# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209471Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107435

**MEETING MINUTES**

AFT Pharmaceuticals, Ltd.
c/o Chesapeake Regulatory Group, Inc.
6574 River Clyde Drive
Highland, MD 20777

Attention: David Zuchero, MS, JD
US Agent for AFT Pharmaceuticals, Ltd.

Dear Mr. Zuchero:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Maxigesic (ibuprofen 97.5 mg/acetaminophen 325 mg) Film-Coated Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on July 9, 2015. The purpose of the meeting was to discuss the results of the Phase 3 acute pain study to support submission and approval of a 505(b)(2) NDA. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

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

If you have any questions, call me at (301) 796-1258.

Sincerely,

*{See appended electronic signature page}*

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
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:** Pre-NDA
**Meeting Date and Time:** July 9, 2015, at 4:00 p.m. (Eastern Time)
**Application Number:** 107435
**Product Name:** Maxigesic 325 (acetaminophen 325 mg and ibuprofen 97.5 mg)
**Indication:** short term management of acute pain (b) (4)
**Sponsor/Applicant Name:** AFT Pharmaceuticals Ltd.

**FDA ATTENDEES (tentative)**
Sharon Hertz, MD; Director
Ellen Fields, MD; Clinical Team Leader
Jacqueline Spaulding, MD; Clinical Reviewer
Dan Mellon, PhD; Supervisor Pharmacology/Toxicology
Newton Woo, PhD; Team Leader, Pharmacology/Toxicology
Carlic Huynh, PhD; Pharmacology/Toxicology Reviewer
Yun Xu, PhD; Team Leader, Clinical Pharmacology
Wei Qiu, PhD; Clinical Pharmacology Reviewer
Ciby Abraham, PhD; Quality Assessment Lead, OPQ
Freda Cooner, PhD; Team Leader, Biostatistics
James Travis, PhD; Biostatistics Reviewer
Allison Meyer; Sr. Regulatory Health Project Manager

**SPONSOR ATTENDEES**
Hartley Atkinson, Managing Director
Ioana Stanescu, Phil.Lic., MSc., Head of Drug Development
David Zuchero, MS, JD, Regulatory Affairs Consultant

## 1.0 BACKGROUND

AFT Pharmaceuticals Ltd. has developed a combination product containing acetaminophen and ibuprofen. The proposed fixed-dose combination is intended to provide an increase in analgesia without increasing the dose of acetaminophen, avoid combination with opioids, reduce the risk of gastrointestinal bleeding and other thromboembolic events, and limit the opportunity for drug interactions between the two acting components.

## 2. DISCUSSION

The questions from the June 8, 2015, meeting package are shown below in *italic* font and the preliminary responses are in **bold font**. Preliminary responses were received by the Sponsor on

July 8, 2015, and clarifying remarks were returned on July 9, 2015. The Sponsor stated that they wanted to discuss Question 7, Additional Statistical Comments, and the PREA Requirements.

*Question 1:*
*The drug substance and drug product specifications have been provided in sections 9.2 and 9.4 of the pre-NDA package. Does the Agency agree with the proposed specifications?*

**FDA Response:**
**The proposed specifications for the drug substance and drug product appear acceptable. Include an additional identification test for acetaminophen and ibuprofen for the release specifications of the drug product. Additional information may be required during the review of the NDA application, and final determination of the adequacy of these specifications will be made upon review of the NDA submission.**

Discussion: There was no further discussion of this question.

*Question 2:*
*Six months accelerated and 24 months real-time stability data are provided for three pilot scale batches. Does the Agency agree that these stability data support a shelf-life of 36 months, when the product is stored below 30$^{o}$C?*

**FDA Response:**
**The determination for the expiry of your product can only be evaluated at the NDA stage when the totality of the CMC information is reviewed.**

Discussion: There was no further discussion of this question.

*Question 3:*
*Process validation data derived from three pilot scale batches are provided for review. Does the Agency agree that these data is sufficient to support the process validation of the commercial scale batches?*

**FDA Response:**
**The information you have provided appears reasonable to support NDA submission. The data will be evaluated during the NDA stage.**

Discussion: There was no further discussion of this question.

*Question 4:*
*Maxigesic 325 is indicated for the short term* (b) (4) *management of acute pain* (b) (4)*. The product (3 tablets every 6 hours, not more than 12 tablets in 24 hours) is indicated in adults* (b) (4)*. Does the Agency agree with the proposed indication and usage?*

**FDA Response:**

**The acceptability of the proposed indication is an NDA review issue. We have reviewed the literature you submitted and it does not appear to be adequate to support an** (b) (4)

(b) (4)

Discussion: There was no further discussion of this question.

*Question 5:*
*The detailed results of the Phase 3 Pivotal Clinical Study (AFT-MX-6) confirmed the superior analgesic effect of the fixed dose combination (Maxigesic 325) versus its individual components. Does the Agency agree that this study is sufficient to support the submission of an NDA for an acute pain indication?*

**FDA Response:**
**Study AFT-MX-6 appears to have met the requirements of an adequate and well-controlled, factorial study; therefore, this study appears adequate to support the submission of an NDA for an acute pain indication.**

Discussion: There was no further discussion of this question.

