CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214154Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 110682

MEETING MINUTES

Estetra SPRL
c/o PharmaLex US Corporation
Attention: Lieselotte L. Bloss, DVM
Sr. Consultant, Regulatory Affairs
302 Lee Hwy #700
Fairfax, VA 22031

Dear Ms. Bloss:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for estetrol (E4)/drospirenone (DRSP).

We also refer to the meeting between representatives of your firm and the FDA on November 6, 2019. The purpose of the meeting was to discuss your upcoming New Drug Application submission.

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

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

Sincerely,

{See appended electronic signature page}

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

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

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 6, 2019, 1:00 – 2:00 PM
Meeting Location: White Oak, Bldg 22, Rm. 1315

Application Number: 110682
Product Name: estetrol (E4)/ drospirenone (DRSP)
Indication: Prevention of Pregnancy
Sponsor Name: Estetra SPRL

Meeting Chair: Gerald Willett, M.D.
Meeting Recorder: Jennifer Dao

FDA ATTENDEES

Division of Bone, Reproductive and Urologic Products
Audrey Gassman, M.D. – Deputy Director, Division of Bone, Reproductive and Urologic Products (DBRUP)
Gerald Willett, M.D. – Medical Team Leader, DBRUP
Anandi D. Kotak, M.D., M.P.H. – Medical Officer, DBRUP
Mukesh Summan, Ph.D., DABT – Pharmacology/Toxicology Supervisor, DBRUP
Kimberly Hatfield, Ph.D. - Pharmacology/Toxicology Team Leader, DBRUP
Jennifer Mercier – Chief, Project Management Staff, DBRUP
Jennifer Dao – Regulatory Health Project Manager, DBRUP

Office of New Drugs Policy; Division of Regulatory Policy
Julieann DuBeau, MSN, RN –Regulatory Policy Advisor

Office of Clinical Pharmacology; Division of Clinical Pharmacology 3
Yanhui Lu, Ph.D. – Team Leader, Division of Clinical Pharmacology III (DCPIII), Office of Clinical Pharmacology (OCP)
Li Li, Ph.D. – Clinical Pharmacology Reviewer, DCPIII, OCP

Office of Pharmaceutical Quality
Mark Seggel, Ph.D. – CMC Lead, New Drug Products Branch V, Division of New Drug Products II (DNDPII), Office of New Drug Products (ONDP)
Yubing Tang, Ph.D- Branch Chief, Office of Process and Facilities (OPF)

Office of Biostatistics
Mahboob Sobhan, Ph.D. – Associate Director, Division of Biometrics III (DBIII)

Weiya Zhang, Ph.D. – Statistician, (DBIII)

SPONSOR ATTENDEES

Maud Jost, E4 Program Director (Estetra SPRL)
Marie Mawet, Medical Director (Estetra SPRL)
Guillaume Chatel, Project Leader (Estetra SPRL)
François Lombart, CMC Project Leader (Estetra SPRL)
Frederic Vanzembergh, Regulatory Affairs Leader (Estetra SPRL)
Terri Nataline, VP Regulatory (Mayne Pharma)
Professor Mitchell Creinin, Senior Medical Advisor
Lieselotte L. Bloss, D.V.M Sr. Consultant, Regulatory Affairs (Pharmalex US Corporation) (US agent)
(b) (4) Principal Consultant Regulatory Strategy & Development
(b) (4) Manager (b) (4)
(b) (4)

BACKGROUND

E4/DRSP is a combined oral contraceptive (COC) containing the steroid hormones estetrol, as a monohydrate (E4) and drospirenone (DRSP) as the active ingredients for the prevention of pregnancy. This COC is provided in a 28 -day cycle with 24 days of combined steroid hormones and 4 days of placebo. The proposed regulatory pathway is a 505(b)(2) regulatory pathway.

FDA sent Preliminary Comments to Estetra SPRL on November 1, 2019.

