

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215401Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 73862

MEETING MINUTES

Noven Pharmaceuticals, Inc.
Attention: Kanan Balakrishnan, Pharm.D.
Senior Director, Regulatory Affairs
11960 SW 144th Street
Miami, FL 33186

Dear Dr. Balakrishnan:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for d-Amphetamine Transdermal System (d-ATS).

We also refer to the telecon between representatives of your firm and the FDA on September 3, 2020. The purpose of the meeting was to discuss outstanding topics for CMC, gain agreement on the proposed clinical package for filing, and discuss the NDA presentation and format.

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

If you have any questions, call Shin-Ye Sandy Chang, at (301) 796-3971, or email Shinye.Chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Acting Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 3, 2020, 11:00 AM to 12:00 PM
Meeting Location: Teleconference

Application Number: 73862
Product Name: d-Amphetamine Transdermal System (d-ATS)
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor Name: Noven Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(2)

Meeting Chair: Tiffany R. Farchione, MD

FDA Attendees

Tiffany R. Farchione, MD	Director (Acting), Division of Psychiatry (DP)
Bernard Fischer, MD	Deputy Director (Acting), DP
Javier A. Muñiz, MD	Associate Director of Therapeutic Review, DP
Pamela Horn, MD	Clinical Team Leader, DP
Heidi Wehring, PharmD, BCPP	Clinical Analyst, DP
Ikram Elayan, PhD	Supervisor, Division of Pharmacology/Toxicology for Neuroscience (DPT-N)
Yongbin Zhang, PhD	Pharmacology/Toxicology Reviewer, DPT-N
Andrei Ponta, PhD	Chemistry Reviewer, Office of Pharmaceutical Quality (OPQ)
Ta-Chen Wu, PhD	Biopharmaceutics Lead, OPQ
Kaushal Dave, PhD	Biopharmaceutics Reviewer, OPQ
Luning (Ada) Zhuang, PhD	Team Leader, Office of Clinical Pharmacology (OCP)
Li Tan, PhD	Clinical Pharmacology Reviewer, OCP
Atul Bhattaram, PhD	Team Leader, Division of Pharmacometrics, OCP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biostatistics (OB)
Thomas Birkner, PhD	Biometrics Reviewer, OB
David Kettl, MD	Clinical Team Leader, Division of Dermatology and Dentistry (DDD)/Office of Immunology & Inflammation
Roselyn E. Epps, MD	Clinical Reviewer, DDD
Jonn Bailey, PharmD, BCACP	Safety Evaluator, OSE/Division of Pharmacovigilance
Kofi Ansah, PharmD, RAC	Senior Regulatory Project Manager, Psychiatry Group, Division of Regulatory Operations for Neuroscience (DRON)

SPONSOR ATTENDEES

Arlette Azua, MS	Manager, Regulatory Affairs, CMC
Kanan Balakrishnan, PharmD	Senior Director, Regulatory Affairs
Sandeep Byreddy	Manager, Biostatistics
Mariacristina Castelli, PhD	Executive Director, Clinical Pharmacology
Monica Escobar, PhD	Senior Director, Regulatory Affairs, CMC
George Harb, MD	Executive Director, Clinical Development
Marina Komaroff, DrPH, MPH, MS	Senior Director, Biostatistics
Robert Lambert, BS	Associate Director, Manufacturing Technical Services, Operations
Joel Lippman, MD	Chief Operating Officer & Chief Medical Officer
Suzanne Meeves, PharmD	Contractor, Clinical Development
Alexandra Park, BSc	Executive Director, Regulatory Affairs & Pharmacovigilance
Jose Sintas, PhD	Executive Director, Analytical Research
Katsumi Suzuki MS	Executive Director, Global Development Liaison
(b) (4)	(b) (4)
	(Consultant)
(b) (4)	(b) (4)
	(Consultant)

1.0 BACKGROUND

Noven Pharmaceuticals has developed a transdermal formulation of d-amphetamine (d-ATS) for the treatment of attention deficit hyperactivity disorder (ADHD). The Sponsor intends to submit a new drug application (NDA) under the 505(b)(2) pathway, proposing to rely, in part, on the Agency's findings of safety and effectiveness for the listed drugs Adderall XR oral extended-release capsules (mixed amphetamine salts, NDA 021303) and Vyvanse oral capsules (lisdexamfetamine dimesylate, NDA 021977).

The IND for d-ATS was originally submitted in October 2006. In August 2010, Study

(b) (4) was put on clinical hold (b) (4). In September 2010, the clinical hold was removed (b) (4).

The Sponsor and the Agency held an End-of-Phase 1 meeting in April 2012 and discussed the design elements of a proposed pediatric phase 2 cross-over study and two proposed phase 3 parallel-group studies, one in pediatric patients and one in adults. The Agency voiced concern over adhesion problems with the d-ATS patches and advised the Sponsor to resolve adhesion problems before proceeding to phase 2 and 3 studies. Although the Agency did not specifically object to a crossover study design for the phase 2 pediatric study, we cautioned the Sponsor about period effects and that the

results of the study would be a matter of review. (Of note, the Sponsor did observe significant period effects in their phase 2 study.)

In January 2014, at a Type C guidance meeting, the Agency provided feedback on the completed phase 2 trial and the results of their Usability and Adhesion Study—including dermal assessments (patch adhesion, discomfort, and irritation at the patch application site). At that time, the Sponsor still planned a pediatric phase 3 study and an adult phase 3 study; both were to be randomized, double-blind, placebo-controlled, parallel-group studies. The Agency strongly recommended that the Sponsor perform the phase 3 studies with their proposed commercial formulation and advised that any changes to the proposed commercial formulation from developmental formulations required sufficient bridging studies.

The Agency met with the Sponsor for an End-of-Phase 2 meeting in December 2015. At that time, the Sponsor had completed the phase 2 cross-over study (N25-006) in children and adolescents and was no longer proposing to conduct a phase 3 pediatric study. The Agency stated that if study N25-006 had established efficacy and safety in children and adolescents—and if an adequate pharmacokinetic bridge could be established between children/adolescents and adults—then, because the Sponsor is planning to submit a 505(b)(2) application referencing products already approved in adults, no adult efficacy trial would be needed. Therefore, the Sponsor did not conduct the previously proposed adult phase 3 study.

