

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208510Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208510

SUPPL #

HFD # 130

Trade Name Vyvanse

Generic Name lisdexamfetamine dimesylate

Applicant Name Shire Development, LLC

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Shire submitted two pivotal biopharmaceutic studies to support this NDA as follows:

- 1) SHP489-126 – To compare the pharmacokinetics of SPD489 60 mg in its capsule formulation and in chewable tablet formulation as assessed by estimates of relative bioavailability
- 2) SHP489-127 – To compare the pharmacokinetics of a single dose of SPD489 60 mg as a chewable tablet in both a fasting and fed state as assessed by estimate of relative bioavailability

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires

metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21977

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of

new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Hiren Patel, PharmD, MS, RAC
Title: Team Leader, Senior Regulatory Project Manager
Date: January 28, 2017

Name of Division Director signing form: Mitchell Mathis, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

HIREN PATEL
01/28/2017

MITCHELL V Mathis
01/28/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208510 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Vyvanse Established/Proper Name: lisdexamfetamine dimesylate Dosage Form: Chewable Tablets		Applicant: Shire Development, LLC Agent for Applicant (if applicable):
RPM: Hiren Patel, PharmD, MS, RAC		Division: Division of Psychiatry Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>January 31, 2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 3
 (*confirm chemical classification at time of approval*)

- | | |
|-----------------------------------------------------------|---------------------------------------------------|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 1/28/17
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> 	8/31/16 8/29/16
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 6/7/16 DMEPA: <input type="checkbox"/> None 11/8/16; 1/9/17 DMPP/PLT (DRISK): <input type="checkbox"/> None 12/1/16 OPDP: <input type="checkbox"/> None 12/12/16 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	6/7/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>12/7/16</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 8/28/15
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/23/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/9/17
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)		1/3/17
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)		1/3/17 (clinical review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵		<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 		<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)		<input checked="" type="checkbox"/> None requested
Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input checked="" type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 12/7/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)		<input type="checkbox"/> None requested 7/1/16

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical		<input checked="" type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)		<input type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews ⁶		
• Tertiary review (indicate date for each review)		<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (indicate date for each review)		<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)		<input type="checkbox"/> None 11/23/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)		11/23/16
<input type="checkbox"/> Review & FONSI (indicate date of review)		
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)		<input checked="" type="checkbox"/> Acceptable (confirmation received 1/27/17) Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

HIREN PATEL
01/30/2017



NDA 208510

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Shire Development LLC
300 Shire Way
Lexington, MA 02421-2101

ATTENTION: Bao Le
Associate Director, Global Regulatory Affairs

Dear Ms. Le:

Please refer to your New Drug Application (NDA) dated and received, March 31, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lisdexamfetamine Dimesylate Chewable Tablets, 10mg, 20mg, 30mg, 40mg, 50mg and 60mg.

We also refer to:

- Your correspondence, dated and received June 07, 2016, requesting review of your proposed proprietary name, Vyvanse
- Our email dated August 14, 2016, requesting clarifying information
- Your amendment, dated and received August 16, 2016, submitting the clarifying information

We have completed our review of the proposed proprietary name, Vyvanse and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact Shin-Ye Chang, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3971.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/31/2016



NDA 208510

MEETING PRELIMINARY COMMENTS

Shire Development LLC
Attention: Mary Beth Wigley, B.S., M.S.
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne PA 19087

Dear Ms. Wigley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyvanse (lisdexamfetamine dimesylate) Chewable Tablets 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg.

