

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208147Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 208147

SUPPL #

HFD # 130

Trade Name Dyanavel XR

Generic Name amphetamine extended-release oral suspension (2.5 mg amphetamine base per ml)

Applicant Name Tris Pharma

Approval Date, If Known October 19, 201

### **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)(2) NDA

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.

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?

3 years

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?

No

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# 21303 Adderall XR

NDA# 11522 Adderall

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:

Study TRI102-ADD-001 was a multicenter, dose-optimized, double-blind, randomized, placebo-controlled study intended to evaluate efficacy of Amphetamine ER Oral Suspension in Pediatric Patients with ADHD in a Laboratory School Study conducted in 108 pediatric patients with ADHD to evaluate the efficacy and safety of this dosage form.

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"):

Study TRI102-ADD-001

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 # 116985      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: Renmeet Grewal, Pharm.D., RAC  
Title: Senior Regulatory Project Manager  
Date: 10/17/18

Name of Office/Division Director signing form: Mitchell V. Mathis, M.D.  
Title: Division Director

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

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/s/  
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RENMEET GREWAL  
10/19/2015

MITCHELL V Mathis  
10/19/2015

**From:** [Grewal, Renmeet](#)  
**To:** [Yulia Pincus](#)  
**Cc:** [Grewal, Renmeet](#)  
**Subject:** NDA 208147 Dyanavel XR labeling/PMR & PMC negotiations  
**Date:** Wednesday, October 14, 2015 4:44:25 PM  
**Attachments:** [Round 3 labeling sent to sponsor 10.14.15.docx](#)  
[NDA 208147 carton 10.14.15.pdf](#)  
[NDA 208147 PMR IR 10.14.15.doc](#)  
**Importance:** High

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Dear Yulia,

We have 2 additional Postmarketing Requirements you must agree to prior to the action of your application. Please respond and provide dates for the Post Marketing Requirement studies (attached). We also understand the two additional studies may affect the proposed dates for the previous agreed upon Postmarketing Requirement. If needed please propose new dates for the previously agreed upon PostMarketing Requirement in the attached document. Additionally, we have updated the PostMarketing Commitment to reflect your request to keep the option of evaluating an alternative discriminatory dissolution method which is reflected in the attached document.

Additionally, Please find the attached labeling. In reference to the carton and container labeling, you must remove the (b) (4) (attached).

Respond no later than COB tomorrow, Thursday, October 15<sup>th</sup>.

Regards,  
Rimmy

*Renmeet Grewal, Pharm.D., RAC, CDR USPHS  
Team Leader, Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: [renmeet.grewal@fda.hhs.gov](mailto:renmeet.grewal@fda.hhs.gov)  
Fax: (301) 796-9838*

1. A single-dose, open-label, randomized pharmacokinetic study of Dyanavel XR oral suspension in male and female children (4 to less than 6 years of age) with ADHD in fed condition.

Final Protocol Submission: Month/ Year  
Study/Trial Completion: Month/ Year  
Final Report Submission: Month/ Year

2. A one year Pediatric Open-Label Safety Study for patients age 4 to 5 years (at the time of entry into Study 1 or Study 2 or at the time of enrollment if directly enrolled into Study 3) with ADHD.

Final Protocol Submission: Month/ Year  
Study/Trial Completion: Month/ Year  
Final Report Submission: Month/ Year

3. A randomized, double-blind, placebo-controlled, flexible-dose titration study of amphetamine extended-release oral suspension (Dyanavel XR) in children ages 4 to 5 years diagnosed with ADHD.

