CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209405Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209405

REFUSAL TO FILE

Exeltis USA, Inc
Attention: Sandy S. Suh, PharmD
Head, Regulatory Affairs (R&D)
180 Park Avenue, Suite 101
Florham Park, NJ 07932

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) dated October 18, 2018, received January 7, 2019, submitted under pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for EV402 (levonorgestrel/ethinyl estradiol) (b) (4) tablets.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR314.101(d)) for the following reasons:

1. You did not provide the analysis datasets and associated data definition files for the following studies: EXS-P1-531, EXS-P3-821, EHE-P4-471, and EHE-P4-469.

   To allow a substantive review of this NDA, please submit the following:
   a. Analysis datasets and associated data definition files (define.xml and/or define.pdf) for the four above-referenced studies.
   b. At minimum, include in the data definition files the analysis dataset metadata and analysis variable metadata as specified in our Information Request (IR) dated February 27, 2019.
2. You provided incomplete and inconsistent SDTM datasets and associated data definition files for all four studies listed in Item # 1. Correct all datasets and data definition files to contain the requested changes previously specified in our IR dated February 27, 2019. Refer to FDA Study Data Standards Resources website for more information regarding study data submission.
   https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

While these are not issues related to our refusal to file of this application, you should address the following issues if the application is resubmitted.

1. Compared to the reference product, in Study EXS-PS-821, administration of EV402 chewed and swallowed without water significantly increased exposure (Cmax and AUC) of EE but no impact on exposure of LNG. Provide an explanation for the observation if you have conducted a root-cause investigation.
2. The hyperlink for validation report LVE-V9-603 (R6) directed the reviewer to validation report EHO-V8-572 (R22). Please provide the location of validation report LVE-V9-603 (R6) or submit the file if it has not been submitted to the NDA.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.'

If you have any questions, call Jennifer Dao, Regulatory Project Manager, at (301) 796-8189 or Jennifer Mercier, Chief, Project Management Staff at (301) 796-0957.

Sincerely yours,

{See appended electronic signature page}

Christine Nguyen, M.D.
Deputy Director of Safety
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

CHRISTINE P NGUYEN
03/08/2019 08:55:06 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 119353

MEETING MINUTES

Exeltis USA, Inc.
Attention: Sandy Suh, Pharm.D.
Head of Regulatory Affairs
180 Park Avenue, Suite 101
Florham Park, NJ 07932

Dear Dr. Suh:

Please refer to your Pre-Investigational New Drug Application (PIND) file for EV402.

We also refer to the meeting between representatives of your firm and the FDA on February 8, 2018. The purpose of the meeting was to discuss the development of EV402 in preparation of a 505(b)(2) New Drug Application.

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

If you have any questions, call Jennifer Dao, Regulatory Project Manager at (301) 796-8189.

Sincerely,

{See appended electronic signature page}

Catherine Sewell, M.D.
Acting Clinical Team Lead
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
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: Thursday, February 8, 2018 12:00 PM – 1:00 PM
Meeting Location: White Oak Bldg 22, Rm 1313

Application Number: PIND 119353
Product Name: EV402
Indication: Prevention of Pregnancy
Sponsor/Applicant Name: Exeltis USA, Inc.

Meeting Chair: Catherine Sewell, M.D., M.P.H.
Meeting Recorder: Jennifer Mercier

FDA ATTENDEES

Division of Bone, Reproductive and Urologic Products
Audrey Gassman, M.D. – Deputy Director
Mukesh Summan, Ph.D., DABT – Pharmacology/Toxicology Supervisor
Miyun Tsai-Turton, Ph.D. – Pharmacology/Toxicology Reviewer
Catherine Sewell, M.D., M.P.H. – Acting Clinical Team Lead
Abby Anderson, M.D. – Medical Officer
Jennifer Mercier – Chief, Project Management Staff