DISCUSSION

General Comments:

We note in Table 5 of your meeting background package that you intend to use published literature to support the nonclinical safety of the drospirenone component of your product, including information that will be included in product labeling (e.g. carcinogenicity, reproductive toxicity). This published literature comprises, (b) (4) In order to utilize this information to support sections of product labeling and the nonclinical safety of drospirenone, you will need to establish a scientific "bridge" (e.g. via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely (e.g. (b) (4), Yaz). See also the response to Question 13 for additional details.

We also note that if you intend to rely on the FDA's finding of safety and/or effectiveness for a listed drug, the drug must be listed in FDA's "Approved Drug

Products with Therapeutic Equivalence Evaluations" (the Orange Book) (i.e., must be U.S. approved).

Chemistry, Manufacturing and Controls

Question 1: *The proposed Executed Batch Records will be included in Module 3.2.R of the NDA for one representative batch from each manufacturing site. Does the Agency concur with this approach?*

FDA Response to Question 1:
We concur with this approach at this time. However, during the NDA review and to aid our assessment, we may request additional executed batch records or relevant information for other batches.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Question 2: *Can the Agency confirm that the cGMP inspection of the drug substance and drug product manufacturers conducted by European Competent Authorities will be acceptable to the FDA based on the Mutual Recognition Agreement?*

FDA Response to Question 2:
There is no Mutual Recognition Agreement for pre-approval inspections (PAIs). The Agency will use all of the information at its disposal to make decisions about whether PAIs are needed when the NDA is submitted.

Please be advised that if the Agency determines that the facility manufacturing the pivotal and registration batches is not in compliance with CGMPs, you will need to provide justification for the bridge to the commercial manufacturing facility.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Nonclinical Questions

Question 3: *Does the agency agree that, based on the available nonclinical and clinical data set, a dedicated photosafety study is not needed (consistent with ICH S10)?*

FDA Response to Question 3:
Yes.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Question 4: *All nonclinical studies, except a few pharmacokinetic studies, that will be part of the planned NDA for E4/DRSP 15/3 mg have been conducted prior to the deadline, December 17, 2016, for implementation of the Standard for Exchange of Nonclinical Data (SEND) format. Therefore, as per the final FDA Guidance on Standardized Study Data published December 17, 2014, the Sponsor does not intend to include the nonclinical data in the SEND format in the NDA. Does the Agency agree?*

FDA Response to Question 4:
Yes.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Clinical

Question 5: *We believe the Clinical Pharmacology studies performed with E4/DRSP, as well as the review and reference of relevant literature and the proposed labeling to address DDI and special population (hepatic and renal impairment) are adequate for filing and review of the NDA. Does the Agency agree?*

FDA Response to Question 5:
The completed clinical pharmacology studies appear sufficient to support NDA submission, but fileability will be determined after receipt of the complete application. In addition, we suggest that you conduct a clinical drug-drug interaction study to determine the effect of weak CYP3A inducers on the pharmacokinetic (PK) of E4 and DRSP.

Discussion:

- The sponsor believes that a study with a weak CYP3A inducer is not necessary and proposed to label E4/DRSP with a similar statement to other COCs, i.e., indicating that a CYP3A inducer can reduce contraceptive efficacy such that alternative or backup contraceptive methods should be used.

- The FDA stated that lack of a DDI study with a weak CYP3A inducer is not a filing issue. However, knowledge in contraceptives drug-drug interactions (DDIs) has evolved. Based on currently available information, moderate and strong CYP3A inducers are expected to decrease DRSP exposure to a clinically significant degree. Therefore, a specific DDI

management strategy can be provided in the label, even studies of E4/DRSP with moderate and strong CYP3A inducers are not conducted. However, for weak CYP3A inducers, it is not clear whether a significant drug interaction would occur with E4/DRSP. Therefore, it is beneficial to conduct a dedicated DDI study to allow for a specific labeling recommendation.