Final Protocol Submission: January 2016  
Study/Trial Completion: January 2017  
Final Report Submission: May 2017

Additionally, we have updated the PostMarketing Commitment to reflect your request to keep the option of evaluating an alternative discriminatory dissolution method:

4. Develop a dissolution method with enough discriminating ability using a single pH media with appropriate ionic strength. Clarify the effects of pH and ionic strength on the dissolution during the development of the dissolution method. Using the developed method test at least five commercial batches and evaluate the stability for the registration/primary batches through at least 12 months of storage under the long-term conditions. These data should be used for the setting of the final dissolution acceptance criteria. You have the option of evaluating an alternative discriminatory dissolution method for (b) (4) in case a common dissolution method cannot be successfully developed for drug product and the (b) (4). The final report with the complete dissolution information/data should be submitted under a supplement to the NDA within 12 months from the action date.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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RENMEET GREWAL  
10/14/2015

**From:** Grewal, Renmeet  
**To:** ["Yulia Pincus"](#)  
**Subject:** NDA 208147 Medguide  
**Date:** Friday, October 02, 2015 2:22:00 PM  
**Attachments:** [NDA 208147 DYANAVEL amphetamine MG 10.2.15.doc](#)  
**Importance:** High

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Dear Yulia,

Please find the proposed medication guide for NDA 208147 attached to this email. Please confirm you received this email and respond with any comments by COB Monday, October 5<sup>th</sup>.

Regards,  
Rimmy

*Renmeet Grewal, Pharm.D., RAC, CDR USPHS  
Team Leader, Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: [renmeet.grewal@fda.hhs.gov](mailto:renmeet.grewal@fda.hhs.gov)  
Fax: (301) 796-9838*

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/s/  
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RENMEET GREWAL  
10/02/2015



NDA 208147

## LABELING PMR/PMC DISCUSSION COMMENTS

Tris Pharma  
Attention: Yulia Pincus, Ph.D.  
Senior Manager, Regulatory Affairs  
2033 Route 130  
Monmouth Junction, New Jersey 08852

Dear Dr. Pincus:

Please refer to your New Drug Application (NDA) dated December 19, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dyanavel XR).

On August 28, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by October 5, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We have the following proposed Postmarketing Requirements/ Commitments:

2970-1. Develop a dissolution method with enough discriminating ability using a single pH media with appropriate ionic strength. Clarify the effects of pH and ionic strength on the dissolution during the development of the dissolution method. Using the developed method test at least five commercial batches and evaluate the stability for the registration/primary batches through at least 12 months of storage under the long-term conditions. These data should be used

for the setting of the final dissolution acceptance criteria. The same dissolution method should be used for the [REDACTED] <sup>(b) (4)</sup>.

The final report with the complete dissolution information/data should be submitted under a supplement to the NDA within 12 months from the action date.

2970-2. A randomized, double-blind, placebo-controlled, flexible-dose titration study of amphetamine extended-release oral suspension (Dyanavel XR) in children ages 4 to 5 years diagnosed with ADHD.

Final Protocol Submission:	November 2015
Study/Trial Completion:	August 2016
Final Report Submission:	January 2017

If you have any questions, contact me, at [Renmeet.Grewal@fda.hhs.gov](mailto:Renmeet.Grewal@fda.hhs.gov) or 301-796-1080

Sincerely,

*{See appended electronic signature page}*

CDR Renmeet Grewal, Pharm.D., RAC  
Team Leader/ Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

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/s/  
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RENMEET GREWAL  
09/29/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 208147

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Tris Pharma, Inc.  
2033 Route 130, Suite D  
Monmouth Junction, NJ 08852

ATTENTION: Yulia Pincus, PhD  
Sr. Manager, Regulatory Affairs

Dear Dr. Pincus:

Please refer to your New Drug Application (NDA) dated December 18, 2014, and received December 19, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine Extended-Release Oral Suspension, 2.5 mg amphetamine base per mL.