We also refer to your June 16, 2015 correspondence, received June 16, 2015, requesting a meeting to reach agreement with the Agency on the plans and overall regulatory content strategy of the eventual VYVANSE Chewable Tablet NDA submission as well as the content of the Chemistry, Manufacturing, and Controls (CMC) modules of the NDA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

Sincerely,

{See appended electronic signature page}

LCDR Shin-Ye Sandy Chang, Pharm.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 2, 2015 2:00 – 3:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: 208510
Product Name: VYVANSE (lisdexamfetamine dimesylate) Chewable
Tablets 10, 20, 30, 40, 50, and 60 mg.
Indication: Attention Deficit Hyperactivity Disorder (ADHD); Moderate to
Severe Binge Eating Disorder (BED).
Sponsor/Applicant Name: Shire Development, LLC

FDA ATTENDEES (tentative)

Ellis Unger, M.D., Office of New Drugs I (ODE I), Director
Mitchell Mathis, M.D., Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, M.D., Deputy Director, DPP
Lucas Kempf, M.D., Clinical Team Leader, DPP
Christina Burkhart, M.D., Clinical Reviewer, DPP
Linda Fossom, Ph.D., Nonclinical Supervisor, DPP
Ikram Elayan, Ph.D., Nonclinical Reviewer, DPP
Hao Zhu, Ph.D., Office of Clinical Pharmacology (OCP) Team Leader
Huixia Zhang, Ph.D., OCP, Reviewer
David Claffey, Ph.D., Office of New Drug Products/Chemistry, Manufacturing, and Controls (ONDP/CMC) Lead
Mariappan Chelliah, Ph.D., ONDP/CMC Reviewer
Angelica Dorantes, Ph.D., Division of Biopharmaceutics (DBP), Biopharmaceutics Branch I (BBI), Branch Chief
Peiling Yang, Ph.D., Biometrics Team Leader, Division of Biometrics 1 (OB)
Jinglin Zhong, Ph.D., Biometrics Reviewer, OB

SPONSOR ATTENDEES

Timothy Whitaker, M.D., VP, Clinical Therapeutic Area Head Neuroscience
Kristen Manion, Director, Global Regulatory Affairs – CMC
Mary Beth Wigley, Director, Global Regulatory Affairs
James Ermer, Senior Director, Clinical Pharmacology and Pharmacokinetics
Susan Hu, PhD, Senior Director, Pharmaceutical Development Lead, Product Development
Paul Fagan PhD, Product Development Contractor, Pharmaceutical Sciences
Ching Kuo Chow PhD, Director, Pharmaceutical Sciences, Product Development
Bridget McNulty, Associate Director, Global Pharmaceuticals Technology, Analytical

Brad Berkowicz, Senior Principal Engineer, Global Pharmaceuticals Technology, Drug Product Manufacturing, Science, & Technology

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 2, 2015, 2:00-3:00 PM, FDA White Oak Building between Shire and the Division of Psychiatry Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Shire is currently developing an alternate formulation for VYVANSE (lisdexamfetamine dimesylate) in the form of a chewable tablet (10, 20, 30, 40, 50, and 60 mg) to aid administration for patients unable to swallow capsules. This NDA will reference existing IND 67,482 and will also cross-reference the approved Vyvanse Capsule NDA 21-977. The Sponsor proposes that information pertaining to the chewable tablet formulation will be added to the label for the VYVANSE Capsules and that the proposed indications for the chewable tablets will be the same as the currently approved indications for VYVANSE Capsules.

An *in vivo* bridging study (SHP489-126) to establish bioequivalence between the approved VYVANSE 60 mg Capsule and VYVANSE 60 mg Chewable Tablets, and a second study (SHP489-127) to support the bioequivalence of the 60 mg chewable tablet in a fasted and fed state are in the data reporting phase. The Sponsor intends to request a waiver of *in vivo* bioequivalence studies for the lower dosage strengths (10mg, 20mg, 30mg, 40mg, and 50mg) of the chewable tablets, noting that they are qualitatively identical in composition to the 60 mg dose strength chewable tablet.