Question 6: *In the NDA submission, the Sponsor plans to request categorical exclusions from environmental assessment (EAs) as per 21 CFR 25.31(b). This request will be supported by:*

1. *Available information for determining a more realistic expected environmental concentration (EEC) and determining a margin of exposure (MOE);*
2. *Available information for assessing environmental effects for these or similar substances; and*
3. *Other available information relevant to assessing the environmental impact.*

FDA Response to Question 6:

FDA agrees with this approach.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 7: *The Sponsor plans to organize the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) as described in the Company Position below. Does the Agency agree that the Summary of Clinical Efficacy (2.7.3) and the Summary of Clinical Safety (2.7.4) are of sufficient detail to serve as the narrative portions of the ISE and ISS, respectively, and that the ISE and ISS tables, figures, and datasets can be placed in module 5 (5.3.5.3)?*

FDA Response to Question 7:

No.

1. The Summary of Clinical Efficacy is acceptable for the efficacy portion of the application.
2. Safety findings should be reported in an Integrated Summary of Safety. The ISS is expected to provide a self-contained and detailed analysis of the findings to support safety. [2] Per FDA guidance, an application to support a new molecular entity could be considered incomplete in the absence of a comprehensive ISS (and/or ISE where applicable).[3]
3. Safety findings within the ISS should be stratified by region, e.g. US/CA vs. EU/RUS.

[2] Integrated Summary of Effectiveness Guidance for Industry. https://www.fda.gov/media/72335/download.

[3] Guidance for Industry. Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. https://www.fda.gov/media/75783/download.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Question 8: *Does the Agency agree with the proposed plan of providing case report forms and subject narratives in the NDA?*

FDA Response to Question 8:
No. In addition to deaths, case report forms and narratives should also be submitted for the following:
1. all serious adverse events
2. all pregnancies (including pre-, on- and post-treatment)
3. all discontinuations due to adverse events.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Question 9: The Sponsor will include the clinical packages listed in the Study Data Standardization Plan (SDSP) in the NDA. Does the Agency agree with the SDSP as proposed?

FDA Response to Question 9:
Your proposed exchange standards for studies that started after December 17, 2016 are acceptable. We acknowledge that exchange standards are not applicable for studies PR3050, PR3054, PR3077, and PR2081. Specify the planned format for the submitted datasets and the terminology standards (e.g., MedDRA version) that were used for adverse events, medical history, and concomitant medications in these four studies.

Discussion:
- The FDA agreed with the sponsor's proposed data and terminology standards for studies PR3050, PR3054, PR3077, and PR2081.
- The FDA asked the sponsor to submit all terminology and keep all terms the same throughout the submission.

Question 10: *Does the Agency agree with the clinical literature cut-off date of July 2019 for E4/DRSP safety information for an NDA submission by December 2019?*

FDA Response to Question 10:
No. Any available clinical literature that would provide safety information on the study drug should be included at the time of the NDA submission. Should additional safety information become available, the associated literature can also be submitted at the time of the 120-day safety update.

Discussion:
The sponsor proposed a shorter cut-off period relating to clinical literature prior to NDA submission and the 120-day safety update (3 months & 2 months respectively). The sponsor assured the Division that any important clinical information would be provided to the Division in a timely manner. The Division agreed with the sponsor's proposals for NDA submission and 120-day safety update.

Question 11: *Does the Agency agree with the proposal for the 120-day safety update?*

FDA Response to Question 11:
Yes.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Question 12: *Does the Agency agree with the list of proposed studies to be included in the NDA to support the requirements in 21 CFR 54 (financial certification and disclosure requirements)?*

FDA Response to Question 12:
Yes.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Question 13: *The Sponsor plans to submit the NDA as a 505(b)(2) application. Does the Agency agree with this approach?*

FDA Response to Question 13:
If you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you or for which you have not obtained a right of reference (e.g., reliance on the FDA's finding of safety and/or effectiveness for a listed drug or published literature), then your marketing application will be a 505(b)(2) application.

