

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210526Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



PIND 129044

MEETING MINUTES

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

Dear Dr. Pincus:

Please refer to your Pre-Investigational New Drug Application (PIND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Amphetamine Extended-Release (b) (4) Tablets 10 mg, 15 mg, and 20 mg.

We also refer to the meeting between representatives of your firm and the FDA on March 3, 2016. The purpose of the meeting was to discuss your clinical program for developing Amphetamine Extended-Release (b) (4) Tablets for use in the treatment of attention deficit hyperactivity disorder.

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, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell Mathis, M.D.
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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: March 3, 2016; 1:00 pm EDT
Meeting Location: FDA White Oak Campus, Bldg. 22, Room #1415
10903 New Hampshire Ave, Silver Spring MD 20993

Application Number: PIND 129044
Product Name: Amphetamine Extended- [REDACTED] ^{(b) (4)} Tablets 10 mg, 15 mg, and 20 mg
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor/Applicant Name: Tris Pharma, Inc.

Meeting Chair: Mitchell Mathis, M.D.

FDA Attendees:

Mitchell Mathis, M.D.	Director, Division of Psychiatry Products (DPP)
Kofi Ansah, Pharm.D., RAC	Senior Regulatory Project Manager, DPP
Jing Zhang, MD	Clinical Team Leader
John Umhau, M.D.	Medical Officer/Clinical Reviewer
Linda Fossom, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Darren Fegley, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, Ph.D.	Clinical Pharmacology, Team Leader, OCP
Huixia Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP
David Claffey, Ph.D.	CMC Lead, Office of Pharmaceutical Quality (OPQ)
Sherita McLamore-Hines, Ph.D.	CMC Lead, Office of Pharmaceutical Quality (OPQ)
Okpo Eradiri, Ph.D.	Biopharmaceutics Lead (Acting), OPQ
Gerlie Gieser, Ph.D.	Biopharmaceutics Reviewer, OPQ

Tris Pharma, Inc.'s Attendees

Name	Title/Function
Sally A. Berry, M.D., Ph.D.	Chief Medical Officer
Norma J. Cappetti	Vice President, Regulatory Affairs
Kalyan K. Kathala	Manager, Product Development
Jhansi Lakkaraju, Ph.D.	Director, Research and Development

Name	Title/Function
Yulia Pincus, Ph.D.	Associate Director, Regulatory Affairs
Shivanand Puthli, Ph.D.	Senior Manager, Product Development

1.0 BACKGROUND

Tris Pharma, Inc., (Tris) is developing a new extended-release solid oral dosage form of amphetamine for the treatment of attention deficit hyperactivity disorder (ADHD). The purpose of this meeting is to obtain the Agency's feedback and agreement on the proposed development plan for this product.

On August 14, 2013, Tris participated in a pre-IND teleconference with the Agency discussing a prototype of this product, amphetamine ER chewable (b) (4) tablet (b) (4) (b) (4)). The participants at this meeting noted that the proposed dosage form of a chewable (b) (4) tablet could be replaced with an oral suspension. As a result, the sponsor proceeded with an oral suspension development program and, on October 19, 2015, Tris received marketing approval for amphetamine ER oral suspension (Dyanavel XR, NDA 208,147). Tris now plans to develop a new solid oral dosage form, intended to be bioequivalent to Dyanavel XR. The sponsor describes this product as a chewable (b) (4) tablet which can be swallowed (b) (4).

Tris is proposing to do a bridging study in adults between Dynavel XR and the proposed tablets to establish bioequivalence. This proposed study is an open-label, randomized, three-way cross-over, single-dose study to evaluate the bioavailability of the proposed chewable (b) (4) tablets under fasted and fed conditions. The study will also evaluate the relative bioavailability of the proposed tablets to the reference product (Dyanavel XR, 8 mL [20 mg]) under fasted conditions.