Office of Clinical Pharmacology
Doanh Tran, Ph.D. – Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCPIII), Office of Clinical Pharmacology (OCP)
Peng Zou, Ph.D. – Clinical Pharmacology Reviewer, DCPIII, OCP

OFFICE OF PHARMACEUTICAL QUALITY; Office of New Drug Products; Division of New Drug Products II; New Drug Products Branch V
Mark Seggel, Ph.D. – CMC Lead

OFFICE OF BIOSTATISTICS; Division of Biometrics III (DBIII)
Weiya Zhang, Ph.D. – Statistical Reviewer

SPONSOR ATTENDEES
Sandy S. Suh, Pharm.D. – Regulatory Affairs (US Agent), Exeltis USA, Inc.
Patrick O'Hara – Project Leader, Exeltis USA
(b) (4)

1. BACKGROUND

The purpose of this meeting is to discuss the overall development of EV402 in preparation of a 505(b)(2) New Drug Application (NDA). Exeltis USA, Inc. has developed a (b) (4) product of levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg combination oral contraceptive. The clinical development program was conducted in Canada. Five trials were completed using two formulations of EV402. The trials in support of this 505 (b)(2) application using the to-be-marketed (TBM) formulation, include two comparative bioavailability trials evaluating the pharmacokinetics (PK) of EV402 with the referenced product Alesse® in the fasted state and one oral tolerability trial. The Sponsor proposes to rely upon these studies and the FDA's findings of safety and efficacy for Alesse®, including literature references.

2. DISCUSSION

GENERAL COMMENTS

- You are proposing to reference information from the FDA reviewers' public summaries in support of safety and/or effectiveness of you proposed product. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. The FDA reviewers' public summaries; however, do not constitute full reports of investigations. See 21 C.F.R. 314.430(e)(2). A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug.
- Additionally, non-US labeling or non-US regulatory authority assessments may not be relied upon as these are neither FDA's findings related to a listed drug, nor are they published literature. If the studies upon which the non-US conclusions are based have been published, you may be able to rely upon that literature.
- We noted that the formulation used in the food effect study (Study EHE-P4-469) was different from the formulation tested in the comparative bioavailability Study EXS-P3-821 and Study EXS-P3-239, and the oral tolerability Study EXS-P3-531. We recommend that you conduct a comparative bioavailability study with your to-be-market formulation and Lutera® (the ANDA product designated as the reference standard in the Orange Book) under fed conditions in addition to the completed relative bioavailability study under fasting conditions. Alternatively, you can conduct a food effect study with your to-be-marketed formulation and demonstrate that food intake does not affect the bioavailability of your drug product.

Discussion during the meeting:

- ***The sponsor requested clarification regarding the need for a relative bioavailability study under fed conditions or a food effect study, citing the fact that Alesse does not have food effect information in the label. FDA clarified that a study is needed to label your product. The sponsor confirmed that food intake affected the bioavailability (45% lower Cmax) of a prior formulation of an EV402 (b) (4) tablet in Study EHE-P4-469. If the sponsor decides to not conduct the recommended study, the label would state the product should be taken on an empty stomach. The sponsor acknowledged our guidance and will plan accordingly.***

- You stated that in your Study EHE-P4-469 and Study EXS-P3-821, the upper bound of the 90% confidence interval for ethinyl estradiol Cmax for the EV402 (b) (4) tablet versus the Lutera® oral tablet was above the 80.00% to 125.00% acceptance range. Clarify the Test/Reference Cmax ratio and the upper limit of 90% confidence interval for ethinyl estradiol. You also noted that the difference in Cmax may be due to the different dosing instruction (b) (4)). Provide rationale/data to support that the patient can adhere to the dosing instruction needed to avoid a higher Cmax.