*Question 6:*
*Since there is only a single pivotal study, could the Modules 2.5 Clinical Overview and 2.7 Clinical Summary take the place of the Integrated Summary of Efficacy and Integrated summary of Safety?*

**FDA Response:**

**You are planning to submit only one clinical trial to support the proposed indication, therefore, we agree that Module 2 can include information that could be included in Module 5 (ISE), and a hyperlink in Module 5 can refer back to Module 2.**

**You must include an Integrated Summary of Safety (ISS) and discuss the data from your studies and any other information you rely upon to support the safety of the product. The safety database must include studies conducted with both the to-be-marketed formulation as well as the "full – dose" formulation. You must also pool safety data as is appropriate based on the doses and dosing interval and duration of the studies.**

Discussion: There was no further discussion of this question.

*Question 7:*
*Does the Agency agree that the CMC, preclinical and clinical data provide an adequate basis for submitting the NDA for Maxigesic 325?*

**FDA Response:**
**We agree that the CMC and nonclinical data appear to support submission of your NDA. Provide the final study reports for all relevant Sponsor-conducted nonclinical studies (e.g. Study 1247-12131 and Study 1247-12072) in your NDA submission.**

**You have stated that you plan to rely on the Agency's previous findings of safety and efficacy of the reference listed drugs to support the pharmacology and toxicology of Maxigesic 325. However, the listed drugs for your planned 505(b)(2) NDA submission were not identified in your meeting package. You must identify your listed drugs and establish a scientific bridge (e.g., via comparative BA data) between your proposed drug product and the listed drugs upon which you propose to rely to demonstrate that such reliance is scientifically justified. See our general comments for the 505(b)(2) regulatory pathway. Use the final to-be-marketed formulation of Maxigesic 325 in the bridging study and clinical studies. Otherwise, provide adequate bridging information or justification why the study results can apply to the final to-be-marketed product. For the PK bridging study between Maxigesic 325 and the listed drugs, you must evaluate your product using the highest recommended dose according to your final proposed product labeling. Food effect using high fat meal on the PK of Maxigesic 325 must be evaluated.**

**Clarify if the final to-be-marketed formulation was used in your completed PK studies and clinical studies. Clarify if a high fat meal was used to evaluate food effect on Maxigesic 325 in your Study AFT-MX-10.**

**The clinical data you are proposing to include appears adequate to support submission of an NDA for an analgesic indication.**

**Final determination of the adequacy of the submitted materials can only be provided at the time of NDA review.**

Discussion: The Sponsor proposed to provide a systematic literature search and discuss the pharmacokinetic, safety, and efficacy data within the context of the integrated summaries of safety

and efficacy, and further compare the Maxigesic 325 clinical data with the publicly available data for the U.S. listed products. The Division stated that a literature based pharmacokinetic bridge will not be acceptable. A 505(b)(2) application that relies in part upon the Agency's previous finding of safety and efficacy for a referenced drug product requires a relative bioavailability (BA) bridging study to compare the new product to the referenced products. A demonstration of bioequivalence is not necessarily required, but, a lack of bioequivalence generally means that additional efficacy and/or safety studies will be necessary to support the NDA.

The Division stated that the Sponsor must use products that have been approved through an NDA, and preferably for the same indication proposed for Maxigesic 325. However, over-the-counter products under a final monograph may be used as comparators. The Division noted that if no NDA product is available on the market, a generic (i.e. ANDA), preferably an RLD, can be used for the relative bioavailability study. The approved NDA product would still be referenced for the 505(b)(2) NDA. The Division recommended submitting a discussion of the proposed reference products and a BA study protocol outline before initiating the study.

The labeling information of the comparator U.S. products should be carefully checked before selecting the reference products intended to be used as comparators. The Division recommended preparing an annotated label for the product, showing what information from the approved labeling will be used for the new product and to determine if there are any relevant gaps that must be filled with new data.

**Additional Nonclinical Comments:**

1. **Include a detailed discussion of the nonclinical information in the published literature and specifically, address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

2. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:**

    a. **You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

    b. **In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14-days duration should be completed.**

    c. **Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels**

**of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf.**

**Refer to guidance for industry: *Q3A Impurities in New Drug Substances*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf**

**and**

**Guidance for industry: *Q3B (R2) Impurities in New Drug Products*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf**

3. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to guidance for industry ICH M7: *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying or controlling these impurities, available at, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product must be identified for assessment. A hazard assessment must be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy must be enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.**

4. **We remind you that any novel excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance document: Guidance for Industry: *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients,* available on the CDER web page at the following http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf.**

**As noted in the document cited above, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration." (emphasis added).**

5. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

6. **We may to refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity, degradant or excipient that exceeds the recommended qualification thresholds that is not justified for safety otherwise.**

7. **We note that all NDA applications filed after June 30, 2015, must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, you should conduct a thorough review of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.**

8. **For general toxicology and supporting nonclinical toxicokinetics studies, we encourage you to both use Standards for the Exchange of Nonclinical Data (SEND) for regulatory submissions and to submit sample or test data sets before implementation becomes required. Sponsors will be provided feedback 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.**