We also refer to:

- Your correspondence, dated December 18, 2014 and received December 19, 2014, requesting review of your proposed proprietary name, Dyanavel XR
- Our email, dated January 7, 2015, requesting clarification of the established name
- Your amendment, dated January 8, 2015, and received January 9, 2015, clarifying the established name

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

If any of the proposed product characteristics as stated in your December 19, 2014, and January 9, 2015, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Renmeet Grewal, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1080.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy 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/  
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TODD D BRIDGES  
03/13/2015



NDA 208147

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Tris Pharma Inc.  
Attention: W. Scott Groner  
Director of Regulatory Affairs  
2033 Route 130, Suite D  
Monmouth Junction, NJ 08852

Dear Mr. Groner:

Please refer to your New Drug Application (NDA) dated and received December 19, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Dyanavel XR (dextroamphetamine and amphetamine) extended-release 2.5 mg/ml oral suspension.

We also refer to your amendments dated January 8, 2015, and February 12, 2015 (2).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any post-marketing commitment requests by September 28, 2015.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

A detailed evaluation of the February 12, 2015, responses to the February 6, 2015, general Chemistry, Manufacturing, and Controls and Microbiology information request will be carried

out in this review cycle. After a preliminary examination of the responses we recommend the following:

1. Include viscosity testing in all on-going stability and in-use testing due to the limited developmental experience with this product.
2. Provide data to demonstrate the acceptability of drug product with (b) (4) (i.e. at the (b) (4))

### **Biopharmaceutics Comments:**

Provide the following information/data:

1. The dissolution method development report including:
  - a. Justification of the dual media used.
  - b. Dissolution method validation report.
2. Data supporting the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e.,  $\pm 10\text{-}20\%$  change to the specification-ranges of these variables) for the most relevant critical manufacturing variables (e.g. (b) (4) distribution, etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.
3. There is no IVIVC approved for your proposed product. Therefore, the selection of the dissolution acceptance criteria limits should be based on the mean target (biobatches) value (b) (4) % and NLT (b) (4) % for the last specification time-point. Implement these acceptance criteria for your proposed product and provide the revised specifications table with the updated acceptance criteria for the dissolution test.
4. The *in vitro* data provided show that more than (b) (4) % of the drug is dissolved within (b) (4) minutes, which seems inconsistent with the ER claim, especially given that the proposed dosing regimen is once daily. Therefore, provide information/data supporting the controlled-release designation claim, such as:
  - a. The drug product's steady-state performance is comparable (e.g. degree of fluctuation is similar or lower) to a currently marketed non-controlled-release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
  - b. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.
  - c. The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.

### **Biostatistics Deficiencies:**

Please clarify whether raw data (i.e., an electronic version of Case Report Form data) were directly collected in (i) CDISC SDTM format or in (ii) a legacy format different from SDTM. If

(ii), we request you submit the legacy format raw data (SAS readable), and programs you used to generate the submitted analysis (or ADaM) datasets from the raw data. Please include documented definitions of the mappings of raw data variables onto the analysis data variables used in the efficacy analyses reported in the clinical study report.

If you have already submitted those, please specify their location.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Psychiatry Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver and partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver and deferral request is denied.

If you have any questions, contact CDR Renmeet Grewal, Pharm.D., RAC, Senior Regulatory Project Manager, at either (301)796-1080 or [Renmeet.Grewal@fda.hhs.gov](mailto:Renmeet.Grewal@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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MITCHELL V Mathis  
03/03/2015



NDA 208147

**NDA ACKNOWLEDGMENT**

Tris Pharma Inc.  
Attention: W. Scott Groner  
Director of Regulatory Affairs  
2033 Route 130, Suite D  
Monmouth Junction, NJ 08852

Dear Mr. Groner:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact me at either (301) 796-1080 or [Renmeet.Grewal@fda.hhs.gov](mailto:Renmeet.Grewal@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

CDR Renmeet Grewal, Pharm.D., RAC  
Team Leader/Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RENMEET GREWAL  
01/05/2015



IND 116985

**MEETING PRELIMINARY COMMENTS**

Tris Pharm, Inc.  
Attention: W. Scott Groner  
Director or Regulatory Affairs  
2033 Route 130  
Monmouth Junction, New Jersey 08852

Dear Mr. Groner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Amphetamine ER Oral Suspension (eq. 20mg amphetamine base per 8ml).