The Sponsor has completed several phase 1 and 2 studies in this development program, including:

- Study N25-002: An open-label comparison of two different d-ATS formulations in healthy male adults
- Study N25-004: An open-label, single-dose, three-treatment crossover study to evaluate pharmacokinetics (PK), pharmacodynamics, safety and tolerability of d-ATS worn for 9 hours, d-ATS worn for 12 hours, and a single 10-mg oral dose of Adderall XR in children with ADHD
- Study N25-005: An open-label, single-dose, three-treatment crossover study in children 6 to 12 years old with ADHD; the primary objective was to compare the PK of three d-ATS formulations
- Study N25-006: A 5-week, flexible-dose, open-label period followed by a 2-week, double-blind, placebo-controlled, crossover study in children and adolescents ages 6 to 17 with ADHD; the primary endpoint was a classroom-based Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) on Day 7 of each crossover period
- Study N25-007: A d-ATS usability study in pediatric and adult subjects with ADHD

- Study N25-010: An application site comparison study evaluating d-ATS bioavailability when applied to five different application sites (hip, flank, upper back, chest, upper arm) in healthy adult subjects
- Study N25-012: A study of the effect of external heat application on d-ATS PK as well as a comparison of relative bioavailability of d-ATS, Adderall XR, and Vyvanse in healthy adults
- Study N25-013: A d-ATS usability and adhesion study including a Daytrana methylphenidate patch arm in adult and pediatric subjects with ADHD
- Study N-25-015: A 4-week, multiple-dose PK study comparing use of the same application site versus rotating among multiple application sites in healthy adults
- Study N25-017B: A human factors d-ATS validation study (ongoing)
- Study N25-018: A randomized, evaluator-blinded study to evaluate d-ATS skin irritation in healthy adults

The purpose of this meeting is to discuss outstanding topics for CMC and gain agreement on the proposed clinical package for filing. Additionally, the Sponsor would like to discuss the NDA presentation and format.

FDA sent Preliminary Comments to the Sponsor on August 28, 2020.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls

Question 1: Does the Agency agree that the d-amphetamine and (b) (4) control strategy, including the specification and testing plan, is adequate for NDA registration?

FDA Response to Question 1: *The adequacy of the release and stability drug product specifications will be determined at the time of NDA submission, when the data may be evaluated in its totality. However, we have the following recommendations regarding the proposed assay and impurity limits at this time:*

- *The proposed stability assay acceptance criterion is (b) (4) % on release and (b) (4) % of the label claim. We recommend tightening the proposed assay specifications.*
- *It is important that impurities/degradants do not exceed levels supported by toxicological qualification studies. As part of the release and stability specifications,*

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you set a limit (b) (4) of NMT (b) (4) % and a limit (b) (4) of NMT (b) (4) %. Tighten to meet ICH Q3B requirements or provide a justification for these limits.

Discussion at Meeting: No further discussion.

Question 2: Does FDA agree with the enhanced backing control to ensure consistency of the backing layer?

FDA Response to Question 2: The adequacy of the backing specifications will be determined at the time of NDA submission, when the data may be evaluated in its totality. We recommend including a justification of the proposed specification in the NDA submission. Results of drug product batches manufactured with backing at the low and high end of the proposed specifications can justify the limit. Include details such as the impact of the backing on the drug product release rate, drug absorption, and in vitro flux.

Discussion at Meeting: No further discussion.

Question 3: Does FDA agree that Noven may amend the NDA with updated in-process stability data and the 18-month stability data obtained during NDA review?

FDA Response to Question 3: We recommend including all stability data at the initial NDA submission to ensure it is reviewed during the NDA review cycle. You may provide additional stability data during the NDA review cycle; however, due to a number of factors (e.g., timing), we cannot guarantee that this additional data will be reviewed.

Discussion at Meeting: No further discussion.

2.2. Clinical

Question 4: Does FDA agree that the Modeling and Simulation approach and PK data across patient populations supports extrapolation of efficacy findings from children and adolescents to adults?

FDA Response to Question 4: We acknowledge that your development program was initiated prior to publication of our 2019 draft guidance for industry, [Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment](#). However, the recommendations in that document represent our current standard for review of stimulant products. Some deviation from those standards may be acceptable for legacy programs, but the design of Study N25-006 deviates from our current standard in

substantial ways that will make it difficult to interpret and will limit its ability to serve as an adequate and well-controlled trial capable of supporting a marketing application.

The 2019 draft guidance states that for amphetamine 505(b)(2) development programs where the drug product is not bioequivalent to a listed drug, the onset and duration of the clinical effect should be evaluated in pediatric patients in an adequate and well-controlled study. Information about the onset and duration of effect is needed to inform product labeling. As noted above, the design of Study N25-006 deviates from the recommended design features described in the draft guidance (in the general considerations section). Specifically, it is a crossover rather than a parallel design study and had an open-label flexible-dose period before randomization and the Division may not consider it an adequate and well-controlled study. The adequacy of the onset and duration of the clinical effect evaluated in Study N25-006 will be a matter of review.

We recognize that you have conducted a bioavailability study (N25-012) in adults with your product and two listed drugs that are approved in adults. If, upon review, these data are found to be an adequate scientific bridge—and you have provided substantial evidence of effectiveness in pediatric patients (including an adequate assessment of onset and duration of effect)—then it may be reasonable to rely on the efficacy findings from the listed drugs in adults in combination with efficacy findings from d-ATS in pediatric patients without the need for additional adult efficacy data.

Sponsor's Comments: Noven is submitting d-ATS via the 505(b)(2) relying on the Agency's PK, efficacy and safety findings for Adderall XR and Vyvanse as described in Table 5 of the Briefing Document. Though our product is not bioequivalent to the LDs, we have confirmed that at each post-dose time point, amphetamine plasma concentrations of the proposed dose range of d-ATS do not exceed those of the range of LDs commercial doses as demonstrated in Study N25-012. Additionally, no evidence of significant accumulation was observed upon multiple once-daily administration in Study N25-015. We can clarify this further at the meeting, if the presentation of summary data in the briefing document was unclear or confusing.