According to the Sponsor, the results from the bridging study (SHP489-126) indicate that the two formulations are bioequivalent. While the inactive prodrug itself does not meet the 80-125% established criteria, the active moiety, d-amphetamine, does meet all parameters tested:

Bioequivalence Results for Study SHP489-126

Analyte	Parameter (unit)	Geometric LS Mean		Geometric LS Mean Ratio Test/Reference (%)	90% CI of Geometric Mean Ratio Test/Reference (%)
		Reference Treatment A	Test Treatment B		
Lisdexamfetamine	Cmax (ng/mL)	35.59	30.93	86.90	(78.01, 96.81)
	AUC (0-last) (h*ng/mL)	41.03	34.72	84.63	(77.46, 92.46)
	AUC (0-1hr) (h*ng/mL)	9.37	17.46	186.33	(150.23, 231.12)
	AUC (1hr-last) (h*ng/mL)	28.40	16.49	58.07	(51.97, 64.89)
	AUC (0-2hr) (h*ng/mL)	34.53	33.38	96.69	(87.39, 106.97)
	AUC (2hr-last) (h*ng/mL)	16.81	8.94	53.20	(37.12, 76.26)
d-Amphetamine	Cmax (ng/mL)	55.91	55.46	99.18	(96.06, 102.41)
	AUC (0-last) (h*ng/mL)	1052.91	1047.53	99.49	(95.72, 103.40)
	AUC (0-inf) (h*ng/mL)	1126.15	1135.46	100.83	(97.35, 104.42)
	AUC (0-4hrs) (h*ng/mL)	114.27	130.85	114.51	(107.92, 121.50)
	AUC (4hrs-last) (h*ng/mL)	931.26	912.70	98.01	(93.87, 102.33)
	AUC (0-5hr) (h*ng/mL)	168.51	183.53	108.91	(104.21, 113.82)
	AUC (5hr-last) (h*ng/mL)	876.51	859.53	98.06	(93.74, 102.59)
	AUC (0-6hr) (h*ng/mL)	220.73	234.77	106.36	(102.56, 110.29)
	AUC (6hr-last) (h*ng/mL)	823.79	807.76	98.05	(93.59, 102.73)
	AUC (0-8hr) (h*ng/mL)	316.26	328.96	104.01	(101.05, 107.07)
	AUC (8hr-last) (h*ng/mL)	726.66	712.03	97.99	(93.21, 103.00)

Treatment A = SPD489 60mg in capsule form administered orally after fasting.

Treatment B = SPD489 60mg in chewable form administered orally after fasting.

Note: A linear mixed effects model is used with the log-transformed pharmacokinetic parameter as the dependent variable, with period, sequence, and treatment as fixed effects, and with subject by treatment modeled as a random effect with the FA0(2) parameterization. The resulting LSM means and Confidence Intervals are exponentiated.

Shire has requested this Type B meeting to reach agreement with the Agency on the plans and overall regulatory content strategy of the eventual NDA submission, as well as the content of the Chemistry, Manufacturing, and Controls (CMC) modules of the NDA which Shire plans to submit in the first quarter of 2016.

2.0 DISCUSSION

2.1 Quality

Question 1: Does the Agency agree with the Sponsor's proposal to cross-reference to the VYVANSE Capsule NDA 21-977 for all drug substance information?

FDA Response to Question 1:

Your proposal appears reasonable.

Question 2: Does the Agency agree with the Sponsor's intention to cross-reference (b) (4) DMF for all applicable information related to the strawberry flavoring excipient?

FDA Response to Question 2: Your plan to cross-reference to the Type-IV DMF# (b) (4) ingredient is acceptable. However, this DMF will be reviewed only as part of the NDA review process; therefore, we are not able to confirm the adequacy of this flavor excipient for the proposed drug product at this time.

Question 3: Does the Agency agree with the Sponsor's intention to cross-reference (b) (4) DMF for all applicable information related to the (b) (4) excipient?

FDA Response to Question 3: Your plan to cross-reference to the Type-IV DMF# (b) (4) from (b) (4) for the excipient (b) (4) is acceptable. However, this DMF will be reviewed only as part of the NDA review process; therefore, we are not able to confirm the adequacy of this excipient for the proposed drug product at this time.

