CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209863

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Antares Pharma, Inc.
100 Princeton South Corporate Center
Suite 300
Ewing, NJ 08628

ATTENTION: Nader Fotouhi, PhD.
Director, Regulatory Affairs

Dear Dr. Fotouhi:

Please refer to your New Drug Application (NDA) dated and received March 29, 2018, resubmitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Testosterone Enanthate Injection.

We also refer to your correspondence, dated and received March 29, 2018, requesting review of your proposed proprietary name, Xyosted.

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

If any of the proposed product characteristics as stated in your March 29, 2018, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, (https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Oyinlola Fashina, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4446. For any other information regarding this application, contact Jeannie Roule, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Danielle Harris, PharmD, BCPS
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

OYINLOLA O FASHINA
05/24/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209863

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Antares Pharma Inc.
100 Princeton South Corporate Center
Suite 300
Ewing, NJ 08628

ATTENTION: Nader Fotouhi, PhD
Director, Regulatory Affairs

Dear Dr. Fotouhi:

Please refer to your New Drug Application (NDA) dated and received December 20, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Testosterone Enanthate Injection, 50 mg, 75 mg, 100 mg.

We also refer to your correspondence, dated and received December 21, 2016, requesting review of your proposed proprietary name, Xyosted.

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

If any of the proposed product characteristics as stated in your December 21, 2016, submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta M. Jackson, MS, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4952. For any other information regarding this application, contact Jeannie Roule, Regulatory Project Manager in the Office of New Drugs, at 301-796-3993.

Sincerely,

{See appended electronic signature page}

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

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/16/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116022

MEETING REQUEST /CANCELLED

Antares Pharma, Inc.
Attention: Nader Fotouhi, Ph.D.
Director, Regulatory Affairs
100 Princeton South, Suite 300
Ewing, NJ 08628

Dear Dr. Fotouhi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for testosterone enanthate auto-injector.

We also refer to your correspondence, dated and received August 11, 2016, requesting a meeting to discuss your upcoming NDA submission. The meeting was granted and scheduled to occur on November 2, 2016.

On October 31, 2016, we provided draft preliminary responses to the questions presented in your September 30, 2016, meeting package. After receipt and review of the draft responses, you informed the Division via email communication on November 1, 2016, that you had two clarification questions. The Division responded to your questions and you then determined that a meeting was no longer necessary. You officially notified us in an email communication, dated November 2, 2016, requesting cancellation of the meeting scheduled for November 2, 2016.

The final version of the Division's responses is enclosed. You are responsible for notifying us of any significant differences in understanding.

If you have any questions, call Jeannie Roule, Regulatory Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Mark S. Hirsch, M.D.
Medical Team Leader
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

INTRODUCTORY COMMENTS

You state in your meeting package that you intend to submit a 505(b)(2) NDA. Clarify 1) the information that you propose to rely upon for approval of your NDA (e.g., FDA's finding of safety and effectiveness for a listed drug, published literature); 2) the sections of your NDA, including the labeling, that you intend to support through such reliance (e.g., nonclinical); and 3) the means by which you will establish the bridge between your proposed drug product and each listed drug upon which you propose to rely (e.g., via comparative bioavailability data). Your NDA should include data to support any aspects of your proposed drug product that represent modifications to the listed drug(s) upon which you propose to rely. You must also establish that reliance on studies described in the literature that are necessary for approval of your NDA, is scientifically appropriate. If you intend to support nonclinical safety and labeling through reliance on a listed drug and/or published literature, provide the bridging information in Module 2.4 and include the literature references in Module 4.

For further information about submitting a 505(b)(2) NDA, see the 505(b)(2) Regulatory Pathway section below.

In addition, we remind you that the proposed testosterone enanthate drug product that is to be delivered via an autoinjector is a drug-device combination product under 21 CFR Part 3 and as such is subject to 21 CFR Part 4 "Current Good Manufacturing Practice Requirements for Combination Products" accessible at: https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products.

Additional DRAFT guidance - Current Good Manufacturing Practice Requirements for Combination Products is accessible at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf.

QUESTIONS AND DISCUSSION

Clinical Questions:

Question 1

Please confirm that planned clinical data from the above studies are adequate for a fileable 505(b)(2) application for the desired indication, treatment of hypogonadal adult male.

FDA Response:
If your safety database satisfies our prior request for data on at least 350 total treated subjects, with at least 200 and 100 subjects exposed for at least 6 months and one year, respectively, then the planned clinical data from your studies appears reasonable. However, a determination on filing is made after the NDA is submitted. The outcome of studies and the quality of the data are review issues.