Following FDA comments and in order to further support the overall data package and provide quantitative understanding of efficacy responses, Noven is planning to perform an integrated population pharmacodynamics/efficacy analyses using longitudinal data from efficacy study N25-006 and the established population PK model using all the completed PK studies. The objectives of these analyses will be to describe the exposure-response relationship for d-ATS efficacy endpoints, quantify covariate effects on efficacy endpoints, and characterize the onset and duration of effect in response to d-ATS administration.

We would like to discuss this additional approach to support the overall data package and if the Agency would be open to reviewing such data in the NDA.

Discussion at Meeting: *The Sponsor proposed to provide additional pharmacometrics analysis to help interpret efficacy and safety data of Study N25-006 (conducted in 2012) because the study design deviates substantially from the design recommendations in the ADHD draft guidance (May 2019). The Agency pointed out that the review will be complicated by the limitations of Study N25-006's design and that the Sponsor should provide as much information as possible to adequately inform prescribers about the performance and risks of d-ATS. Although lower exposures than comparator products observed over the entire PK curve in study N25-012 allays safety concerns to some extent, there is still concern for how the specific PK profile of d-ATS may impact stimulant-related adverse events such as insomnia. However, the final determinations would be a matter of review.*

The Agency asked the Sponsor to provide the detailed pharmacometrics analysis plan for further review. In addition, the Agency noted that there is a significant difference in the PK shapes between their product and the two listed drugs, especially within the first 8 hours; their product has consistently lower exposure than the two listed drugs. Therefore, quantitative analysis should adequately address whether the lower exposure within the first 8 hours would impact clinical outcomes. The Agency asked the Sponsor to consider a time-course of PK/PD analysis in addition to an exposure-response analysis using summary PK and PD endpoints. The Sponsor agreed to provide the plan as soon as possible.

Question 5: *Does FDA agree that the completed relative BA Study (N25-012) and the Modeling and Simulation data provide a sufficient bridge to the proposed listed drugs, Adderall XR and Vyvanse?*

FDA Response to Question 5: *Based on the information provided, this appears reasonable. However, the adequacy of the scientific bridge will be a matter of review. Provide the PK comparison of d-amphetamine for your product and the two listed drugs rather than the racemic mixture.*

Discussion at Meeting: *No further discussion.*

Question 6: *Does FDA agree that the overall dermal safety profile of d-ATS has been fully characterized for use in the intended populations?*

FDA Response to Question 6: *We cannot agree that the local safety profile has been fully characterized prior to reviewing the data in the NDA. However, although the study report is not complete, the information from the irritation/sensitization study N25-018 appears adequate for filing, the number of subjects is acceptable, and additional provocative dermal safety studies in healthy subjects for your proposed transdermal system are not necessary.*

Discussion at Meeting: No further discussion.

2.3. Electronic Submission/NDA Content & Format

Question 7: Does the Agency agree that the efficacy and safety data are, on face, adequate (b) (4)?

FDA Response to Question 7: We do not agree. It is premature to comment on the adequacy of the data in the proposed application, and labeling will be a matter of review if the NDA is filed.

See also our response to Question 4. The clinical safety data in the d-ATS development program appear to be inadequate to support NDA filing. Based on the 2019 draft guidance, Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment, if an amphetamine product has a duration of effect of more than 12 hours, an evaluation of long-term growth in pediatric patients is needed. The PK data provided in the briefing package and the efficacy results at 12 hours in the study report for Study N25-006 indicate that the duration of effect could be expected to exceed 12 hours. Your briefing package does not appear to summarize exposure by time, but, based on Table 7 in the briefing package, the longest pediatric exposures to your drug product were 6 weeks (Study N25-006; N=106). In order to evaluate long-term growth, a 12-month safety data in pediatric patients is required for your product prior to NDA submission. Propose a minimum safety database size for the 12-month safety data that you believe will be adequate to evaluate long-term growth. The study should also include assessments of short-term adverse events of special interest (changes in vital signs, insomnia, decreased appetite, weight loss, irritability or mood changes, and psychosis). If you choose an open-label study design, all adverse events observed in the study will be attributed to your drug. Your proposal should also specify the distribution of ages and the doses to be studied.

Discussion at Meeting: No further discussion.

Question 8: Does FDA agree to waive the requirement to submit an Integrated Summary of Efficacy for this NDA and only summarize the efficacy in Module 2.7.3. Summary of Clinical Efficacy (SCE)?

FDA Response to Question 8: As there is only one study with efficacy data, an ISE separate from the SCE is not warranted. However, the information in the SCE or hyperlink to the SCE should also be included in Module 5 for ease of review.

Discussion at Meeting: No further discussion.

Question 9: Does FDA agree with Noven's plan of how to present the systemic and dermal safety profile of d-ATS in the Summary of Clinical Safety and the Integrated Summary of Safety?

FDA Response to Question 9: *We do not agree. Based on the number of studies that collected clinical safety data in the clinical development program, and the need for a full characterization of the safety experience with this novel d-amphetamine transdermal system, a complete ISS in the usual format will be required for filing of the NDA application.*

Sponsor's Comments: We confirm that we will submit a full ISS per 21CFR 314.50 (d)(5)(vi)(a) in the NDA and we seek to align on the exact content and format given the nature of the d-ATS development program. We request your direction on how the safety data should be analyzed and presented for the ISS if the Agency does not agree with the sponsor's ISS proposal of grouping comparable studies; integrating safety data over a number of different factors (TEAEs, vital signs, weight, physical examination, ECG, laboratory tests, C-SSRS, adhesion, irritations, discomfort, pain, sensitization, and adhesive residue) and presenting the trial safety data side-by-side.

Discussion at Meeting: *The Sponsor confirmed they will be preparing both an SCS and ISS, to be located in Modules 2 and 5, respectively, for NDA filing. The Agency confirmed that, based on the level of detail provided in the meeting package, the Agency does not object to the planned grouping of studies or planned data presentations. The Sponsor will be prepared to address questions during the review cycle, should they arise.*

Question 10: Does FDA agree with the data exchange standards and controlled terminology versions utilized in developing the submission ready datasets for the d-ATS program and the overall study data standardization plan?