Discussion during the meeting:

- ***The sponsor clarified that the upper limit of the 90% confidence interval of the Test/Reference ratios for ethinyl estradiol were 151 and 129% for the two studies, which is above the acceptance range. The sponsor plans to submit literature on oral contraceptive pills to support that a higher Cmax is not a safety concern. FDA recommended that the sponsor concentrate on more recent published literature with assays that are currently used. FDA expressed concerns with the applicability of such cross-study comparisons.***
- ***The sponsor also asserted that the dosing instructions that instruct patients to chew and swallow immediately with water is typical for many medications and patients should be able to adhere to the instructions.***

Regulatory

Question 1: *Does the Agency agree this 505(b)(2) NDA will contain sufficient information for the Division to make a filing decision?*

FDA Response to Question 1:

It is premature to determine whether the NDA will contain sufficient information to make a filing decision. See GENERAL COMMENTS above. In general, it is acceptable to rely on the FDA's findings of safety and effectiveness for a listed drug, literature, as well as pharmacokinetic studies as described in the GENERAL COMMENTS above.

Question 2: (b) (4)

FDA Response to Question 2:

(b) (4)

Discussion during the meeting:

(b) (4)

Chemistry, Manufacturing, and Controls (CMC)

Question 3: *Does the FDA agree with the content, structure, and eCDT format for presenting Chemistry Manufacturing and Controls information provided for Module 2.3 and Module 3?*

FDA Response to Question 3:

No. Module 3.2.S, Drug Substance, of the NDA should include general information and physico-chemical properties under 3.2.S.1, and all manufacturing, packaging and testing sites should be identified in section 3.2.S.2. Section 3.2.S.4 should include the tests and acceptance criteria used at the drug product manufacturing site for acceptance of the active ingredients from the manufacturers. Include representative Certificates of Analysis for each drug substance.

Note that the adequacy of the Drug Master Files (DMF) is a review issue and any deficiencies will be communicated directly with the DMF holders.

(b) (4)

Please see additional comments about dissolution data presentation.

Discussion during the meeting:

- ***The sponsor confirmed that they will comply with the recommendations.***

Question 4*: Does the Agency agree with this categorical exclusion for environmental assessment for this 505(b)(2) NDA?*

FDA Response to Question 4:
Clarify whether the proposed claim of a categorical exclusion from the preparation of an Environmental Assessment is based on "no increased use" (p. 10) or is based on an Estimated Introduction Concentration ($EIC_{aquatic}$) below 1 part per billion although there is increased use (p. 24).

Discussion during the meeting:

- ***The sponsor explained that they intended to claim a categorical exemption as outlined on page 24 of the meeting package, and asked if this was acceptable. FDA stated that a claim based on "no increased use" appeared appropriate, but would follow-up in a post-meeting comment after discussion with the environmental assessment review team.***

POST MEETING COMMENT:
It is unclear how approval of the application would increase the use of the active moieties. Unless the (b) (4) levonorgestrel and ethinyl estradiol tablet is expected to increase use, such as by being preferable to (and taking market share away from) contraceptive products with higher doses or different active ingredients, a categorical exclusion based on 21 CFR 25.31(a) would be appropriate.

Nonclinical

Question 5: *Module 4 will not contain any original nonclinical studies since the Sponsor did not perform any non-clinical studies. The non-clinical safety will be based on the referenced listed drug (Alesse®) and also summarized in Modules 2.4 and 2.6. The Sponsor will rely upon the Agency's prior findings of safety from the reference listed product. Appropriate literature references will be provided in Module 4, if any. Is this acceptable?*

FDA Response to Question 5:
Your approach is generally acceptable provided that there is adequate clinical data to bridge your product to the listed drug (Alesse®) and that the impurity profile of EV402 is adequately assessed. Submit all referenced literature at the time of NDA submission.

In addition, we remind you that your application must conform to the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR), see PRESCRIBING INFORMATION section below.

Clinical

Question 6: *The NDA will not include an ISE and ISS due to the limited data from the Phase 1 clinical trials. The safety and efficacy of EV402 will be summarized in Module*

2.7.4 and 2.7.3, respectively. Efficacy and safety will be mainly provided from the referenced listed drug (Alesse®). The Sponsor will rely upon the Agency's prior findings of safety and efficacy from the reference listed product. Is this NDA acceptable for filing without an ISE and ISS?