In addition, confirm that the drug-device combination product that was used in studies QST-13-003 and QST-15-005 was the to-be-marketed combination product.

Sponsor's Clarification Question Received on November 1, 2016, via email:
In our Meeting Briefing Book, the Sponsor quoted two prior Information Request/Advice letters from FDA dated (see below excerpts from those IR letters) in which the FDA repeatedly used the word "approximately" when referring to the total numbers of subjects exposed at the various time intervals. Now, however, in response to our Question 1, the FDA is using the words "at least" when referring to the total numbers of subjects exposed. This is also inconsistent with the FDA's response to the Sponsor's Question 2, in which the FDA states "If your studies reflect our prior discussions in terms of numbers of subjects exposed and durations of exposure, then the data appear acceptable for review."

Our NDA will contain a total of 379 subject exposures, including 240 and 99 subjects exposed to QST for 6 months and 1 year, respectively. These numbers are consistent with the FDA's prior Advice Letters.

As we stated above, the FDA's prior written advice to the sponsor with reference to the total numbers of patient exposure has been preceded by the word "approximately" (see below excerpts):

01/7/2015 Advice Letter/IR request following the review of the protocol for study QST-13-003, the FDA stated: "Approximately 350 subjects should be exposed to your product, with approximately 200 subjects and 100 subjects exposed for at least 6 months and 1 year, respectively."

05/21/2015 Advice Letter in response to Antares's proposal for a new study to enrich the safety population, the FDA stated, "Yes. We agree with your proposal to conduct new Phase 3 Study QST-15-005 to accumulate more data from approximately 100 patients to reach 350 total exposed subjects. We emphasize that repeat patient exposure is important in studying potential allergic reactions, thus, in addition to 350 total patient exposures; we remind you of our request for safety information from approximately 200 subjects and 100 subjects exposed for at least six months and one year, respectively."

We reiterate, our NDA will contain a total of 379 subject exposures, including 240 and 99 subjects exposed to QST for 6 months and 1 year, respectively. These numbers are consistent with the FDA's prior Advice Letters.

Please confirm and clarify that these meet the FDA's requested numbers of and durations for subject exposure suggested to us throughout the development program for QST, and that the NDA will be acceptable for review, at least from a standpoint of "subject totals" in terms of both numbers and durations of exposure.

FDA Response:
We concur with Antares' understanding of DBRUP's prior recommendations for the safety database. DBRUP's prior request was for "approximately" 350 total patients treated, with "approximately" 200 patients and "approximately" 100" patients treated for 6 months and 1 year, respectively; and not for "at least" 350 total treated patients, or for at "at least" 200 patients or

"at least" 100 patients treated for 6 months or 1 year, respectively. We hope this clarifies our original preliminary response to Q1.

Question 2
Please confirm the above meets the standard for acceptability for review (see briefing document pages 8-9, including Table 3).

FDA Response:
If your studies reflect our prior discussions in terms of numbers of subjects exposed and durations of exposure, then the data appears acceptable for review. We remind you that the quality and quantity of data generated by your studies, and the outcomes of the studies, are NDA review issues. Your NDA should provide justification for the proposed dose adjustment scheme and for other key safety and efficacy issues.

Question 3a
Please confirm that the proposal not to merge and reanalyze data from multiple studies for the ISE is acceptable.

FDA Response:
The proposal not to merge multiple studies for the ISE is acceptable.

Question 3b
Please confirm the Agency's agreement that study QST-13-003 can form the basis for the PK data in our label.

FDA Response:
It is premature to confirm that study QST-13-003 can form the basis for the PK data in the label because additional PK data were collected in study QST-15-005. The PK data that will be included in labeling is a review issue and will be considered in the totality of the data.

Question 4
Please confirm the acceptability of the planed pooling of data for the ISS.

FDA Response:
The plan to pool data for the ISS is acceptable.

We have the following safety-related Clinical comments and requests for additional safety information:

- The ISS should include a separate detailed section on safety and feasibility of self-injection therapy, including a discussion of the observations from human factors studies and the data from clinical studies in support of safe self-injection.

- The NDA should specify the total number of subjects exposed and the total numbers exposed for at least 6 months and 1 year, respectively.

- The observed increases in blood pressure in studies QST-13-003 and QST-15-005 will a review issue. These increases appear potentially clinically significant. The ISS should provide a detailed discussion of the BP results, with specific comments on the clinical significance, and if appropriate, comparisons to blood pressure data available for approved testosterone products. Fasting lipid profiles, which were collected in your studies, should be included and discussed in your submission. The Division of Cardiovascular and Renal Products (DCRP) will be consulted to assist in the review of this data.