FDA Response to Question 10: *The data exchange standards described in the briefing document are acceptable except for your proposal to submit the datasets for Study N25-002 in (b) (4) format. Submit SDTM datasets in SAS Transport Format Version 5. Please refer to [Study Data Technical Conformance Guide](#) (July 2020), page 6.*

Discussion at Meeting: *No further discussion.*

Question 11: Does FDA agree with the proposal for electronic case report forms (eCRFs) to be included in the NDA submission?

FDA Response to Question 11: *We agree that it is acceptable to submit eCRFs for serious adverse events (SAEs), deaths, and participants who withdrew from studies due to adverse events and that, if there were no SAEs or deaths in the development*

program, then submitting eCRFs only for participants who withdrew from studies due to adverse events. You should also be prepared to provide eCRFs upon request for participants who experienced adverse events of special interest, such as known adverse reactions associated with stimulant medications and severe local toxicity reactions.

Discussion at Meeting: No further discussion.

Question 12: Does FDA agree with the proposal for narratives to be included in the NDA submission?

FDA Response to Question 12: It is acceptable to submit narratives for serious adverse events (SAEs), deaths, and participants who withdrew from studies due to adverse events and that if there were no SAEs or deaths in the development program, then submitting narratives only for participants who withdrew from studies due to adverse events is acceptable. You should also be prepared to provide narratives upon request for participants who experienced adverse events of special interest, such as known adverse reactions associated with stimulant medications and severe local toxicity reactions.

Discussion at Meeting: No further discussion.

Question 13: Noven plans to submit financial disclosures for Studies N25-006 and N25-012. Does FDA agree?

FDA Response to Question 13: We agree it is acceptable to submit financial disclosures for the phase 2 dose optimization efficacy study N25-006 in children and adolescents and the PK study N25-012, which you intend to use as the scientific bridge to the proposed listed drugs.

Discussion at Meeting: No further discussion.

Question 14: Does FDA agree with the proposal of how to fulfill the Office of Scientific Investigations (OSI) Bioresearch Monitoring Program (BIMO) request?

FDA Response to Question 14: It appears that providing OSI BIMO information for study N25-006, which is the only study with efficacy data in the development program, is acceptable.

Discussion at Meeting: No further discussion.

Question 15: Since all studies will be complete at the time of filing, with no new or ongoing studies planned for d-ATS at this time, Noven does not plan to submit a 4-month safety update. Does FDA agree?

FDA Response to Question 15: *If there are no new or ongoing studies at the time of NDA submission and your product is not marketed in any other country, then a 4-month safety update will not be necessary.*

Discussion at Meeting: *No further discussion.*

Additional Comments from Pharmacology/Toxicology

For your NDA application, please refer to the guidance for industry, [Providing Regulatory Submissions in Electronic Format — Standardized Study Data](#). In addition, Standard for Exchange of Nonclinical Data (SEND) datasets are required along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide (SENDIG) version. The FDA Data Standards Catalog, which can be found on the [Study Data Standards Resources web page](#), lists the supported SENDIG versions and associated implementation dates.

Discussion at Meeting: *No further discussion.*

3.0 OTHER

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-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP 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.

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For additional guidance on the timing, content, and submission of the iPSP, including an iPSP 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*.² In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- 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 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.

Pursuant to the PLLR, you should include the following information with your application

² When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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 guidance for industry *Assessment of Abuse Potential of Drugs*.⁶

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).⁷ 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 Regulations.gov).⁸

⁶ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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⁸ <http://www.regulations.gov>

If you intend to submit a 505(b)(2) application that relies for approval 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 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. by trade name(s)).

If you intend to rely 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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 is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). 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 the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the 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 effectiveness 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 A</i>
<i>(3) Example: NDA YYYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</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 items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁹

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*.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

⁹ <https://www.fda.gov/media/85061/download>

Sponsor to provide PK/PD data analyses and modeling, as soon as possible, for the Agency's feedback and input.

6.0 ATTACHMENTS AND HANDOUTS

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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09/30/2020 03:14:07 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 73862

MEETING MINUTES

Noven Pharmaceuticals, Inc.
Attention: Kanan Solanki, Pharm.D.
Associate Director, Regulatory Affairs
11960 SW 114th Street
Miami, FL 33186

Dear Dr. Solanki:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for d-Amphetamine Transdermal System (d-ATS).

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2015. The purpose of the meeting was to meeting to obtain FDA agreement on the adequacy of the overall nonclinical, clinical pharmacology and abuse liability package; the data from the Usability-Adhesion Study N25-013; the proposed adult Phase 3 clinical study (b) (4) and overall safety database; the proposed draft label for d-ATS based on completed studies and RLD label language to support initiation of Phase 3 and registration of d-ATS.

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, call Shin-Ye Sandy Chang, Regulatory Project Manager at (301) 796-3971, or email shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. 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: B
Meeting Category: End of Phase 2

Meeting Date and Time: December 15, 2015, 10:30 AM – 12:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 73862
Product Name: d-Amphetamine Transdermal System (d-ATS)
Indication: Attention Deficit Hyperactivity Disorder
Sponsor/Applicant Name: Noven Pharmaceuticals, Inc.

Meeting Chair: Mitchell Mathis, M.D.
Meeting Recorder: Shin-Ye Sandy Chang, Pharm.D.