FDA Response to Question 6:
Yes, we agree that your NDA does not need an ISS or an ISE for filing. Provide references to inform the label on clinical use (Sections 6, 8, and 14).

Provide a comprehensive safety update of LNG 0.1 mg/EE 0.02 mg combined oral contraceptive products (COCs). Your safety update should include current references and global postmarketing data.

ADDITIONAL COMMENTS

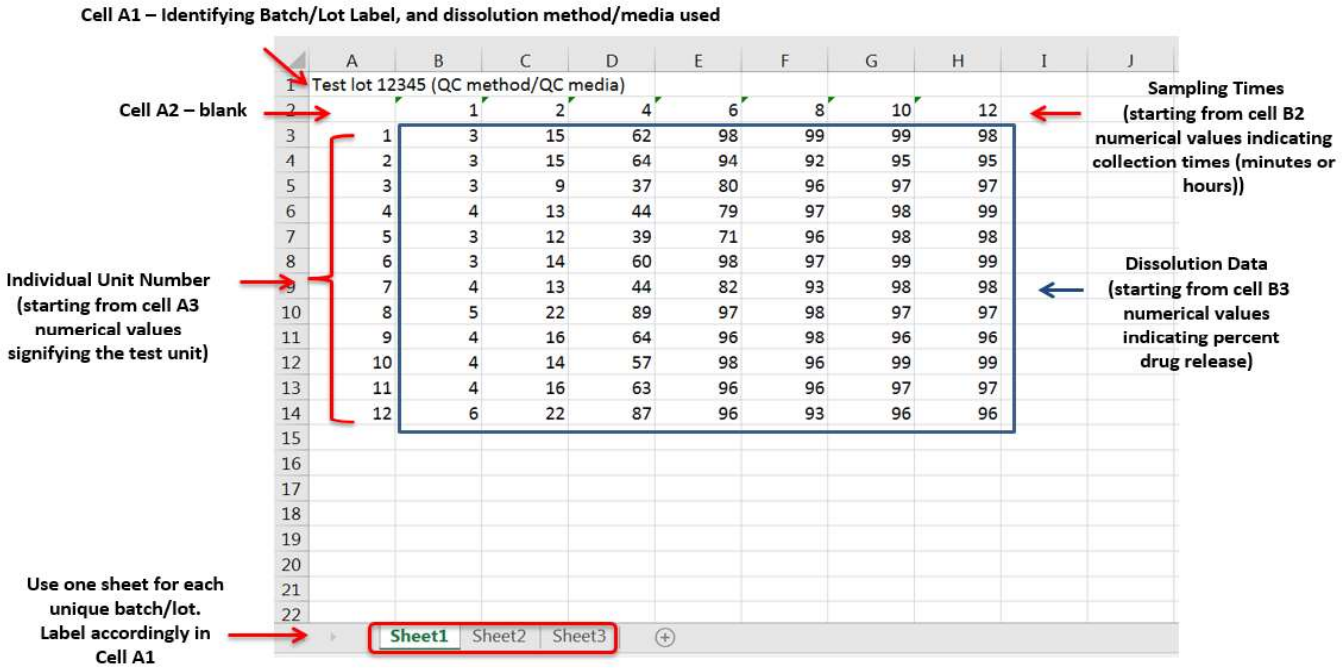
Clinical Pharmacology

- Include in your NDA a summary table of all clinical formulations evaluated. The table should delineate which formulation(s) were used in each of your clinical studies.
- Submit in the NDA pharmacokinetic analysis datasets and pharmacokinetic parameter datasets in SAS Transport (.xpt) format.