The objectives of the meeting are to obtain agreement on:

- 1) The scope of pharmacokinetic studies required to bridge the proposed product to the approved oral suspension formulation.
- 2) Acceptance criteria for the pharmacokinetic studies, including evaluation of dissolution properties.
- 3) Potential labeling options for the multimodal administration of the proposed product

2.0 DISCUSSION

2.1. Regulatory

Question 1: Tris intends to submit a 505(b)(2) NDA for the Amphetamine ER (b) (4) (b) (4) Tablet with a bridge to Dyanavel XR as the RLD. **Does the Agency concur that Dyanavel XR is an acceptable RLD?**

FDA Response to Question 1: *An applicant may cross-reference a previously approved 505(b)(2) application for which it is the NDA holder to support approval of its new NDA, if scientifically appropriate.*

If the cross-referenced portions of the applicant’s previously approved 505(b)(2) application involve reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or published literature (as distinguished from any cross-referenced investigations that were conducted by or for the applicant or for which the applicant has obtained a right of reference or use), then the new NDA should be submitted pursuant to section 505(b)(2) of the FD&C Act. The applicant’s new 505(b)(2) application should identify this/these listed drug(s) as relied upon for its new 505(b)(2) application in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification/statement and notification), apply to each listed drug upon which an applicant relies.

Sponsor’s Comments: Based on the fact that Dyanavel XR application (N208147) contains original relevant efficacy information and a comprehensive literature review in place of the nonclinical data, Tris believes that Dyanavel XR should be the only RLD listed in the application. Does the Agency agree?

Supporting Information

Provided below is a table summarizing information to be referenced in the newly proposed 505(b)(2) application for the Amphetamine ER (b) (4) Tablets. Please note that the proposed RLD, Dyanavel XR, was a 505(b)(2) application which referenced Adderall Tablets (N011522). In the Dyanavel XR application, the information cross-referenced to the RLD was the nonclinical findings which were further substantiated by literature and adverse events captured in the labeling. Also, please, note that labeling for the Dyanavel XR was largely developed based on the most current class label for Vyvanse (per the Agency’s recommendation and confirmation that Vyvanse was not an RLD at the November 14, 2014 pre-NDA meeting for NDA 208147), clinical findings in the efficacy study conducted by Tris with Dyanavel XR, and other representative stimulant class labeling for extended release products (including other non-RLD products, e.g. Quillivant XR).

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	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
Dyanavel XR, N208147	Module 2.4 (literature based nonclinical overview), Module 2.5 (reference to the efficacy study in pediatric population, pediatric and adult pharmacokinetics)
Dyanavel XR, N208147	Module 1.14, Labeling

Discussion at Meeting: *We will consult with the 505(b)(2) committee and provide additional advice in a follow-up letter.*

Question 2: As detailed in Section 6.2 of this document, Tris intends to submit a 505(b)(2) NDA for the Amphetamine ER [REDACTED] (b) (4) Tablet with a bridge between the RLD, Dyanavel XR, and the new product based on a single dose pharmacokinetic study in adults (also including a food effect arm). **Does the Agency agree that an adult pharmacokinetic study establishing bioequivalence between the two products is an appropriate bridge to support a 505(b)(2) filing?**

FDA Response to Question 2: *Yes, we agree.*

Discussion at Meeting: *No further discussion.*

2.2. Biopharmaceutics/Clinical Pharmacology

Question 3: As part of NDA 208147 for Dyanavel XR, Tris reported a pharmacokinetic study in pediatric patients with ADHD. Based on the results from the pediatric and adult pharmacokinetic studies, Tris established that the shape of the plasma curve in different age groups was essentially the same, with only differences attributed to the differences in body size. Provided the bioequivalence between Dyanavel XR and the Amphetamine ER [REDACTED] (b) (4) Tablet is established in adults, Tris concludes that no additional pediatric pharmacokinetic data is necessary to support the new application because pharmacokinetic profile in the pediatric population is predictable. **Does the Agency agree with this rationale?**

FDA Response to Question 3: *Yes, we agree. If BE is demonstrated, no additional study in in children 6 years and older is needed.*

Discussion at Meeting: *No further discussion.*

Question 4: Synopsis of the pharmacokinetic study being proposed to establish a bioequivalence bridge between Dyanavel XR and Amphetamine ER [REDACTED] (b) (4) Tablet, and a food effect on the new drug product is being provided in Section 10.2. **Does the Agency agree with the proposed study design and the bioequivalence acceptance criteria proposed?**

FDA Response to Question 4: *On face, the study design appears to be reasonable. Regarding the BE acceptance criteria, in addition to traditional BE metrics, partial AUCs (i.e., AUC₀₋₅, AUC_{5-t_r}) for both d- and l-amphetamine need to meet BE limit, per the [BE guidance for Amphetamine XR products](#).*