- Submit case narratives and case report forms for all SAEs and discontinuations secondary to AEs.

- For all SAEs and discontinuations secondary to AEs, provide serum testosterone levels at screening, at baseline, at periodic visits, and at the time of the AE. In addition, provide the date of dosing relative to the AE, and any testosterone levels obtained after the AE.

- Adverse events of depression and suicide, and cardiovascular and cerebrovascular AEs, will be review issues. Provide as much detail as possible for each event to allow for an informed assessment of causality.

- Adverse laboratory results of increased hematocrit and increased serum PSA are review issues.

Question 5

Based on lack of significant new safety signals, and contingent on confirmation during the FDA review of the NDA:

a. Please confirm preliminary lack of need for Advisory Committee Meeting.

FDA Response:
It is premature to confirm the lack of need for an Advisory Committee (AC) meeting. Reports of increased BP, cardiovascular and cerebrovascular adverse events, and depression/suicide may prompt the need for an AC.

b. Please confirm preliminary lack of need for labeling due to POME.

FDA Response:
It is premature to confirm the lack of need for labeling due to POME.

c. Please confirm preliminary lack of need for REMS, assuming the sponsor includes a patient information leaflet within the drug product packaging.

FDA Response:
At this time, there is insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug

outweigh the risks, and if it is necessary, what the required elements would be. We will determine the need for a REMS during the review of your application.

Question 6
Please confirm that the data for assessment of pain associated with self-injection can be included in the safety section of label.

FDA Response:
Although discussions of specific labeling for safety results are premature, adverse events from the safety database in from the phase 3 study may be included in labeling,

As stated at our previous meeting on May 1, 2014, results from the Self-Injection Assessment Questionnaire (SIAQ), as well as binary information on pain from human factors studies are considered exploratory and are not acceptable for labeling. In general, secondary endpoints such as pain from injection may be included in labeling if they are agreed upon in advance by the Division, appropriately addressed in the statistical analysis, and evaluated using an appropriately validated instrument.

Human Factor Questions

Question 7
Please confirm that the FDA concurs with this approach (see briefing document, pages 15-17, including Table 9).

FDA Response:
For ease of review, it would be optimal to submit all of your individual reports, including the Human Factors iterative study reports, to the NDA. Clarify whether there is some specific reason that this cannot be done.

Your Human Factors study results should be placed in eCTD section 5.3.5.4 – Other Study Reports and Related Information.

In addition, we have the following comments and requests for information:

1. Your proposal to provide an overview of the key results as illustrated in Table 9 in the briefing package is not sufficient for our review of your Human Factors (HF) validation summative study report. The results of your HF Validation Study will be reviewed under the marketing application. The following should be submitted at the time of the marketing application :

    - A summary of preliminary analyses and evaluations, including formative studies: Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis.

    - An updated risk analysis for your product.

- Detailed HF validation study, including detailed information about each use error event, close call, or use difficulty experienced by each participant in the study, as well as subjective feedback from each participant. This information should be accompanied by a root cause analysis for each event. See Appendix A of the FDA Guidance entitled, *Applying Human Factors and Usability Engineering to Medical Devices*, available online at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf for a description of elements to include in the HF validation study report.

- Intend-to-market labels and labeling, including an editable word version of the Instructions for Use (IFU).

- Five intend-to-market samples of product.

- Summary of any changes made to the user interface (e.g., product design or label and labeling changes) after completion of the human factors validation study, including a description of how the changes were validated. If changes to the IFU were made, provide a side-by-side comparison that points out the differences between the tested version and the intend-to-market version.

2. If you have not yet commenced study CLS-1022, consider conducting one single validation study including all three user groups. If you plan to conduct separate human factors validation studies for the different intended user populations, summarize the differences in the study design and methodology between the two studies. We remind you of our prior recommendations, provided on May 16, 2016, in regard to the design of the HF validation protocol CLS-1022.

Device Questions

Question 8a
Please confirm that the FDA agrees that the types of information provided in the Appendix 5 will constitute a MAF acceptable for review

FDA Response:
You have provided a detailed plan of testing within Device Master File (MAF). In addition to the detailed plan of testing that you provide in the MAF, you will also need to provide testing on biocompatibility and shipping studies on the final finished device, if you do not provide that testing within the NDA.

In addition to the information that you plan to provide in the MAF, you will need to address the design requirements, specification and risk analysis documents within the NDA. While it is acceptable to provide the verification data within the MAF, you will need to justify/explain how that information is relevant to your stated specifications.