Based on your meeting background package it appears that you are relying on the FDA's finding of safety and/or effectiveness for the listed drugs (b) (4) Yaz Tablets (NDA 021676). 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)).

(b) (6)

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.

Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

Discussion:

- The FDA stated that bridging for DRSP systemic exposure via cross-study comparisons would not be acceptable due to potential large PK variabilities introduced from different bioanalytical assays and study populations. The FDA recommended that the sponsor conduct a relative bioavailability (BA) study to allow for a direct comparison between E4/DRSP and the listed drug(s) (U.S. Yaz® (b) (4)

ADDITIONAL COMMENTS:

1. To support the proposed change in product manufacturing (b) (6), at least three months accelerated data on at least three batches manufactured at the commercial site

should be provided in the NDA. Include a side-by-side comparison of (b) (6) processes that specifies the equipment, scale, critical process parameter ranges, results of critical in-process tests (specifying the test procedure and acceptance criteria), yield, and reconciliation data. See comments below on dissolution test data needed to bridge the pivotal clinical batches and registration stability batches to the commercial product.

Discussion: The sponsor had considered not proceeding (b) (6)

2. Provide a summary table of all drug product batches manufactured in support of the proposed NDA. The information should include the following: formulation, site of manufacture, date of manufacture, batch size, disposition including the associated clinical protocol numbers and the study purposes, and batch numbers of the drug substances. Any differences in manufacturing process should be noted.

3. Please note that product strength should be expressed on the basis of anhydrous estetrol.

   Discussion: The sponsor proposed adding the anhydrous estetrol strength (14.16 mg) in the relevant CMC section of Module 2 (see sponsor's slide #11). The FDA stated that the estetrol strength will need to be updated throughout Module 3, as appropriate. For example, Section 3.2.P.1, Description and Composition of the Drug Product, 3.2.P.5 Specification(s), and 3.2.P.3.2, Batch Formula, will need to be revised. The FDA also noted that the revised strength of estetrol (anhdyrous basis) will need used in product labeling. The sponsor indicated that labeling for European markets would reflect the strength of estetrol as the monohydrate (i.e., 15 mg).

4. Provide the quantitative composition of the film-coating and the quality standards for each of the components. This may be provided directly in the NDA or by cross-reference to a Drug Master File with a Letter of Authorization.

5. Submit any finalized nonclinical study reports to the IND that have not already been submitted in order to ease and facilitate review of your application.

   Discussion: Final carcinogenicity study reports can be submitted to the IND prior to NDA submission. Tumor.xpt files should also be submitted in conjunction with these study reports.

6. FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VI. Please note that this is a preliminary determination,

based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. (see DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION section below)

Biopharmaceutics

1. You may submit comparative multipoint in vitro dissolution data for the pre-change and post-change products to bridge the original manufacturing site (b) (4) in your NDA submission provided there are no other major changes. Submit similarity testing results obtained with appropriate statistical test (e.g., similarity factor (f2)) comparing the pre-change and post-change product whenever feasible. Provide complete dissolution data (individual, mean +/- SD, mean profile, n=12/batch) and complete batch information (batch No. and batch manufacturing date, testing site(s), batch size, and the dates of dissolution testing).

2. You have mentioned that PSD has no significant effect on the dissolution of the drug product. However, there are no data to support the statement. Also provide PSD for both components (E4 and DRSP) for Pivotal clinical batches and registration batches. We recommend that you submit data showing that the proposed dissolution method can discriminate for meaningful changes in particle size distribution. Please see additional comments below.

3. You have stated that (b) (6) Submit data to support this statement.

4. We have the following recommendations regarding the dissolution information (method and acceptance criterion/criteria) that should be provided in the NDA submission.