FDA ATTENDEES

Mitchell Mathis, M.D., Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, M.D., Deputy Director, DPP
Lucas Kempf, M.D. Clinical Team Leader, DPP
Aeva Gaymon-Doomes, M.D., Clinical Reviewer, DPP
Ikram Elayan Ph.D. Pharmacology/Toxicology Reviewer, DPP
Peiling Yang, Ph.D. Statistical Team Leader
Thomas Birkner, Ph.D., Statistical Reviewer
Shin-Ye Sandy Chang, Pharm.D. Regulatory Project manager, DPP
Hao Zhu, Ph.D. Office of Clinical Pharmacology Team Leader
Di Zhou, Ph.D., Office of Clinical Pharmacology Reviewer
David Claffey, Ph.D. Pharmaceutical Assessment Lead, Office of New Drug Assessment I (ONDQA I)
Caroline Strasinger, Ph.D., Chemistry Reviewer, ONDQA II
Danielle Harris, Pharm.D., BCPS, Team Leader, Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis (OSE/DMEPA)
Danielle Harris, Pharm.D., BCPS, Team Leader, OSE/DMEPA
Denise Baugh, Safety Evaluator, OSE/DMEPA
Ethan Hausman, M.D., Medical Reviewer, Division of Pediatric and Maternal Health (DPMH)

SPONSOR ATTENDEES

Dana Annunziato, Senior Director, Clinical Research

Sailaja Bhaskar, Ph.D., RPh, Executive Director, Clinical Research
Amy Buchwald, Ph.D., Director, Clinical Pharmacology
Mariacristina Castelli, Ph.D., Senior Director, Clinical Pharmacology
Paul Johnson, Ph.D., Senior Director, Core Development Team Leader
Robert Kirshoff, Associate Director, Clinical Research
Jeffrey Klein, Ph.D., DABT, Senior Manager, Pharmaceuticals, Preclinical
Marina Komaroff, Associate Director, Biostatistics
Joel Lippman, M.D., Exec. VP Product Development & CMO
Snehal Shah, Pharm.D., Senior Director, Regulatory Affairs
Kanan Solanki, Pharm.D., Associate Director, Regulatory Affairs

1.0 BACKGROUND

Noven Pharmaceuticals is developing d-Amphetamine Transdermal System (d-ATS), a transdermal patch which is designed to be an alternative to current oral formulations of amphetamine. The intended regulatory pathway for d-ATS is via the 505b(2) route utilizing FDA's assessment of efficacy, safety, clinical pharmacology and nonclinical toxicology of Adderall XR (mixed salts of a single entity amphetamine product) and Vyvanse (lisdexamfetamine) for clinical pharmacology as the reference listed drugs, for which Noven does not have a right of reference.

To date the following studies have been completed:

- Three Phase 1 pharmacokinetic studies (*N25-002*, *N25-004* and *N25-005*) with the current d-ATS formulation and one Phase 1 study (*N26-001*) with a previous formulation (d, l-ATS) have been conducted. These studies evaluated the pharmacokinetics, bioavailability and dose proportionality of amphetamine from d-ATS in children with ADHD and healthy adults
- Multiple Application Site PK Study (*N25-010*): A study conducted to compare the bioavailability of amphetamine from d-ATS when applied to five different application sites (hip, flank, upper back, chest, upper arm) in healthy adult subjects
- Label Comprehension Study (*N37-001*): A study to evaluate user comprehension of instructions for use of a transdermal patch to treat ADHD
- Usability Study (*N25-007*): An investigational study to evaluate the usability of d-ATS in a naturalistic setting in children, adolescents and adults with ADHD
- Usability and Adhesion Study (*N25-013*): An investigational study to evaluate usability of d-ATS in a naturalistic setting and to assess adhesion of d-ATS and Daytrana in a naturalistic and clinic setting in children, adolescents and adults with ADHD
- Phase II Study (*N25-006*): A double-blind, placebo-controlled, randomized, crossover design, analog classroom study in children and adolescents ages 6 to 17 years who meet the DSM-IV criteria for ADHD

In addition to the previously completed studies, Noven is planning to conduct the following studies to support filing and registration of d-ATS:

- Heat PK (*N25-012*): A randomized, single dose, two way crossover study to determine the effect of external heat on the pharmacokinetics of d-ATS in healthy adults

The completed and planned studies outlined above are designed to support the following indication:

- *d-ATS is central nervous system (CNS) stimulate indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).*

The purpose of this meeting is to obtain FDA agreement on the adequacy of the following items to support initiation of Phase III and filing/ registration of d-ATS:

- The overall nonclinical, clinical pharmacology and abuse liability package
- The data from the Usability-Adhesion Study N25-013
- The proposed adult Phase III clinical study (b) (4) and overall safety database

The proposed draft label for d-ATS based on completed studies and the approved labeling of the RLDs

FDA sent Preliminary Comments to Noven on December 11, 2015.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls

Question 1: Does FDA agree that a separate meeting at a later date to discuss CMC related topics with the appropriate FDA representatives can be requested if need?

FDA Response to Question 1: *Yes, we agree.*

Discussion: *No further discussion.*

2.2. Nonclinical

Question 2: Overall Nonclinical Program

Question 2a: Does FDA agree the overall nonclinical program described in the briefing package is adequate for the initiation of the Phase III study and sufficient to support registration for the proposed indication?

FDA Response to Question 2a: *On face, we agree. However, as always, the adequacy of the studies will be a matter of review. We acknowledge our agreement to waive the carcinogenicity studies for this product, as we communicated to you on July 16, 2014.*

Discussion: *No further discussion.*

Question 2b: Does FDA agree in principle the proposed label will present d-ATS nonclinical data in Section 8 (8.1 and 8.4) and Section 13 along with additional language adopted from the RLD Adderall XR labeling as outlined in Appendix 1?

FDA Response to Question 2b: *In principle we agree with your proposal; however, this will also be a review issue for the NDA.*

We remind you of the requirements of the Pregnancy and Lactation Labeling Rule (PLLR). Refer to the [Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format](#).

Discussion: *No further discussion.*

2.3. Clinical Pharmacology

Question 3: Overall Clinical Pharmacology Program

Noven has completed or plans to complete the following clinical pharmacology studies with the current formulation of d-ATS:

- N25-002 (completed): An open-label, randomized, single-dose, 2-treatment, 2-period, cross-over, bioavailability study in healthy adult subjects
- N25-004 (completed): An open-label, randomized, single-dose, 3-treatment, 3-period, cross-over, bioavailability study comparing to Adderall XR in children diagnosed with ADHD
- N25-005 (completed): An open-label, randomized, single-dose, 3-treatment, 3-period, cross-over, dose-proportionality study of 5 mg/ 4.76 cm², 10 mg/ 9.52 cm² and 20 mg/19.05 cm² in children diagnosed with ADHD
- N25-010 (completed): A randomized, single dose, five-way crossover study to compare the bioavailability of d-Amphetamine after application of d-Amphetamine Transdermal System (d-ATS) to five different application sites (hip, flank, upper back, chest and upper arm) in healthy adult subjects
- N25-012 (*planned*): A randomized, single dose, two-way crossover study to determine the effect of external heat on the pharmacokinetics of d-Amphetamine Transdermal System (d-ATS) in healthy adult subjects

Noven has completed the following clinical pharmacology study with a previous formulation of d-ATS:

- N26-001 (completed): An open-label, single dose, randomized, 3-treatment, 3-period, cross-over bioavailability study of a previous formulation containing d,l amphetamine.