Sponsor's Comments: Tris would like to have a further discussion with the Agency regarding the BE requirements between the new drug product Amphetamine ER [REDACTED] (b) (4)

Tablet and the RLD, Dyanavel XR, mentioned above. Tris believes that the aforementioned requirements are not relevant to the Amphetamine ER [REDACTED] (b) (4) Tablet product for the following reasons:

1. The BE Guidance for Amphetamine XR products does not apply to this 505(b)(2) product. Amphetamine ER [REDACTED] (b) (4) Tablet is not a pharmaceutical equivalent to Dyanavel XR and therefore will be single sourced upon approval, will be designated as RLD, and will not have a TE code.
2. The two products are related based on their controlled release technology and a match in dose strength (as there are no other possible comparators), however, the two are different dosage forms and therefore are not pharmaceutically equivalent.
3. Amphetamine has a longer half-life and therefore its efficacy is less sensitive to fluctuations in the PK profile in the later part of the day (typically identified through pAUCs), in contrast to methylphenidate.
4. Tris understands that the pAUCs in the BE specific guidance for amphetamine XR products had been developed based on Adderall XR label allowing for the interchangeability between an Extended Release and an Immediate Release products (see excerpt below).

[...The Adderall XR® Capsule labeling states that “Adderall XR® capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from Adderall XR® compared to the conventional Adderall (immediate-release) tablet formulation.” Further, the label states that “patients taking divided doses of immediate-release Adderall®, (for example, twice daily), may be switched to Adderall XR® at the same total daily dose taken once daily.”

Thus, Adderall XR® is a multiphasic, modified-release formulation designed to mimic the drug release of two Adderall [immediate release (IR) mixed amphetamine] tablet formulations taken four hours apart....]

Such is not present in the Dyanavel XR label.

Discussion at Meeting: *The Agency clarified that, for drugs that have multiphasic release profiles and a strong PK/PD relationship, selected partial AUC(s) also need to pass BE limits to ensure adequate similarity between the test and reference products. The product under development has the aforementioned properties. With a study showing that their product does not pass the BE limit for recommended pAUCs, the sponsor agreed to conduct a clinical trial to evaluate its safety and effectiveness in pediatrics 6-12 years old in a classroom setting. In addition to the clinical trial, the sponsor will also conduct a PK study in 6-12 years old. The overall development program will be similar to that of their recently approved product, Dyanavel XR.*

2.3. Chemistry, Manufacturing, and Controls

Question 5: In Section 10.3(F), Tris has provided details pertaining to the dissolution method developed for this drug product. Dissolution data for the release and stability samples for nine (9) lots corresponding for each 10 mg, 15 mg and 20 mg strengths are provided in Tables 4 – 6, and Figures 2 –4. The three time points listed in the specification for dissolution test cover the early, middle and late stages of the release profile ($(b) (4)$ %, $(b) (4)$ % and $> (b) (4)$ % drug release respectively), as specified in the FDA guidance document.(1)

The discriminatory properties of the method were evaluated during method development, in order to ensure that the method is a meaningful predictor of *in-vivo* performance of the drug and an accurate quality control tool for evaluation of batch to batch reproducibility. The discriminating properties of the method will be further substantiated by data in the NDA.

Does the Agency agree with the proposed dissolution method and selected time points?

FDA Response to Question 5: *From a Biopharmaceutics perspective, it is premature for us to address your question. When you have all the supporting information including evidence of discriminating power, IVIVC (if available), etc., submit the full method development report either to the IND or as part of the NDA. The suitability of the proposed drug product dissolution specification values and time points will be determined at the time of NDA review when cumulative data from the clinical and primary stability batches are available for evaluation. Until such time, we recommend that you continue to collect full in vitro dissolution profiles (including time points other than 1, 3, and $(b) (4)$ hours).*

Discussion at Meeting: *No further discussion.*

2.4. Labeling

Question 6: To support the ER claim for Dyanavel XR, Tris submitted as part of the NDA an *in silico* steady-state simulation justification referencing reduction in C_{max} and frequency of the administration relative to the immediate release reference product. Provided bioequivalence is established in the single dose pharmacokinetic study between the Amphetamine ER $(b) (4)$ Tablet and the RLD, does the Agency agree that the steady-state pharmacokinetic study is not necessary for the newly developed product and that the ER claim for the new dosage form is self-evident?