Biopharmaceutics

- In the narrative portion of the dissolution report, include individual vessel data as much as possible, particularly regarding investigation of selection of equipment, media, agitation speed, etc.
- In addition to the mean dissolution data presented in graphical and tabular formats, submit in the "Batch Analysis" section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel ".xls or .xlsx" format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.
- Provide in your NDA the dissolution data as described in the example below.

Example - Reporting of individual vessel dissolution data



	A	B	C	D	E	F	G	H
1	Test lot 12345 (QC method/QC media)							
2		1	2	4	6	8	10	12
3	1	3	15	62	98	99	99	98
4	2	3	15	64	94	92	95	95
5	3	3	9	37	80	96	97	97
6	4	4	13	44	79	97	98	99
7	5	3	12	39	71	96	98	98
8	6	3	14	60	98	97	99	99
9	7	4	13	44	82	93	98	98
10	8	5	22	89	97	98	97	97
11	9	4	16	64	96	98	96	96
12	10	4	14	57	98	96	99	99
13	11	4	16	63	96	96	97	97
14	12	6	22	87	96	93	96	96

Follow the instructions provided in "**Specifications for File Format Types Using eCTD Specifications**" – updated March 2, 2017 (link below).
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf

3. PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* 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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4. 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.
- 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).

5. SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA,**

ANDA, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

6. 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.				

7. 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 on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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

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

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

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

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

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
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.

8. 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

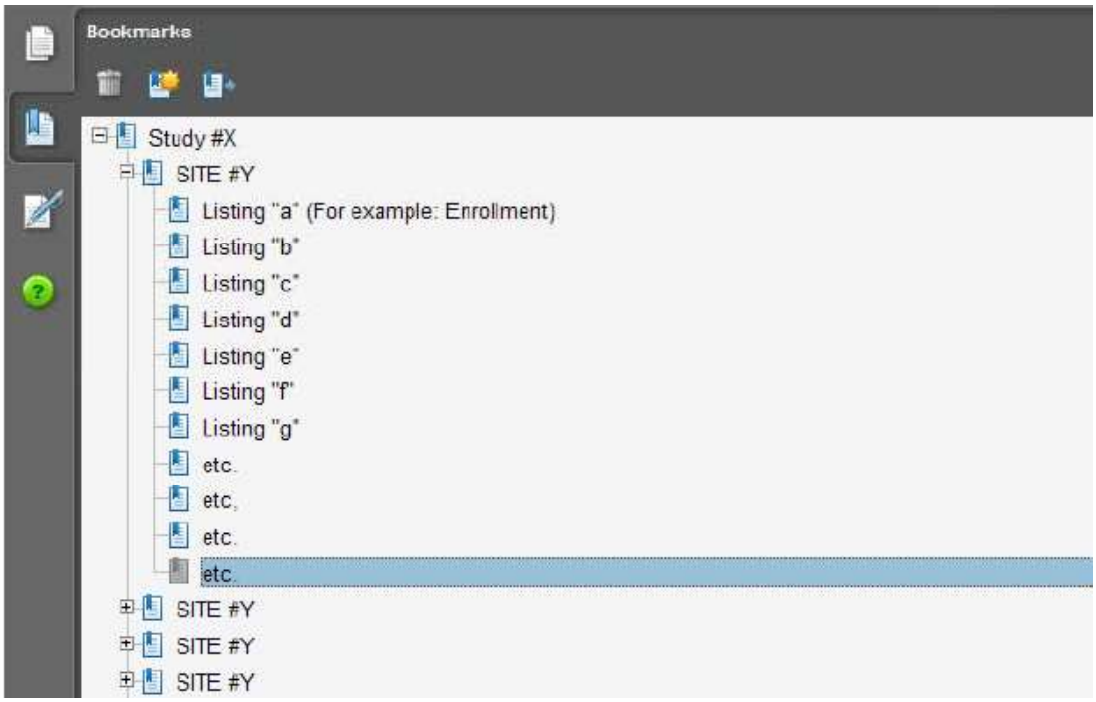
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, 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

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

/s/

CATHERINE A SEWELL
02/20/2018