Question 4: The eighteen primary registration/stability batches (three batches per strength) have been manufactured for Vyvanse Chewable Tablets and placed on stability. The Sponsor is considering further optimizing the drug product manufacturing process prior to NDA submission. If the Sponsor opts to perform additional process optimization (one or more of the changes as detailed below), the Sponsor would provide appropriate supporting data at time of NDA submission to bridge the optimized process that will be used commercially with the process used for primary registration/stability batches. Does the Agency agree?

FDA Response to Question 4: We understand that you propose to implement the following changes to the manufacturing process post-registration for commercial production: (b) (4)

Your proposed approach to demonstrate equivalency between the registration batches and the batches manufactured using the proposed commercial manufacturing process seems reasonable. However, determination of equivalency of the product (b) (4) would be made only after review of the data provided in the submission. Additionally, the agency recommends that you consider including the following in the NDA:

- a. Data from proposed in-process tests/controls to demonstrate equivalency between the registration and commercial batches, that includes at least more than one commercial scale batches which includes (b) (4) (b) (4)
- b. Three months accelerated stability data (b) (4) manufacturing process
- c. Multipoint dissolution profiles (b) (4) comparing the 20 mg and the 50 mg tablets manufactured before and after the change

Question 5:

- a. Does the Agency agree that the Sponsor will have adequately developed and determined the appropriate discriminatory power of the proposed dissolution procedure for the chewable tablet?

FDA Response to Question 5a: We agree with your plan to determine the effect of tablet crushing strength (b) (4) on the dissolution of the intact chewable

tablets. To provide robust evidence of the discriminatory capability of the dissolution method developed specifically for the lisdexamfetamine chewable tablets, we recommend that all tablet strengths be tested for the following additional variables: disintegrant level, tablet hardness, and coating level (if applicable).

Note that the adequacy of the selected dissolution method and the proposed acceptance criterion will be determined during the review of the NDA. See the additional FDA (Biopharmaceutics) comments for general recommendations regarding the dissolution information to be included in the NDA submission.

b. Does the Agency agree with the Sponsor's proposal to demonstrate that routine disintegration and hardness testing on release and stability could be used in lieu of routinely performing dissolution testing as per ICH Q6A decision tree 7 for the chewable tablet?

FDA Response to Question 5b: We agree with your plan to assess the discriminatory power of disintegration in parallel with that of the dissolution method. We also agree with your plan to use disintegration testing in lieu of dissolution testing should you find that the former is more sensitive than the latter for drug release testing and to comply with ICH Q6A Decision Tree #7, as well as the plan to retain dissolution testing (b) (4)

(b) (4) We recommend the submission of both dissolution and disintegration data in the NDA to permit assessment of the more appropriate test for batch release and stability. You may also investigate a potential correlation between dissolution and disintegration and include the findings in the NDA submission.

Question 6: Does the Agency agree that the Sponsor's approach is acceptable for requesting a waiver of in vivo bioequivalence requirements using in vitro dissolution for Vyvanse (lisdexamfetamine dimesylate) Chewable Tablets 10, 20, 30, 40, and 50 mg strengths?

FDA Response to Question 6: We agree that a biowaiver request could be submitted for the 10, 20, 30, 40 and 50 mg strengths of the chewable tablet (b) (4)

(b) (4)

(b) (4)

ADDITIONAL FDA COMMENTS

Biopharmaceutics:

For immediate release solid oral dosage forms, we have the following recommendations regarding the dissolution information that should be provided in the NDA.

- 1) Dissolution method development report:** *The report should include the following information.*
 - a. Solubility data for the drug substance over the physiologic pH range.*
 - b. Detailed description of the dissolution test parameters (i.e., equipment/apparatus, type and volume of media, agitation/rotation speed, pH, temperature, etc.). Include a narrative of why these parameters were selected and how the test conditions were optimized (e.g., sink conditions, stability considerations). If applicable, the type and the amount of surfactant added to the dissolution medium, and/or the use of strength dependent dissolution methods should be justified. The dissolution–time profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached; initial sampling time points typically include 10, 15, 20, 30, 45, 60, 90 and 120 min. At least twelve samples should be used per testing variable.*
 - c. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test (variant) products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10 -20% change to the specification-ranges of these variables). If available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent to the reference (target) product.*
 - d. A list of the critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution.*
 - e. Summary figures and tables showing mean and %RSD cumulative amount of drug released at each sampling timepoint, and if applicable, f_2 (profile similarity) values.*
 - f. Validation data for the dissolution method (i.e., method robustness, etc.) and analytical*

method (precision, accuracy, linearity, stability, etc.).