FDA Response to Question 6: *Yes, we agree. However, it will be helpful to have the simulated PK profiles following multiple dose administration for your ER claim. Based on the Code of Federal Regulations, [21 CFR 320.25 (f)*], an ER claim should be supported by (among other things) evidence that 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.*

Other than comparing the fluctuation index of the test and reference drug products, you should also provide any other rationale you may have, including your current rationale in the meeting package and/or other supporting justification for the ER claim when the NDA is submitted.

Discussion at Meeting: *No further discussion.*

Question 7: The Amphetamine ER (b)(4) Tablet was developed to provide patients and health practitioners a superior level of flexibility when administering a solid dosage form of the extended-release amphetamine. To confirm ability of the product to retain its pharmacokinetic performance under different modes of drug administration (i.e. chewed, dispersed in water, and swallowed whole), Tris conducted a four-way pilot pharmacokinetic study. Provided that bioequivalence is established between the different modes of administration, Tris believes it is critical to communicate this information on the dosage form to the patients and health practitioners in the labeling of the drug product. The following are the questions related to this matter:

(a) Based on the pilot PK study results provided in Section 10.4(A) of this Briefing Document would the Agency allow the statement “(b)(4) be chewed (b)(4) or swallowed whole,” to be included in the Dosage and Administration section of the drug product labeling?

FDA Response to Question 7(a): *This will be a review issue. In addition, we have the following points for your confirmation/clarification:*

- 1) *Please confirm the formulation used in your study is the to-be-marketed formulation.*
- 2) *In addition to your current analysis provided in the study synopsis, please perform statistical analysis using your planned default route of administration as the reference.*
- 3) *Please clarify why (b)(4).*

Sponsor’s Comments:

- 1) Yes, the formulation used in the pilot PK study is the intended marketed formulation.
- 2) The default route of administration for this dosage form is chewing (Treatment A). Statistical analysis in the pilot study, intended to determine the BE between RLD (Treatment D) and Test (Treatment A) was performed. The BE between the different modes of administration (Treatment B, ODT or Treatment C, Swallowed Whole), were also performed against the Treatment A (Chewed).

(b)(4)

Discussion at Meeting: *The Agency recommended that the sponsor use the exposure values (e.g., AUC) from the default route of administration (i.e., chewing) as the denominator when performing the statistical analysis; the sponsor agreed to this recommendation.*

In terms of product administration, [REDACTED] (b) (4)

Question 7(b): Does the Agency agree that the data from study 2016-4009 can be used to support the proposed labeling text?

FDA Response to Question 7(b): This will be a matter for review.

Discussion at Meeting: No further discussion.

Question 7(c): [REDACTED] (b) (4)

FDA Response to Question 7(c): This will be a matter for review.

Discussion at Meeting: No further discussion.

Question 8: Based on the product development information available to date on the physical properties of the dosage form and [REDACTED] (b) (4), Tris would like to have the Established Name for the drug product to be *Amphetamine Extended-Release* [REDACTED] (b) (4) Tablet. **Does the Agency agree with the proposal?**

FDA Response to Question 8: On face, we do not agree with the proposed established name (*Amphetamine Extended-Release* [REDACTED] (b) (4) Table) given that the dosage form is not consistent with [USP <1151>](#). [REDACTED] (b) (4)

[REDACTED] (b) (4). Be advised that the final determination of the dosage form designation will be a review issue after NDA submission; we recommend that you provide justification for the proposed dosage form designation.

Sponsor's Comments: [REDACTED] (b) (4)

[REDACTED] (b) (4) It is not clear to Tris how Amphetamine ER [REDACTED] (b) (4) Tablet is different from the aforementioned product and respectfully requests the Agency to clarify.

Tris proposes to have an established name “Amphetamine ER [REDACTED] (b) (4) Tablet” and in the Dosing and Administration section, to have detailed instructions pertaining to different modes of administration.