We also refer to the meeting between representatives of your firm and the FDA on Thursday, November 6, 2014. The purpose of the meeting was to discuss NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact CDR Renmeet Grewal at either [Renmeet.Grewal@fda.hhs.gov](mailto:Renmeet.Grewal@fda.hhs.gov) or 301-796-1080.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** November 6, 2014 1:00pm  
**Meeting Location:** White Oak, Building 22, Room 1313  
**Application Number:** IND 116,985  
**Product Name:** Amphetamine ER Oral Suspension (eq. 20mg amphetamine base per 8ml)  
**Indication:** Treatment of Attention Deficit Hyperactivity Disorder (b) (4)  
**Sponsor/Applicant Name:** Tris Pharma, Inc

**FDA ATTENDEES**

Mitchell Mathis, M.D. Division Director, Division of Psychiatry Products (DPP)  
Tiffany Farchione, M.D., Acting Deputy Division Director, DPP  
Linda Fossom, Ph.D., Pharmacology/Toxicology Supervisor, DPP  
Ikram Elayan, Ph.D., Pharmacology/Toxicology Reviewer, DPP  
Renmeet Grewal, Pharm.D., RAC, Project Manager, DPP  
David Claffey, Ph.D, Team Leader, Office of Pharmaceutical Quality (OPQ)  
Thomas Wong, Ph.D., Reviewer, OPQ  
Hao Zhu, Ph.D., Team Leader, Office of Clinical Pharmacology  
Andre Jackson, Ph.D., Reviewer, Office of Clinical Pharmacology  
Peiling Yang, Ph.D., Team Leader, Office of Biometrics  
Andrejus Parfionovas, Reviewer, Office of Biometrics  
Irene Chan, Pharm.D., Team Leader, Office of Surveillance & Epidemiology (OSE), Division of Medication Error, Prevention, & Analysis  
Loretta Holmes, Pharm.D., Reviewer, OSE, Division of Medication Error, Prevention, & Analysis  
Danny Gonzalez, Pharm.D., Reviwer, OSE, Division of Risk Management  
Vasantha Ayalasonmayajula, Pharm.D., Project Manager, OSE

**SPONSOR ATTENDEES**

Dr. Sally A. Berry, Chief Medical Officer, Tris Pharma  
Ms. Norma J. Cappetti, Vice President of Regulatory Affairs, Tris Pharma  
Mr. Kalyan Kathala, Group Leader, Product Development, Tris Pharma  
Dr. Yulia Pincus, Senior Manager of Regulatory Affairs, Tris Pharma  
Dr. Yu-Hsing Tu, Vice President of Research and Development, Tris Pharma

## 1.0 BACKGROUND

The sponsor proposes to evaluate amphetamine ER oral suspension (TRI102) for the treatment of attention deficit hyperactivity disorder (ADHD), (b) (4) under this IND. The sponsor describes this compound as a non-catecholamine sympathomimetic amine that has the ability to stimulate central nervous system (CNS) activity.

The sponsor outlines the rationale for developing this product, noting that the drug product is intended to provide convenience to patients who prefer oral dosage forms but have difficulty swallowing solids. There are currently no available long-acting liquid amphetamine formulations. Because children are often unable to swallow pills, and because children comprise a large subset of the ADHD patient population, the sponsor anticipates this product will fill an unmet need.

The sponsor proposes to rely upon FDA's general findings of safety and efficacy for an immediate release formulation of Adderall. The sponsor notes that Adderall tablets (Teva Womens NDA 011522) have been discontinued, and proposes to use the RLD dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate tablet (ANDA 040422, (b) (4) Barr Laboratories, Inc.).