**Additional Statistics Comments**

**Please provide the following for each adequate and well-controlled clinical study (per 21 CFR 314.126) that you plan to include in your eventual NDA submission:**

a. **All clean/locked clinical data sets presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.**

b. **All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets incorporate the modeling approaches described by the latest CDISC/ADaM standard along with both the CDER Data Standards Common Issues Document and the Study Data Specifications document (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm). We recommend that the data definition file comply with the latest CDISC/Define.XML standard.**

c. **A Study Data Reviewer's Guide (SDRG) along with an Analysis Data Reviewer's Guide (ADRG).**

d. **A well commented and organized software program written for each analysis dataset and efficacy table created.**

Discussion: The Division stated that the requirement is for properly constructed electronic datasets, utilizing SAS Version 5 Transport, along with the annotated case report for (CRFs) and a thorough data definition file. This applies to all clinical studies included in the NDA submission. The Division also stated that an integrated safety dataset for all the clinical studies must be included in the NDA submission.

## PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (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.

In addition, your PSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

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.

Discussion: The timing of the submission of an iPSP was discussed. The Division emphasized that the iPSP application should be submitted as soon as possible, at least 210 days prior tothe NDA submission. The Sponsor explained that Maxigesic 325 in its current formulation is not intended for the pediatric population. The Sponsor has developed a different liquid formulation, which is currently planned to be registered in Europe. The Division indicated that the iPSP must contain an outline of the pediatric studies intended to be conducted, using age-appropriate formulations, with special attention on the age groups. Any request for a deferral or waiver should be accompanied by the supportive documentation. The iPSP must be agreed upon in order to file an NDA. Refer to the guidances noted above for details regarding timing and content of the iPSP.

**ACTION ITEMS**

The Sponsor will:

- Submit the list of potentially suitable comparators for Division comment prior to conducting the BA studies

- Provide the synopsis of the proposed BA studies (fasted/fed - 3way cross-over studies) for comment prior to conducting the BA studies.
- Include the following studies AFT-MX-10 (PK study), AFT-MX-3 (supportive dental), AFT-MX-3 (dose response), AFT-MX-6E (arthroscopy) and AFT-MX-6 (pivotal dental study) in the NDA submission
- Prepare and submit the iPSP as soon as possible

## PRESCRIBING INFORMATION

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

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

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

## 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.

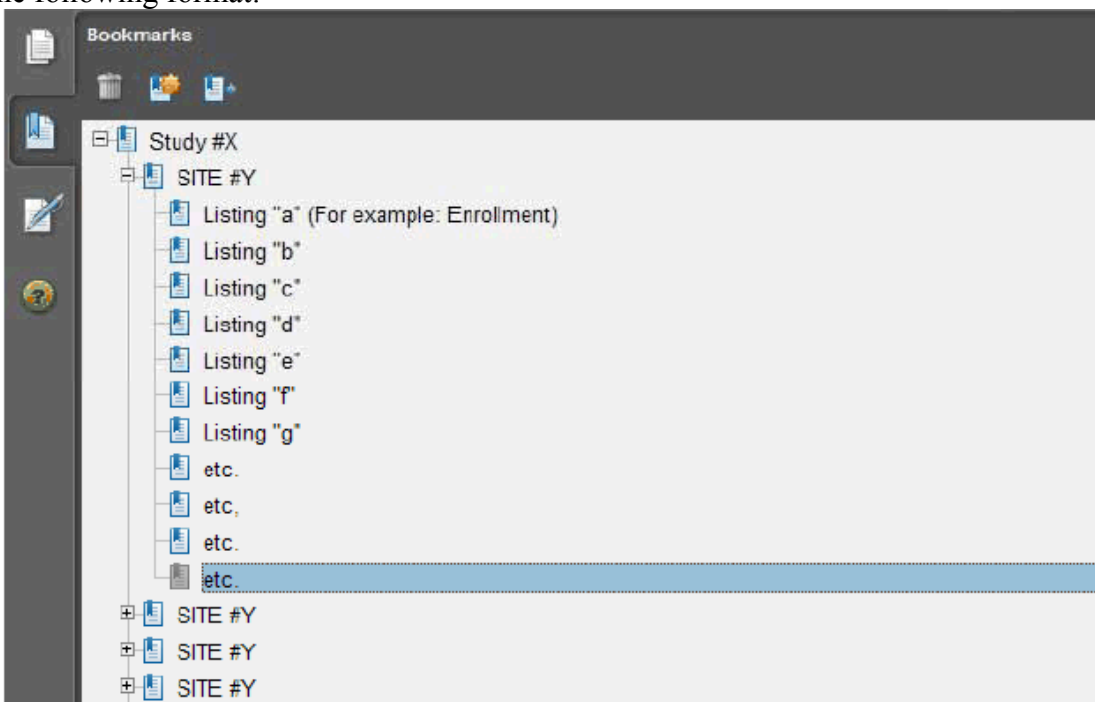
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

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

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/s/

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ALLISON MEYER
08/05/2015