g. A detailed justification of the proposed dissolution acceptance criteria.

2. Dissolution Acceptance Criteria: *For the selection of the dissolution acceptance criterion(a) for the product, the following points should be considered.*

- a. In setting the dissolution acceptance criteria of the product (i.e., specification- sampling time point and specification value), use the dissolution profiles of the pivotal clinical batches, i.e., based on USP Stage 2 dissolution testing (n = 12) of the batches at the time of manufacture and during long-term storage for the duration of the trial(s). In addition, the dissolution profiles of the primary (registration) and supportive stability batches during long-term storage should be considered.*
- b. The specification time point should be where Q=80% drug dissolution occurs. However, for a slowly dissolving product, specifications at two time points may be appropriate. The first time point should be selected during the initial dissolution phase (e.g., 15-30 minutes about 40-50% dissolution) and the second time point should be where Q = 80% dissolution occurs.*

3. Supporting Data: *The following detailed experimental data should be submitted to support the dissolution method development and setting of acceptance criterion(a):.*

- a. As much individual vessel data as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.*
- b. Analysis datasets in “.xpt” format, and their define files. The dataset should contain individual vessel data for all sampling timepoints.*
- c. Batch release and stability dissolution data presented graphically. The plot(s) of individual vessel data for the clinical and stability batches should include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.*

Question 7: *The Sponsor seeks any Agency “Advice” concerning the provided background information prior to its incorporation into the NDA submission particularly with respect to the development of a flavored, chewable tablet for pediatric use.*

FDA Response to Question 7: *We recommend [REDACTED] (b) (4) [REDACTED] that you document and justify any changes during development. The Agency does not have any other specific advice at this point.*

Additional Comment: Note that if you propose to use “chewable” in the established name we expect that the product will meet the USP <1151> definition of a chewable tablet, i.e. one that must be chewed, rather than one that may be chewed.

2.2. Regulatory

Question 8: Shire plans to provide a cross-reference to the Vyvanse NDA 21-977 for safety and efficacy information supporting the chewable tablet formulation. Does the Agency agree?

FDA Response to Question 8: If the two formulations are determined to be bioequivalent, this would be acceptable.

Question 9: Shire plans to submit a combined package insert for the chewable tablet and the capsule formulations. Does the Agency agree?

FDA Response to Question 9: If the two formulations are determined to be bioequivalent, this would be acceptable.

Question 10: Shire concludes that additional pediatric studies under the Pediatric Research Equity Act (PREA) associated with this application will likely not/should not be required at time of NDA approval. Does the Agency agree?

FDA Response to Question 10: If the two formulations are determined to be bioequivalent, additional pediatric studies under PREA will likely not be required. This will be determined at the time of the NDA review after consultation with the Pediatric Review Committee. Please also refer to 6/19/2015 Agency correspondence to the Sponsor.

Question 11: It is Shire’s position that the current protocols (SHP489-126 and SHP489-127) for establishing bioequivalency between the proposed chewable tablet and approved capsule formulations designed to be conducted and completed in Healthy Adults are adequate to support the filing of the NDA for Vyvanse Chewable Tablets and no additional information is considered necessary by the Agency for incorporation into the NDA prior to its submission. Does the Agency agree?

FDA Response to Question 11: If the two formulations are determined to be bioequivalent, we agree. Please also refer to 6/19/2015 Agency correspondence to the Sponsor.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

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/s/

SHIN-YE CHANG
08/28/2015