Dissolution Method: Provide in your submission the dissolution method development report supporting the selection of the proposed dissolution test evaluating the proposed drug product. Include the following information in the dissolution method development report:

a. Solubility data of the drug substance over the physiologic pH range.

b. Detailed description of the dissolution method being proposed for the evaluation of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the

equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc.). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions associated with each method development study should be clearly specified. The dissolution profile should be complete or whenever a plateau is reached (i.e., no increase over 3 consecutive time-points). It is recommended the use of at least twelve dosage units per testing variable and sampling time points (e.g., 10, 15, 20, 30, 45 60, etc. min).

c. Data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., ± 10-20% change to the specified values or ranges for these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., *f2* values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.

d. A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.

e. Supportive validation data for the dissolution methodology (bench testing) and analytical method used for assaying the dissolution samples (specificity, precision, accuracy, linearity/range, stability, robustness, etc. For general recommendations on method validation, refer to the USP Chapters "The Dissolution Procedure: Development and Validation" <1092> and "Validation of Compendial Methods" USP Chapter <1225>.

f. Complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, % CV at each time point and mean profiles). The dissolution data should be reported as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim). For the submission of the dissolution data, refer to data presentation below.

Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion of the proposed drug product, consider the following:

g. The multi-point dissolution data (n=12) from the pivotal clinical/PK drug product-batches should be used for the setting of the dissolution acceptance criterion of the proposed drug product (i.e., sampling time points and limits).

h. The in vitro dissolution profile should be complete or if incomplete dissolution occurs, where the plateau of drug dissolved is reached (i.e., no increase over 3 consecutive time-points).

i. The dissolution acceptance criterion should be based on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12).

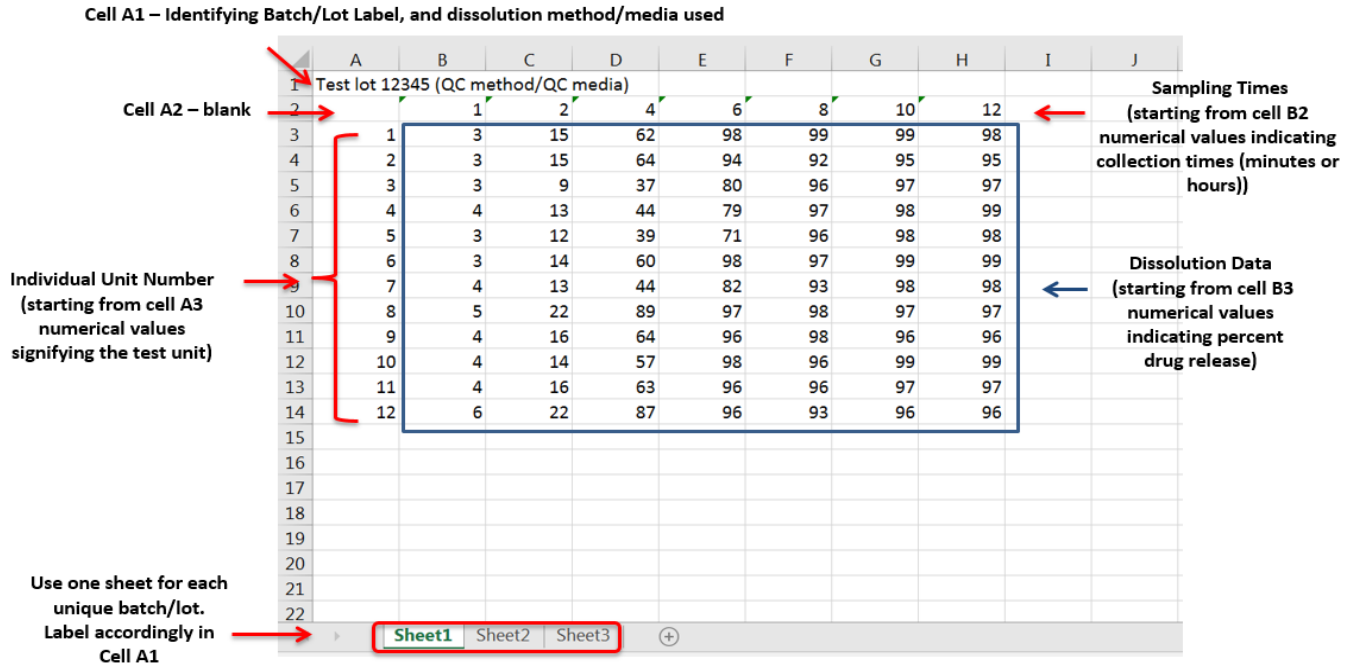
j. The selection of the sampling time point should be where Q = (b) (6) % dissolution occurs.

k. Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the eCTD.

Dissolution Data Presentation: In the dissolution method development report and/or batch analysis section of the future NDA, present detailed experimental dissolution data as follows:

- 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 IND/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	I	J
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		
15										
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21										
22										

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 22, 2019 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the

time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[4]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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

[4] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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*.[5] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[6]

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[7] and Pregnancy and Lactation Labeling Final Rule[8] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[6] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[7] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[8] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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).[9] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[10]

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

[9] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[10] http://www.regulations.gov

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

ATTACHMENTS AND HANDOUTS

The sponsor provided PowerPoint slides for the meeting to facilitate the discussion. The slides were focused on the questions discussed. The slides are attached to the meeting minutes.

[11] https://www.fda.gov/media/85061/download

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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/

GERALD D WILLETT
11/22/2019 01:46:35 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 110682

MEETING MINUTES

Estetra S.A
c/o AptivSolutions
Attention: Jenny Vestal
Global Director, Regulatory Strategy
2803 Slater Road, Suite #125
Morrisville, NC 27560

Dear Ms. Vestal:

Please refer to your Pre-Investigational New Drug Application (PIND) file for estetrol/drospirenone tablets.

We also refer to the meeting between representatives of your firm and the FDA on October 25, 2012. The purpose of the meeting was to discuss your End-of-Phase 2 results and drug development program.

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 Mercier, Chief, Project Management Staff at (301) 796-0957.

Sincerely,

{See appended electronic signature page}

Lisa Soule, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Slide Presentation

MEMORANDUM OF MEETING MINUTES

Meeting Type: **B**
Meeting Category: **End-of-Phase 2**

Meeting Date and Time: **October 25, 2012, 12:00 PM, EST**
Meeting Location: **WO, Building 22, Conference Room 1311**

Application Number: **PIND 110682**
Product Name: **Estetrol/drospirenone tablets**
Indication: **Prevention of Pregnancy**
Sponsor: **Estetra S.A.**

Meeting Chair: **Lisa Soule, M.D.**
Meeting Recorder: **Jennifer Mercier**

FDA ATTENDEES

Hylton V. Joffe, M.D., M.M.Sc. - Director, Division of Reproductive and Urologic Products (DRUP)
Lisa Soule, M.D. – Clinical Team Leader, DRUP
Ronald Orleans, M.D. – Medical Officer, DRUP
Kimberly Hatfield, Ph.D. – Pharmacologist/Toxicologist, DRUP
Myong-Jin Kim, Pharm.D. – Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCPIII) Office of Clinical Pharmacology (OCP)
Li Li, Ph.D. – Clinical Pharmacology Reviewer, DCPIII, OCP
Donna Christner, Ph.D. – CMC Lead, Branch IV, Division of New Drug Quality Assessment II, Office of New Drug Quality Assessment
Mahboob Sobhan, Ph.D. – Statistical Team Leader, Division of Biometrics III (DBIII)
Xin Fang, Ph.D. – Statistical Reviewer, DBIII
Roy Blay, Ph.D., Reviewer, Office of Scientific Investigations (OSI)
Kalesha Grayson – Project Specialist, DRUP
Jennifer Mercier – Chief, Project Management Staff, DRUP