Question 3a: Does FDA agree the proposed clinical pharmacology program is adequate for Phase III initiation and registration?

FDA Response to Question 3a: *In addition to the completed studies, we recommend that you conduct a multiple-dose study to determine the potential exposure change of d-ATS after repeated dosing up to four weeks. Please refer to the Daytrana (methylphenidate transdermal system) label, in which significant exposure increase was observed after four weeks of administration. We recommend you submit a protocol for a multiple dose study for OCP to review. Furthermore, you also need to address whether there is PK profile/exposure change for patients with various degrees of dermal reaction (i.e., “burning”).*

Discussion: *The sponsor indicated that the dermal reactions are transient (i.e., usually occur 0.5 to 2 hours post-dose), observed in most pediatric and adult patients, and thought to be related to the initial release of amphetamine from the patch. The sponsor agreed with the Agency’s recommendation, and plans to conduct a 4-week multiple dose PK study in adults in which, in addition to the previously discussed objectives, application site effect on d-amphetamine PK will be assessed in patients receiving the patch on the same application site versus in patients receiving the patch at different application sites each time. Furthermore, the onset, duration, severity, and type of dermal reactions will be collected in the study to allow a direct evaluation of potential exposure and PK profile changes in these patients with various degrees of dermal reactions. The sponsor will submit the protocol to FDA for review prior to conducting the study.*

Question 3b: **Does FDA agree in principle the proposed label will present d-ATS clinical pharmacology data in Section 2 (2.5), Section 7, Section 8 and Section 12 along with additional language adopted from the RLD Adderall XR and Vyvanse labels as outlined in Appendix 1?**

FDA Response to Question 3b: *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](#). Please refer to Dyanavel (amphetamine) extended-release oral suspension for class language and formatting preferences. Updates have been made for consistency with labeling regulations, guidances, and best practices. Before you submit 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 submitting your revised PI, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

OCP: In general, we agree that the proposed label will present d-ATS clinical pharmacology data in Section 2 (2.5), Section 7, Section 8 and Section 12 along with additional language adopted from the RLD Adderall XR label. You propose to reference information from the Vyvanse summary basis of approval (SBA), FDA reviewers' public summaries, or advisory committee materials to support the safety and effectiveness of d-ATS. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. The SBA, FDA reviewers' public summaries and advisory committee materials, however, do not constitute full reports of investigations. See [21 CFR 314.430\(e\)\(2\)](#). A 505(b)(2) applicant that seeks to rely on the agency's finding of safety and effectiveness for a reference listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the reference listed drug.

Discussion: *The sponsor proposed to include Vyvanse as a RLD on the basis of their bridging study between d-ATS and Adderall XR, and the relative BA study between Adderall XR and Vyvanse conducted by the sponsor of Vyvanse. However, the information on the relative BA study between Adderall XR and Vyvanse is not included in the Vyvanse label. Hence, the agency recommends the sponsor conduct a PK bridging study to directly link d-ATS and Vyvanse.*

2.4. Clinical

Question 4: Usability and Adhesion Study Results

Does FDA agree that the data from the completed Usability-Adhesion study (N25-013) supports initiation of Phase III?

FDA Response to Question 4: *During the January 17, 2014 Type C Guidance meeting, we noted that:*

...dermal application site adverse reactions were very common and relatively severe in some cases. A number of subjects discontinued from the study or required premature removal of patches because they developed pain, 'burn,' burning sensation, pruritus, erythema, irritation, edema, and discomfort. Furthermore, application site reactions may have been under-reported in the studies. The protocol states that signs and/or symptoms of skin discomfort were not recorded as adverse events unless they occurred at a site different from the application site, spread significantly beyond the application site, if the subject terminated prematurely from the study due to the discomfort, or, in the opinion of the investigator, the discomfort was an adverse event.

To address these concerns, Noven conducted a Usability-Adhesion study (N25-013).

In this study (N25-013), marketed Daytrana was used as a control arm in the study to provide context to adhesion data collected for d-ATS.

We remain concerned about application site reactions. Among the children included in study N25-013, two subjects had application site pain (both subjects received 20 mg d-ATS), and three subjects had application site erythema (one subject received 5 mg d-ATS and two subjects received 20 mg d-ATS). Among the adolescents, one subject had application site erythema (20 mg 15 d-ATS) and one subject had application site pruritus (one subject received 5 mg d-ATS). Among the adults, one subject had application site pain (5 mg d-ATS). For Subject (b) (6) who had application site pain and erythema, study drug was withdrawn and the subject was discontinued from the study.

In addition, reports of “burning” at the site of application appear to be a continued issue, in the same study on Day 1, within 30 minutes of patch application, 27.6%, 12.1% and 1.7% of subjects reported mild, moderate or severe discomfort, respectively. More subjects in the d-ATS 20 mg treatment arm reported moderate (17.9%) discomfort compared to the d-ATS 5 mg treatment arm (6.7%). At 0.5 hour post patch removal, the most severe irritation reported was definite edema with a slightly glazed appearance with one (3.6%) d-ATS 5 mg patch; and at 1 hour post patch removal, the most severe irritation reported was definite erythema, readily visible or minimal edema or minimal papular response with a slightly glazed appearance with two d-ATS patches. Some of the adverse reactions discussed above may have been dose-related. It is possible that some subjects had excessive amphetamine exposures.