Two clinical studies have been conducted to support approval through the 505(b)2 pathway:

- Study 2014-3401—single-dose, 3-way bioavailability and PK study in healthy adult subjects with the study drug and the reference product dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablet (ANDA 040422) under fasting conditions. This study also included a food-effect arm for the Tris product.
- TRI102-ADD-001—placebo-controlled, Phase 3, efficacy and safety trial in pediatric patients (ages 6-12 years old) with ADHD. The primary study endpoint was the SKAMP (Swanson, Kotin, Agler, M-Flynn, and Pelham) combined score four hours post-dose.

## 2.0 DISCUSSION

### 2.1. Clinical

**Question 1:** Tris has conducted a phase 3 efficacy study in pediatric (6-12 year old) patients with ADHD and a phase 1 pharmacokinetic study in adult volunteers, to support this 505(b)(2) application. Results of the studies are provided in Section 10.1.1 and in Section 10.1.2, respectively. (b) (4)

**FDA Response to Question 1:**

*We do not agree. Pharmacokinetic studies in the target population (ages 6-12) will be required, because, for extended-release stimulant products, the shape of the PK curve has a direct relationship to efficacy.*

**Sponsor Response:**



(b) (4)

(b) (4)

**Discussion at Meeting:**

*The Division acknowledged that the lack of PK comments on the initial iPSP was an oversight on our part. However, the PK study in children ages 6-12 years will still be required.*

*We normally request PK data for the target population prior to conduct of a clinical trial to inform dose selection. In this case, the clinical study has already been completed, so that rationale no longer applies. However, you are seeking an indication for adolescents as well. You currently have PK data in adults and clinical data in children ages 6-12 years; in the absence of PK data in children, there is no basis for interpolation of efficacy in adolescents.*

*At the meeting, you proposed to conduct a pediatric PK study including both children 6-12 years of age and adolescents. Your proposal is acceptable to us. Our general requirements for a pediatric PK study have been provided to you through our recent communication on your iPSP. Please ensure the requirements will be met when you design the study. We recommend you submit your pediatric PK study protocol for us to review prior to conducting the study.*

(b) (4)

**Question 2:** For the ADHD indication, does the Agency agree that study TRI102-ADD-001 (Section 10.1.1) confirms the efficacy of our drug product and is adequate to support the NDA filing and review from an efficacy perspective?

**FDA Response to Question 2:**

*This will be a matter of review upon receipt of the NDA.*

**Discussion at Meeting:**

*No further discussion.*

**Question 3:** Does the FDA concur that the results for the study TRI102-ADD-001 (Section 10.1.1), meet the Agency's expectations to support the (b) (4)

**FDA Response to Question 3:**

*Again, this will be a matter of review.*

**Discussion at Meeting:**

*No further discussion.*

**2.2. Clinical Pharmacology**

**Question 4:** Tris has conducted a relative bioavailability study on Amphetamine ER Oral Suspension compared to a reference product, Dextroamphetamine Saccharate, Amphetamine Aspartate Monohydrate, Dextroamphetamine Sulfate, and Amphetamine Sulfate, A040422 ( (b) (4) Barr Laboratories, Inc.), in adult volunteers (Study #2014-3401). Results of this study are summarized in Section 10.1.2.

**FDA Response to Question 4:**

*No. We disagree. Please refer to our response to question 1.*

**Discussion at Meeting:**

*No further discussion.*

**2.3 Pharmacology/Toxicology**

**Question 5:** In this 505(b)(2) application, Tris will reference the Agency's previous findings of nonclinical safety for the RLD, Adderall®, N011522, held by Teva Womens. The content of nonclinical information in the application will include an overview of the current amphetamine literature in Module 2.4. No new impurities, inactive ingredients, excipients, or degradents will be reported for this drug product. Tris does not intend to conduct any additional nonclinical studies and therefore proposes not to include Module 2.6 in the NDA. Does the Agency agree Module 2.6 is not required for this 505(b)(2) application?