Sponsor's Clarification Question Received on November 1, 2016, via email:
In this response, the FDA states that "In addition to the detailed plan of testing that you provide in the MAF, you will also need to provide testing on biocompatibility and shipping studies on the final finished device, if you do not provide that testing in the NDA." Biocompatibility studies will of course be in the device MAF. Shipping studies, however, are generally not conducted until immediately prior to the product's commercial release and launch; they are not usually conducted prior to an NDA filing. Accordingly, we were not planning on having or including results from shipping studies in either the NDA or the MAF. This is consistent with both industry standard practice as well as our prior recent approved NDA/ANDAs for Otrexup (NDA 204-824) and Sumatriptan (ANDA 78-319) auto-injectors. Also, this is not a combination product for "emergency use".

Please clarify if it is still considered acceptable for the Sponsor not to include results of shipping studies in either the NDA or in the MAF at the time of the NDA/MAF filing that will occur this coming December, 2016. The Sponsor can commit to including the shipping study results in the 1st year's NDA Annual Report and the 1st Annual MAF update, if the FDA would like.

FDA Response:
We continue to request that this information be provided as part of your NDA submission. Specifically, you should provide the shipping studies on the final finished combination product within the NDA based on ASTM D4169.

If the information is not part of your NDA submission, it will be a review issue. If the information is not included with your NDA submission, it will not be a filing issue. If your NDA is filed, the information will be requested in the 74 day letter.

Question 8b
Please confirm our planned filing approach for MAF on a searchable CD is acceptable

FDA Response:
We will not review a searchable CD. If you plan to submit your Device Master File (MAF) to the FDA, you will need to submit it to the Document Mail Center. Instructions and the complete mailing address can be found at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm313794.pdf

Regulatory Questions

Question 9
Consistent with labeling of all testosterone containing products, Antares will include "Drug Abuse and Dependence" information in the proposed labeling for its testosterone enanthate injection.

Please confirm that with the inclusion of this information in labeling, no other abuse potential assessment is required at the time of NDA submission.

FDA Response:
Upon submission of an NDA, it is standard for all products classified as a scheduled drug (your drug product is a schedule III drug), to undergo review by the Controlled Substance Staff (CSS). As part of that review, CSS will decide whether any abuse potential assessments will be required.

If your NDA is approved, the product label, specifically section 9, Drug Abuse and Dependence, will include the most current class labeling for testosterone products.

Post Meeting Note:
The CSS has completed their review of your briefing document and has the following additional comments and recommendations:

- Perform an analysis of the clinical trial data using abuse potential terms. Refer to the FDA Guidance for Assessment of Abuse Potential of Drugs; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf). For your convenience, a summarized list of abuse potential terms from the FDA Guidance is attached at the end of this document.

- Provide all clinical trial data relevant to misuse, diversion and overdose.

- Perform an evaluation of dependence and withdrawal at the end of any ongoing studies. If studies are not currently being conducted, and no additional studies are planned, then perform an evaluation of dependence and withdrawal based on subject data from post-treatment follow-up visits in all completed clinical studies. A particular concern is the report of a completed suicide (Subject # (b) (6) page 53 of your meeting package) which appeared to occur during the post-treatment period. Depression and suicides have been reported in users of testosterone and anabolic androgenic steroids (AAS).

Question 10
Please confirm this application qualifies for review within 10 month of receipt in accordance with current PDUFA goals and the types of data the sponsor proposes to include in this NDA appear to meet the statutory definition of clinical data to potentially qualify for 3 years of product exclusivity.

FDA Response:
Yes. Your NDA review will be assessed in accordance with the current 10-month PDUFA goals.

Your product could potentially qualify for 3 years of exclusivity. However, FDA does not make exclusivity determinations pursuant to Sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food Drug and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described in 21 CFR 314.50(j), an applicant should include in its NDA a description of the exclusivity to

which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity after approval of the application.

ADDITIONAL INFORMATION

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

2. Please include the following information in a tabular format, *by site,* in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