From a usability perspective, we agree that the data collected from Study N25-013 supports initiation of Noven’s Phase III development program. However, we note that the use-related hazards observed in the study indicate that the Instructions for Use (IFU) may not be optimized for safety. Specifically, the IFU does not include information regarding what the user should do if the patch falls off during the recommended wear time or information regarding water exposure while wearing the patch. Thus, Noven should include this important information in the IFU since it will be utilized in the Phase III program.

Given the residual clinical concerns regarding application site reactions, FDA would like to discuss this question in further detail during the face-to-face meeting.

Discussion: *The Sponsor agreed to add language to the IFU which addresses actions which should be taken if the patch falls off and language which tells the user what to expect if they are exposed to water during their routine daily activities. Additionally, the user will be instructed on appropriate actions to take if the patch causes irritation. The Sponsor is aware that labeling will be a review issue.*

Question 5: Registration Studies Supporting Indication

Does FDA agree in principle the following two placebo-controlled and adequately powered safety/efficacy studies are adequate to support filing and registration for d-ATS treatment of ADHD in children, adolescents and adults?

- Study N25-006 (completed): A double-blind, placebo-controlled, randomized, crossover design, analog classroom study in children and adolescents aged 6 – 17 years who meet the DSM-IV criteria for ADHD

(b) (4)

FDA Response to Question 5: *Yes, in principle; however, while Noven has also characterized the pharmacokinetics and dermal characteristics of the d-ATS patch, given the results of the adverse reactions at the site of application, it is not clear that it has demonstrated safety of the drug product at doses higher than 5mg.*

We acknowledge Noven plans to conduct a study in the simulated workplace environment to demonstrate safety and efficacy in adults who meet the DSM-5 criteria for ADHD for this change in formulation.

OCP: *Regarding the proposed Phase III study in adults (Study (b) (4)), assuming that you have established efficacy and safety in children and adolescents from the existing clinical trial (Study N25-006), and that you are planning to submit a 505(b)(2) application referencing products already approved for use in adults, you may partially extrapolate efficacy and safety findings from children and adolescents to adults without additional efficacy and safety trials provided you have PK data to support this approach.*

Discussion: *The sponsor indicated that they do not intend to market doses higher than that of Adderall XR (maximum adult dose of 20 mg) in adults. The agency confirmed that if adequate PK bridge could be established between children, adolescents and adults, no adult efficacy trial is needed.*

Question 6: Children and Adolescent Study N25-006

Noven has completed a double-blind, placebo controlled, randomized crossover, analog classroom study in children and adolescents patients aged 6 to 17 years who met the DSM-IV criteria for ADHD as presented at the Type C Meeting (January 2014).

- Primary Efficacy Endpoint: To assess efficacy of d-ATS compared to placebo as measured by SKAMP Total Score
- Key Secondary Endpoint: To assess onset and duration of efficacy of d-ATS compared to placebo in SKAMP Total Score

Does FDA agree in principle the proposed label will present the data from this study in Section 14 as outlined in Appendix 1?

FDA Response to Question 6: *Labeling will be a matter of review. Please refer to our response to Question 3b.*

Also, a statistically significant sequence effect has been noted in the CSR. It will be a matter of review whether data from period 2 can be included in the efficacy evaluation.

Discussion: *The sponsor noted that their approach of testing for a carry-over effect was pre-specified in the SAP and that the results based on Period I data only are consistent with the results when using data from both periods. The statistical reviewer indicated that, on face, the strategy of basing the efficacy evaluation on data from Period I only (due to the presence of a differential carry-over effect) would be acceptable, but it would be ultimately a matter of review.*

Question 7: Adult Study (b) (4)

(b) (4)

Does FDA agree with the following aspects of study (b) (4)

Question 7a: (b) (4)

(b) (4)

FDA Response to Question 7a: (b) (4)

(b) (4)

(b) (4)

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Question 8: Overall Development Plan and Safety Database

Question 8a: Does FDA agree that the safety database at filing will be adequate to support registration of d-ATS in children, adolescents, and adults based on all completed Clinical Pharmacology studies, the completed Children and Adolescent study, the two Usability studies and the planned pivotal Adult study along with known experience from previously approved amphetamine products?

FDA Response to Question 8a: *A total of 517 subjects will be exposed to various doses of d-ATS in the clinical development program once completed. The safety database for d-ATS includes 166 children (ages 6 – 12 years) subjects with ADHD, 79 adolescent (ages 13 – 17 years) subjects with ADHD, 52 adult subjects with ADHD, and 58 healthy adult subjects. The planned simulated adult workplace study will include 162 adult patients with ADHD.*

The number of subjects exposed to various doses of d-ATS appears adequate in the context of 1315 subjects were exposed to various doses of Adderall XR in the clinical development program which included 635 pediatric patients, 350 adolescent patients, 248 adult patients, and 82 healthy adult subjects (Adderall XR USPI).

Discussion: *No further discussion.*

Question 8b: *Does FDA agree in principle the proposed label will present the safety data from the d-ATS development program in Section 4, 5 and 6 along with additional language adopted from the RLD Adderall XR labeling as outlined in Appendix 1?*

FDA Response to Question 8b: *Labeling will be a matter of review. Please refer to our response to Question 3b.*

Discussion: *No further discussion.*

Question 8c: *Does FDA agree that the overall clinical program represents an adequate safety and efficacy package to ultimately support registration of d-ATS for the treatment of ADHD in children, adolescents and adults?*

FDA Response to Question 8c: *No. We remain concerned about the potential of dermal reactions at the site of patch application; the safety of the patch does not appear to have been demonstrated at this point given the ongoing reports of adverse dermal reactions from the two-day usability study.*

Discussion: *No further discussion.*

Question 9: Pediatric Plan

Provided in [Appendix 5](#) is the draft Pediatric Study Plan (PSP) as required under PREA Requirements. Noven is requesting a partial waiver of pediatric assessments for ages 0 – 5 years and the remaining requirement has been fulfilled through the Phase II classroom study in children and adolescents. The final PSP will be filed to the IND within 60 days of this meeting.

Does FDA agree with Noven's approach to fulfill PREA requirements?

