintegration time of 'NMT (b) (4)) is anticipated to result in an average dissolution of at least (b) (4) % in the QC dissolution medium within (b) (4) for all 6 strengths of the chewable tablets; whereas a disintegration time of NMT (b) (4)) would result in at least (b) (4) % dissolution in (b) (4) min. Note that the approved dissolution acceptance criterion ( $Q = (b) (4) \%$  at 15 min) for the Vyvanse® capsules would also be acceptable for Vyvanse® chewable tablets; however, it is acknowledged that dissolution is not proposed to be included in the Finished Drug Product Specifications of the chewable tablets. (5) Based on the DOE data, (b) (4) min is the maximum disintegration time of the chewable tablets (including the 20 mg strength when tested in a point-to-point orientation; see Figure 2) with an observed tablet crushing strength of (b) (4) (as per the recommendation of the FDA Guidance on Chewable tablets). Additionally, based on DOE data, all the batches intentionally manufactured with varying levels of disintegrant ( (b) (4) % w/w), levels of tablet hardness within dose strength, (b) (4) had maximum disintegration times of NMT (b) (4)

*On 9/15/2016 (SDN-12), the Applicant agreed to the FDA's recommendation to use a disintegration time of 'NMT (b) (4)) for the routine release and stability testing of all six strengths of the proposed chewable tablets.*

(b) (4)

**Dissolution Method and Acceptance Criteria: ACCEPTABLE**

The dissolution method approved for Vyvanse® capsules [USP Apparatus 2 (paddles) at 50 rpm, 900 mL of 0.1 N HCl, (b) (4)] is suitable for the dissolution testing of Vyvanse® chewable tablets. Drug quantification is accomplished using reversed-phase HPLC with UV detection ( $\lambda = 205$  nm). In method development studies, the use of alternative paddle speed (b) (4) and alternative dissolution media (pH (b) (4)) did not result in a significant difference in the dissolution test results. In analytical validation studies, the pre-specified acceptance criteria were met for linearity, accuracy, precision, repeatability, specificity, and robustness (HPLC parameters, as well as paddle speed (b) (4) rpm, bath temperature (b) (4) and dissolution media concentration (b) (4)). The method was also validated for solution stability ( (b) (4) ).

The method was able to detect differences in dissolution of chewable tablets intentionally manufactured with different disintegrant levels, (b) (4) and tablet hardness but only at the (b) (4) dissolution sampling time point (not at the later time points).

Note that the dissolution acceptance criterion approved for the Vyvanse capsules was implemented for the QC testing of the 60 mg strength chewable tablet (Lot 3129446R) evaluated in the Pivotal BE Study (SPD489-126), and the other primary registration lots manufactured using the current process over 12 months of long-term storage, as well as the representative proposed commercial process lots over 3 months of long-term storage. All these lots showed an individual tablet dissolution greater than (b) (4)% at 15 min during Stage 1 (n=6) of dissolution testing.

### ***Bridging of Formulations***

The formulation of the Vyvanse® chewable tablets did not change during development but the manufacturing process was optimized with respect to equipment use and number of processing steps after the Pivotal BE and the Food-effect studies were conducted, and after the stability testing of the primary registration batches was initiated. The process changes include: (b) (4)

Per the Applicant, their decision not to develop a 70 mg strength chewable tablet was based on (b) (4) for the 70 mg strength of the Vyvanse® capsules.

### **Reviewer's Assessment: ACCEPTABLE**

*In vitro* disintegration and dissolution profile data generated at batch release and over 12 months of long-term storage were provided for the bio-batch (60 mg; Lot # 3129446R). This bio-batch is one of the 14 of 18 primary registration/stability lots with disintegration and dissolution profile data, and were manufactured by the current process/site ( (b) (4) using API from two suppliers ( (b) (4) Note that 2 lots each of the (b) (4) 20 mg and 50 mg tablets were put on storage but not analyzed. Bridging data are available to compare the dissolution, disintegration, and other CMC data for 1 lot each of the 20 mg and 50 mg registration batches and for one lot each of the 20 mg and 50 mg chewable tablets produced using the optimized proposed commercial process (by the non-GMP developmental manufacturer).

Dissolution. Based on the Reviewer's analyses, the clinical/registration lot (60 mg) and the other registration lots (10, 20, 30, 40, 60 mg) manufactured using the old process, as well as the proposed commercial lots (20 and 50 mg) manufactured using the optimized process all exhibited very rapid dissolution (i.e., (b) (4)% dissolved within 15 min, when tested using the proposed dissolution QC method; see Figure 3) up to 12 months and up to 3 months, respectively, of long-term and accelerated stability testing.

Disintegration. Based on the Reviewer's analyses, the 20 mg strength that was manufactured using the optimized process exhibited a disintegration time that was more in alignment with

that of bio-strength/bio-lot (60 mg Lot # 3129446).

(b) (4)

#### **Biowaiver Request**

A waiver of *in vivo* bioequivalence studies for lisdexamfetamine dimesylate chewable tablets, 10, 20, 30, 40 and 50 mg strengths was requested, based on the following criteria:

All five lower strength tablets are compositionally proportional to the 60 mg dose strength chewable tablet, (2) all tablets have the same dosage form (chewable tablet), manufacturing process and drug release mechanism, (3) like the 60 mg strength tablet that was shown to be BE to Vyvanse® 60 mg oral capsule (in Study SHP489-126), all five tablet strengths are very rapidly dissolving ( (b) (4) % dissolves within 15 minutes in pH 1.2, pH 4.5, p 6.5 and pH 7.5 media.