**FDA Response to Question 5:**

*Yes, we agree.*

*Additional Pharmacology/Toxicology comments:*

*Regarding the nonclinical advice we recently provided for your iPSP, we have determined, after further consideration, that it will not be necessary for you to provide data from a study in juvenile animals to support use in children less than 13 years of age or for use in labeling. We sincerely apologize for this confusion.*

*Discussion at Meeting:*

*No further discussion.*

## 2.4 Chemistry and Manufacturing Controls

*Question 6:* Tris will submit updated stability data to the NDA file (12 months data under the room temperature conditions) within three (3) months of the date of the NDA submission. At the time of the NDA submission, Tris intends to include at least nine (9) months of stability collected under the room temperature condition ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\%\text{RH}$ ); nine (9) months of stability collected under the intermediate condition ( $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \pm 5\%\text{RH}$ ) and six (6) months of stability under the accelerated ( $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\%\text{RH}$ ) condition for three exhibit test batches. Will this be acceptable to the Agency?

*FDA Response to Question 6:*

*We recommend that the long-term stability testing cover a minimum of 12 months duration at the time of NDA submission, as per ICH Q1A(R2) guidance.*

*Sponsor's Response:*

We interpret the Agency's response to mean that NDA submission with 9 months of room temperature stability data is not going to result in a Refuse-to-File (RTF) determination for this NDA. Please confirm.

*Discussion at Meeting:*

*Submitting the NDA with only nine months of stability data might not result in an RTF, but this determination will be made after NDA submission.*

*Question 7:* Tris has conducted the *in vitro* alcohol ([Section 10.2.1](#)) and dissolution profiling studies under various pHs on the clinical exhibit test batches ([Section 10.2.2](#)) and has included the study designs and results in the Briefing Package for this Pre-NDA Meeting. Does the FDA agree the data are sufficient for the NDA filing and review?

*FDA Response to Question 7:*

*The experiments you have conducted to investigate pH-dependent dissolution and the impact of alcohol on the dissolution rate of the proposed drug product seem adequate for NDA filing and review purposes with regards to the evaluation of the alcohol dose dumping potential of your proposed product. However, provide in your NDA*

*experimental data that confirm the adequacy of the proposed dissolution method for your proposed product; the selection of developmental parameters and the discriminating capability of the method should be investigated and reported. Please refer to the Additional Biopharmaceutics Comments for the dissolution data and information to be provided in the NDA.*

**Discussion at Meeting:**

*No further discussion.*

**Question 8:** In the STUDY MAY PROCEED letter, dated January 9, 2014, the Division stated the following: “As development progress, you should monitor the d:l ratio of the (b) (4) and implement with appropriate control limits.” In [Section 10.2.4](#), Tris provides the evidence demonstrating the ability to maintain an appropriate d:l ratio throughout the manufacturing process, plus an outline of the control strategy for the manufacturing of this drug product. This will also be included in the future NDA. Does the Agency agree the available data and the proposed control strategy support the goal of controlling the ratio of d and l- enantiomers in the drug product?

**FDA Response to Question 8:**

*On face, the information you provided appears to sufficiently control the ratio of d-and l- enantiomers in the drug product; however, the final determination will be made during review of the application. Include the justification with supporting data in the NDA submission.*

**Discussion at Meeting:**

*No further discussion.*

## 2.5 Labeling

**Question 9:** In the IND, the strength of the Amphetamine ER Oral Suspension is expressed as 20 mg amphetamine base per 8 mL. However, for the final labeling (insert, bottle, label, etc.) Tris proposes to express the strength of the drug product as 2.5 mg amphetamine base per mL. The finished product specification and stability protocol would be updated to reflect this strength convention. Will this be acceptable to the Agency?