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

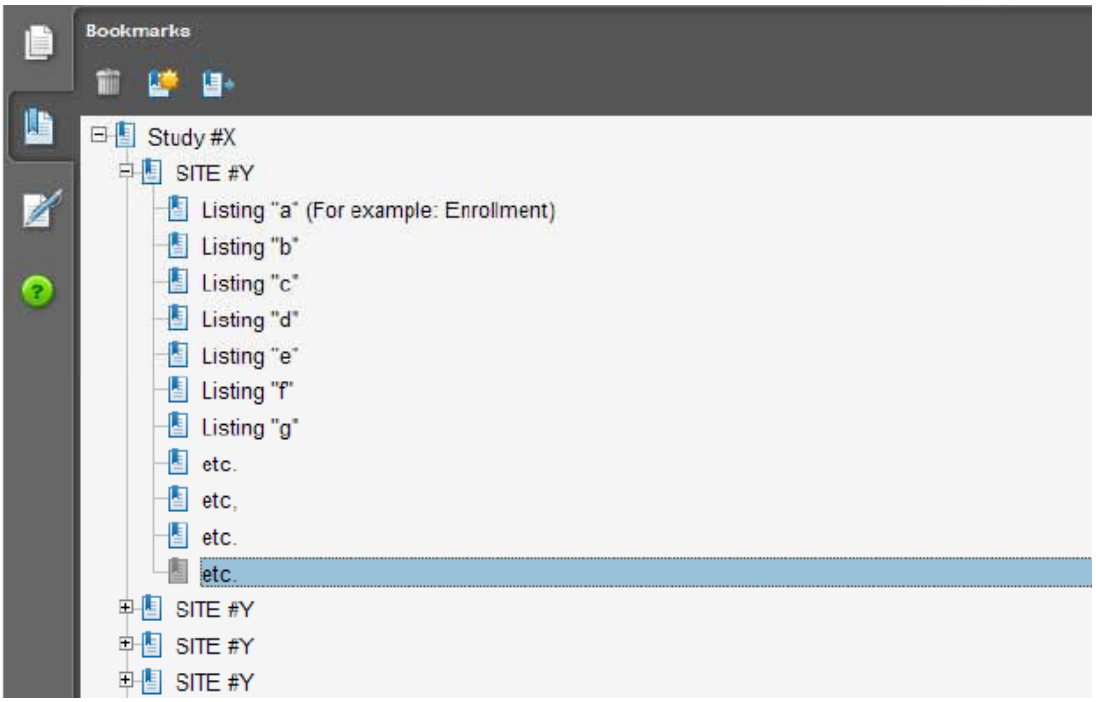
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

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

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

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

Expanded list from page 20 of the Guidance:

C. Clinical Trial Data Relative to Abuse Potential Assessments

The evaluation of the adverse events profile of a drug from clinical trials can provide a signal of abuse potential. The systematic categorization, tabulation, and analysis of safety data for mood elevation, sedation, and psychotomimetic events can provide useful information. The incidence of euphoria-type adverse events (including euphoria, euphoric mood, elevated mood, mood alteration, feeling drunk, feeling abnormal) and hallucination (visual and auditory) are a few of the more prominent MedDRA terms that should be considered. MedDRA 12 terms for inappropriate affect, which include the following lower level terms: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter, inappropriate mood elevation, should also be considered. A prospective evaluation of withdrawal adverse events after abrupt discontinuation of treatment can provide information relevant to dependence. Various quantitative measurements will be useful in providing objective data to assess dependence (e.g., opioid and benzodiazepine withdrawal scales and psychiatric rating scales). Data related to serious psychiatric and neurological adverse events and the need for hospitalization is relevant to the public health risks and abuse potential of the drug.

Abuse-Related AE Terms for Use in Clinical Efficacy Studies

All clinical studies should be evaluated for indicators of abuse potential. The list below is a compilation of abuse-related adverse events terms, based on our experience to date. The list includes specific terms that are in the MedDRA 12.0 dictionary as well as frequently used verbatim terms, words or phrases. Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The presence of euphoria or other positive mood changes are key observations that may influence the assessment of abuse potential and a recommendation for scheduling. However, all data submitted in an NDA are critical in determining whether scheduling will be recommended, and if so, into which schedule the drug will be recommended for placement.

Euphoria-related terms:

Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high*, high* feeling, laughter. (* Exclude terms that clearly are not related or relevant such as “high blood pressure,” etc.)

Elevated mood*:* mood elevated, elation.

Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny

episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.

Feeling of relaxation: feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

Dizziness*:* dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts.

Hallucination*:* (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

Inappropriate affect: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laugher, inappropriate mood elevation.

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor.

Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative/psychotic terms:

Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia.

Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity.

Euphoria-related terms:

Euphoric mood
(* Exclude terms that clearly are not related or relevant such as "high blood pressure," etc.)
Elevated mood
Feeling abnormal
Feeling drunk
Feeling of relaxation
Dizziness
Thinking abnormal
Hallucination
Inappropriate affect

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

Somnolence
Mood disorders and disturbances
Mental impairment disorders
Drug tolerance
Habituation
Drug withdrawal syndrome
Substance-related disorders

Dissociative/psychotic terms:

Psychosis
Aggressive
Confusion and disorientation

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

/s/

MARK S HIRSCH
11/28/2016