FDA Response to Question 9: *You will need to address dose-related application site adverse reactions (see Question 7a).*

We agree with your plan to request a partial waiver for pediatric studies in affected children ages 3 years and younger because the condition is difficult or impossible to diagnose in this age group, rendering studies highly impracticable or impossible. We disagree with your rationale regarding a partial waiver of pediatric studies in affected children ages 4 to younger than 6 years and recommend that you request a plan to defer

pediatric studies in this age group, pursuant to completion of safety and efficacy assessments in older patients.

Discussion: *FDA informed the sponsor that use data from other stimulant medication products for treatment of ADHD supports the ability to diagnose and treat patients ages 4 to younger than 6 years. FDA deferred in-depth discussions of study design, but informed the sponsor that:*

- *Complete extrapolation of efficacy from older children to patients 4 to younger than 6 years would not be accepted*
- *Establishment of pediatric safety requires clinical data from an adequate numbers of affected patients in the age groups to be studied, including ages 4 to younger than 6, and that patients ages 4 through younger than 6 would likely need to be studied separately from patients 6 years and older.*
- *The iPSP should address potential compliance and safety issues regarding inappropriate patch removal, particularly for patch use for 4-5 year old patients to include administration site where subjects will be less likely to remove the patch outside the context of labeled use (i.e., inappropriate removal)*
- *In addition, the iPSP will need to include a description of nonclinical data that supports conducting trials in patients as young as 4 years of age, including a plan for juvenile animal studies if needed.*
- *An open-label dose optimization scheme followed by randomized withdrawal will not provide informative safety data in patients 4 through younger than 6 years.*

Additional comment: The sponsor may explore study of affected patients ages 4 to younger than 6 years under a Pediatric Written Request. If interested, the sponsor should submit a PPSR mechanism.

2.5. Abuse Liability Potential

Question 10: Abuse Liability Program

Noven plans to rely on results of the previously performed in-vitro laboratory assessment, along with extensive published literature and experience in the abuse potential of amphetamine for a future NDA filing.

Question 10a: Does FDA agree this will enable an assessment of abuse potential as described in the January 2010 FDA Draft Guidance for Industry, “Assessment of Abuse Potential of Drugs”?

FDA Response to Question 10a: *Because no abuse potential studies (in vitro, animals, or humans) have been performed with **this product or technology**, CSS recommended that the sponsor should submit either original or referenced in vitro receptor binding and abuse-related animal study data, e.g., drug discrimination and self-administration relative to similar substances listed in the CSA. The ease of manipulation and*

extractability of the amphetamine API, compared with other available formulations, remains a potential concern that should be evaluated.

Discussion: *We agreed that the Abuse Liability Program seems complete based on the testing conducted to determine the ease of physical manipulation and extraction of d-amphetamine from the product*

Question 10b: Does FDA agree in principle Section 10 of the proposed label for d-ATS will adopt language from the RLD Adderall XR labeling as outlined in Appendix 1?

FDA Response to Question 10b: *Labeling will be a matter of review. Please refer to our response to Question 3b.*

Discussion: *No further discussion.*

2.6. Regulatory

Question 11: General Feedback

Based on the data presented, the planned studies for d-ATS and FDA's experience of approved amphetamine, methylphenidate and other non-stimulant compounds for the proposed indication, does FDA have any additional feedback on the proposed development program for registration?

FDA Response to Question 11: *We have no additional comments at this time.*

Discussion: *No further discussion.*

3.0 PREA REQUIREMENTS

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

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

regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

4.0 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 (cdet-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>

5.0 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>.

6.0 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>.

7.0 505(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 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.

8.0 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).

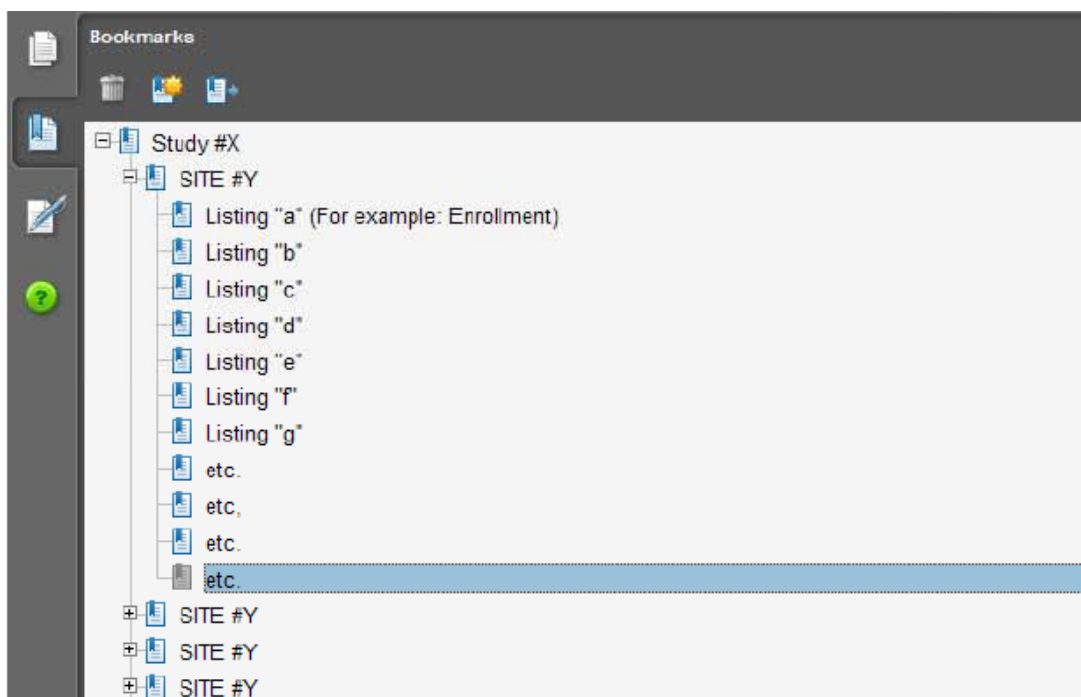
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
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.

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

9.0 **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>.

10.0 **NEW PROTOCOLS AND CHANGES TO PROTOCOLS**

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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
01/14/2016