**FDA Response to Question 9:**

*Yes we agree, the expression of the strength on per mL basis.*

**Sponsor Response:**

Tris wishes to clarify that the NDA application will contain documents that will express strength of the product in two different formats, of which only narratives, labeling, and

finished product specifications and stability protocol will state the strength as 2.5 mg/mL. Please confirm this is acceptable.

**Discussion at Meeting:**

*This was found acceptable.*

**Question 10:** Tris plans to compile the safety section of the proposed drug product labeling based on the following: adverse events information in the RLD label and other amphetamine products, and adverse events observed in the clinical trial TRI102-ADD-001, and class labelling (warnings and precautions). Does the Division agree this safety data shall adequately support the NDA when filed for Amphetamine ER Oral Suspension?

**FDA Response to Question 10:**

*On face, this appears adequate. The details of this strategy and the adequacy of the resultant labeling language will be a matter of review.*

**Discussion at Meeting:**

*No further discussion.*

**Question 11:**

In this 505(b)(2) application, Tris will reference Adderall®, N011522, held by Teva Womens as the RLD. However, the innovator product is discontinued and the currently available labeling has not been updated to the required PLR format. To satisfy NDA submission requirement, Tris intends to use the PLR labeling format for development of the label for Amphetamine ER Oral Suspension following the Guidance for Industry entitled *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements*, dated February 2013. Does the Agency agree with the proposed strategy?

**FDA Response to Question 11:**

*Yes. In addition, you may wish to refer to the current Vyvanse label (NDA 021977). That label was recently updated to reflect current guidance. Because that product is also a stimulant, it would be the most appropriate model.*

**Sponsor Response:**

Tris interprets the Agency's response to mean that Tris is permitted to use the (Class) label text of Vyvanse for label development while only listing Adderall IR as the RLD.

**Discussion at Meeting:**

*This is correct.*

**Question 12:** In this 505(b)(2) application, Tris will reference Adderall®, N011522, held by Teva Womens, as the RLD. Per RLD labeling, Tris is seeking an indication in ADHD (b) (4). Does the Division agree with the language in the proposed indications?

**FDA Response to Question 12:**

(b) (4)

**Discussion at Meeting:**

*No further discussion.*

**2.6 Other**

**Question 13:** Tris will conduct a clinical study in children 4-5 years with ADHD post approval as per the Agreed Pediatric Study Plan. (b) (4)

(b) (4)

. Does the Agency agree?

**FDA Response to Question 13:**

*In order to qualify for additional exclusivity, your study must be completed in response to a Pediatric Written Request. You may ask FDA to issue a Written Request for you pediatric studies. Please refer to the guidance entitled "[Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act](#)" for additional details.*

**Sponsor Response:**

Tris interprets the Agency's response to mean that once a Pediatric Written Request is requested, received, and the study produces positive results, (b) (4)

(b) (4)

. Please confirm.

**Discussion at Meeting:**

A (b) (4)

*We strongly recommend that you reach agreement on the protocol/SAP before trial initiation.*

**Question 14:** The NDA will include a single-dose pivotal phase 1 pharmacokinetic study and a phase 3 efficacy study in pediatric patients with ADHD. As detailed in [Section 10.4](#), Tris proposes to provide a summary of clinical safety, summary of clinical efficacy and clinical overview for these pivotal studies with no integrated summary of safety or integrated summary of efficacy. Does FDA agree that integrated summaries of safety and efficacy are not required?

**FDA Response to Question 14:**

*You are not required to submit an integrated summary that combines pediatric and adult data. However, data from the pediatric clinical and pharmacokinetic trials (see response to Q1, above) should be included in integrated summary of safety.*

**Discussion at Meeting:**

*No further discussion.*

**Question 15:** Are there other areas/questions/issues that the Division believes Tris must address as it moves from this Pre-NDA meeting in order to have a complete and adequate NDA?