#### **Reviewer's Assessment: ACCEPTABLE**

The Reviewer agrees that the 40 and 50 mg strengths of the chewable tablets are compositionally proportional to the 60 mg strength because they all come from the (b) (4). The reviewer is considering the 10, 20, and 30 mg strengths to be proportionally similar to the 60 mg strength because of the (b) (4) w/w difference in the API content (b) (4); see 3.2.P.1, Table

3) between (b) (4) and considering that the drug substance appears to exhibit high solubility and high permeability and the drug product is very rapidly dissolving in various pH media.

*[Note that the Clinical Pharmacology reviewer confirmed the bioequivalence of the 60 mg chewable tablet to that of the 60 mg oral capsule.]*

The Applicant indicated that the 70 mg strength of the chewable tablet was not developed because based on (b) (4) for the 70 mg strength of the approved Vyvanse capsules has been rather low. This Reviewer believes that should there be a need to combine available strengths (e.g., 60 + 10 mg, 40 + 30 mg) of the Vyvanse chewable tablets to produce the maximum daily dose of 70 mg, similar systemic exposures to lisdexamphetamine (a highly soluble and highly permeable drug substance) could be anticipated based on: (1) the comparable in-vitro dissolution profiles across the proposed commercial strengths of the chewable tablets, (b) (4) used to manufacture the six strengths, and (3) the reported PK linearity and dose-proportionality of lisdexamphetamine when dosing Vyvanse capsules over the 30 to 250 mg range.

***List of Deficiencies:***

None.

***OVERALL RECOMMENDATION***

From a Biopharmaceutics perspective, NDA 208510 for Vyvanse® Chewable Tablets is recommended for APPROVAL.

***Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (9/28/2016)***

***Secondary Reviewer Name and Date: Okpo Eradiri, PhD (10/6/2016)***



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### ATTACHMENT I: Final Risk Assessment

a) Drug Product: NDA 208510 Vyvanse (lisdexamfetamine) Chewable Tablets; 10, 20, 30, 40, 50, and 60 mg; 100-ct bottles for treatment of ADHD (adults and pediatrics older than 6 yrs) and Binge Eating Disorder (adults)

**Lisdexamfetamine is considered a high risk drug due to the DEA Schedule II classification and associated abuse potential.**

From Initial Risk Identification			Review Assessment		
CQA	Factors that can impact CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay	Raw materials Formulation Container Closure Process Scale/Equipment Site	Release – Low Shelf-Life - Medium	Appropriate end product testing Master batch record (MBR) and In-process controls (IPC) for drug substance (DS) charge	Acceptable	<b>Confirm no new degradation observed when updated drug product stability data submitted</b>

From Initial Risk Identification			Review Assessment		
CQA	Factors that can impact CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Physical stability	Raw materials Formulation Container Closure Process Scale/Equipment Site	Medium	Appropriate environmental controls during manufacturing Desiccant is component of commercial packaging Labeled storage conditions Appropriate end product testing for water content	Acceptable	DS is hygroscopic Risk increases once product is dispensed from commercial packaging; reliance on labeled storage conditions, pharmacy practice, and patient compliance to store properly <b>Monitor AERS/FAERS reports for incidences of tablet integrity issues at pharmacy and at point of use</b>

From Initial Risk Identification			Review Assessment		
CQA	Factors that can impact CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Content uniformity	Raw materials Formulation Process Scale Equipment Site	Medium	Appropriate IPC and end product testing	Acceptable	<p>Low drug load for all strengths Potential for (b) (4)</p> <p>(b) (4) will be reverified through appropriate change control in the event of raw material change PPQ campaign will include (b) (4)</p> <p>testing on minimum 3 batches <b>Confirm PPQ results and compliance with change control procedures</b> (b) (4) on inspection</p>

From Initial Risk Identification			Review Assessment		
CQA	Factors that can impact CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Microbial limits	Raw materials Formulation Container Closure Process Scale/Equipment Site	Low	(b) (4) appropriate environmental controls Microbiological quality controlled at raw material level and included as annual test in stability program	Acceptable	<b>Confirm microbiological quality test results when submitted by applicant</b>
Hardness	Raw materials Formulation Container Closure Process Scale/Equipment Site	Low	Appropriate IPC and end product testing	Acceptable	Proposed changes to raw materials, formulation, process, and container closure should be evaluated for impact on tablet hardness
Palatability	Raw materials Formulation Process Scale/Equipment Site	Medium	Formulation development and clinical organoleptic studies provided sufficient evidence that the product is palatable	Acceptable	Proposed changes to (b) (4) choices and amounts should be evaluated for impact on palatability

From Initial Risk Identification			Review Assessment		
CQA	Factors that can impact CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Dissolution	Raw materials Formulation Container Closure Process Scale/Equipment Site	Medium	Disintegration in lieu of dissolution accepted for end product testing	Acceptable	Approved Vyvanse capsule (b) (4) dissolution method found appropriate to use in evaluation of post-approval changes and biowaiver requests
Disintegration	Raw materials Formulation Container Closure Process Scale/Equipment Site	Not included	Stability-indicating method developed; correlation between hardness and disintegration time established Appropriate acceptance criteria determined to enable for end product testing	Acceptable	Method considered stability-indicating and appropriate for use in both release and end product testing

From Initial Risk Identification			Review Assessment		
CQA	Factors that can impact CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Tablet size/shape	Formulation Process Scale/Equipment	Not included	<div style="background-color: #cccccc; padding: 5px;">(b) (4)</div> <p>End product testing for appearance visually confirms shape</p>	Acceptable	<p><b>Monitor AERS/FAERS reports for incidences of choking and/or bowel obstruction due to swallowing tablet whole</b></p> <p><b>Generic drug products should follow recommendations in FDA Guidance Size/Shape (see reference 3 in executive summary) to reduce potential for medication errors associated with mixing up strengths of different sizes/shapes as well as potential safety risks from swallowing tablets whole, especially for pediatric population</b></p>



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