Question 9: Dyanavel XR labeling indicates that the starting dose for the drug product is “2.5 mg or 5mg” and “The dose may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days up to a maximum dose of 20 mg per day”. Tris does not have a 2.5 mg dose available for the Amphetamine ER (b) (4) Tablet. **Please confirm that the dosing recommendation for the starting dose of Amphetamine ER (b) (4) Tablet in the final labeling will be (b) (4) and the titration recommendation will be “The dose may be increased in increments of (b) (4) to 10 mg per day every 4 to 7 days up to a maximum dose of 20 mg per day”.**

FDA Response to Question 9: *We do not agree. Dosing instructions for this product must be congruent with those of the reference product, Dyanavel XR, which allows for a starting dose and titration increment of 2.5mg. If the proposed formulation will not be provided in a 2.5 mg strength, then the label must refer to another product (such as the Dyanavel XR) to provide the starting dose and titration increment of 2.5 mg.*

Sponsor’s Comments: Tris acknowledges FDA’s response but would like to point out that in the efficacy study conducted with Dyanavel XR, provided in the NDA 208147, only ~2% of the patients received the lowest titration dose. This is consistent with the expectations for the tablet product, as well.

Also, Tris is aware of other products (i.e. RISPERDAL M-TAB) on the market that do not offer an exact strength combination as the 505(b)(2) product.

Tris respectfully requests FDA to elaborate on the rationale behind this request. Tris understands the Agency’s proposal to mean that Amphetamine ER (b) (4) Tablet labeling would recommend to use Dyanavel XR 2.5 mg dose, if such is necessary to provide the starting dose and titration increment of 2.5 mg.

Discussion at Meeting: *The sponsor noted that they are considering developing a 5 mg scored tablet; this would allow for a 2.5 mg dose. The Division also noted that if the sponsor conducts a clinical study in children with the new formulation, using a minimum incremental dose of (b) (4) and a starting dose of (b) (4) would allow them to eliminate the dosage and administration instructions pertaining to the 2.5 mg dose, provided that the (b) (4) starting dose is well-tolerated.*

2.5. Other

Question 10: If the newly proposed drug product is demonstrated to be bioequivalent to Dyanavel XR, **can Tris reference the Dyanavel XR’s post-approval committed studies to fulfill any pediatric requirements?**

FDA Response to Question 10: *Additional studies to meet the PREA requirement for children ages 4 to 5 years for Dyanavel XR are at present deferred. If the proposed product is shown to be bioequivalent to Dyanavel XR, then the pediatric studies conducted under IND 116,985 for Dyanavel XR will suffice for the purposes of complying with PREA.*

Discussion at Meeting: *No further discussion.*

Question 11: Does the Agency require any other studies for this NDA in addition to those outlined in the meeting request?

FDA Response to Question 11:

Biopharmaceutics:

- i) *To determine whether your extended release (ER) product may release its entire contents (“dose dumping”) when used with alcohol, we recommend that you conduct an in vitro drug-alcohol interaction study with your ER product. You should conduct in vitro drug release testing initially using the highest strength and you may have to follow up with an in vivo study, depending on the results of the in vitro testing. You should discuss the results of your in vitro study with the Agency prior to NDA submission.*
 - a. *The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.*
 - b. *Generally, a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.*
 - c. *Report f2 values to assess the similarity (or lack thereof) in the dissolution profiles.*
 - *Examine the shape of the dissolution profiles to see if the modified release characteristics are maintained, especially in the first 2 hours.*
 - *The report should include the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.*
- ii) *Although not a study, provide evidence of ER characteristics of your proposed product in the NDA to support the ER claim that will be made in the drug product label. Please refer to response to Q6.*

Non-clinical:

We would like to remind you that any impurities or degradants that exceed ICH thresholds may need to be reduced or qualified in appropriate non-clinical studies as per ICH Q3A and ICH Q3B.

Other:

[Redacted] (b) (4)

Sponsor’s Comments:

[Redacted] (b) (4)

Does the Agency agree that based on this, abuse is not likely for this product and therefore no supportive information is necessary?

Discussion at Meeting: *We will provide additional guidance from our Controlled Substance Staff in a follow-up letter.*

3.0 OTHER INFORMATION

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>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards

specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

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.

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	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<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 YYYYYYY “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.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's Supportive Material (Adderall-XR PI PK).

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

/s/

MITCHELL V Mathis
04/01/2016