**FDA Response to Question 15:**

**Additional Biopharmaceutics Comments:**

*The following general guidelines should be taken into consideration for the dissolution data and information to be provided in the NDA:*

- A. Dissolution Test:** *Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:*
- i) Solubility data for the drug substance over the physiologic pH range;*
  - ii) Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution 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 three consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;*
  - iii) Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim)*

- iv) *Data to support the discriminating ability of the selected 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 products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm 10$ -20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent; and*
- v) *Include the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).*

**B. Dissolution Acceptance Criteria:** *For the selection of the dissolution acceptance criteria of your product, the following points should be considered:*

- i) *The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).*
- ii) *The acceptance criteria should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
- iii) *A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least 80% of drug is released. If the maximum amount released is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.*
- iv) *In general, the selection of the dissolution acceptance criteria ranges is based on mean target value +10% and >80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model.*

***Additional Biometrics Comments:***

*In your future NDA submission, please include the following information for the efficacy trial TR1102-ADD-001:*

- *all raw as well as derived variables in .xpt format,*
- *the SAS programs that produced all efficacy results,*
- *the SAS programs by means of which the derived variables were produced from the raw variables, and*
- *a full list of all relevant communications (e.g., IND/serial numbers and submission dates for all amendments).*

**Discussion at Meeting:**

*No further discussion.*

## **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) 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.

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](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

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

## **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

## **505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR

314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

### **Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

#### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

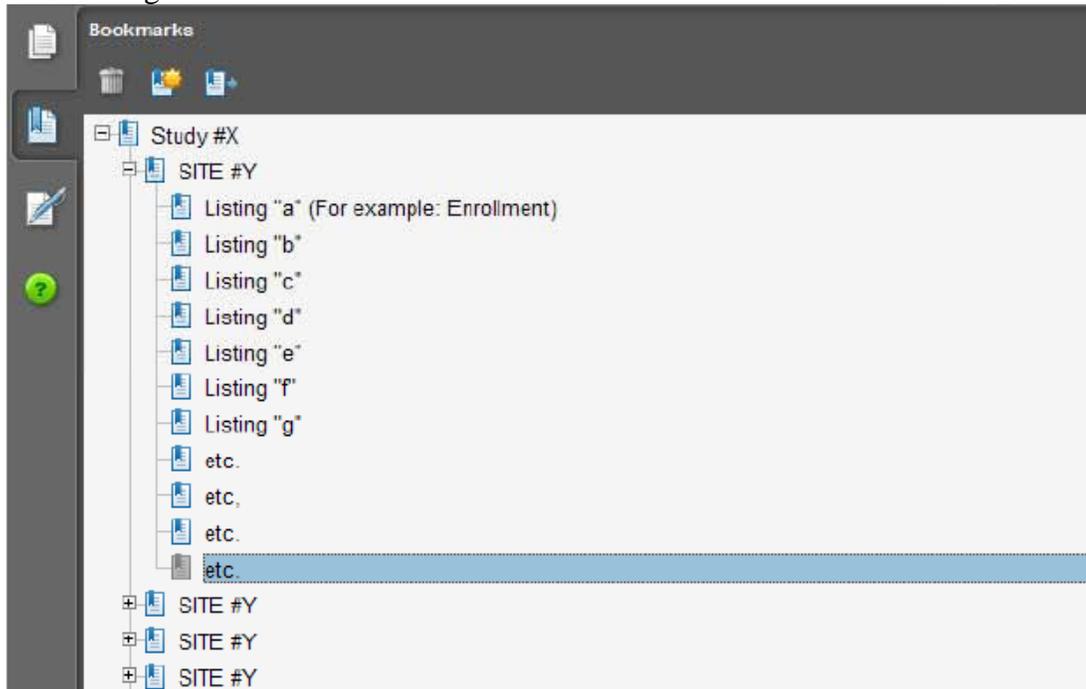
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
  - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> ) for the structure and format of this data set.

**Attachment 1****Technical Instructions:****Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

<b>DSI Pre-NDA Request Item<sup>1</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MITCHELL V Mathis  
11/19/2014