ESTETRA S.A. ATTENDEES

Prof Jean-Michel Foidard, CSO
Ludivine Petit, Project Leader
Maurizio Passanisi, Clinical Project Leader
Linda Lebon, Regulatory Affairs & Drug Development Expert
Ria Vos, Nonclinical Expert
Jenny Vestal, Consultant to Estetra, Aptiv Solutions (authorized US representative)

BACKGROUND

Estetra has completed their phase 2 development for the prevention of pregnancy indication and is moving into phase 3 development of their drug product. The Sponsor seeks guidance from the Division on the acceptability of the phase 3 program and of the comparability protocol based on

[redacted] (b) (6)

DISCUSSION

1. *Estetra believes that the completed studies (Phases 1 and 2) have provided exploratory safety and efficacy data, including information on cycle regulation and contraceptive efficacy. Does the Agency agree that the clinical results collected so far would support initiation of the Phase 3 program, including the selection of the COC, the proposed dose range and the dosing regimen, to support the NDA?*

   DIVISION RESPONSE:
   Yes.

   Additional Discussion at the Meeting:
   Estetra has selected drospirenone (DRSP) as the progestin for its COC (see slides 3 and 4), but was concerned that recent epidemiologic studies of DRSP-containing COCs might lead the Division to discourage use of DRSP in future products. The Division clarified that it is the Sponsor's decision as to which specific progestin to utilize. With respect to DRSP specifically, a joint Advisory Committee meeting was recently convened to discuss DRSP-containing COCs and the Committee voted that the benefits generally outweighed the potential risks of these products. The Division concurs and has not restricted marketing of these products. Based on currently available information, DRSP remains an acceptable progestin for inclusion in a COC. The Sponsor stated that it had received [redacted] (b) (6)

2. *Are the PK studies (completed or planned) sufficient to support the evaluation of the drug pharmacokinetics for the NDA?*

   DIVISION RESPONSE:
   The Division recommends that the Sponsor conduct a food effect study prior to the phase 3 study. Understanding the effect of food on drug exposure could impact the phase 3 study design.

   Please keep in mind that the Clinical Pharmacology section of the NDA should include (but not be limited to) the following information for the investigational drug and its major metabolite(s) (if applicable):

   - Absorption, distribution, metabolism (including metabolic pathway, inhibition and induction potential of CYP enzymes), and excretion (ADME)
   - Single and multiple dose pharmacokinetics (PK), including information on dose proportionality and accumulation potential.
   - Exposure/Dose-Response analysis
   - Effect of renal impairment on the PK of the drug
   - Effect of hepatic impairment on the PK of the drug
   - Effect of race and other covariates (e.g., body mass index [BMI]) on the PK of the drug

- Potential for QT prolongation
- Drug-drug interactions
- If the formulation used in the clinical studies differs from the to-be-marketed formulation, a bridging study may be required

In addition, the Division recommends that the Sponsor consider increasing the sample size for the mass balance study. If E4 has high variability, a meaningful result may not be obtained with a limited sample size.

Additional Discussion at the Meeting:
The Sponsor agreed to conduct a food effect study prior to the phase 3 study.

An ADME program including an *in vitro* drug-drug interaction (DDI) study is planned for the NDA, as well as a mass balance study (see slide 6). Inclusion of six postmenopausal women in the mass balance study appears adequate. The Division confirmed that the Sponsor plans to measure concentrations in the plasma, urine and feces.

The Sponsor confirmed that a PK program including single dose and multiple dose PK studies is planned for the NDA. The Division confirmed that what the Sponsor has proposed for the evaluation of dose proportionality and accumulation potential (see slides 7 and 8) is adequate. It would be acceptable to hold the DRSP dose fixed; however, the Sponsor plans to vary the doses of each component proportionally to evaluate potential interaction between E4 and DRSP.

For the single dose and multiple dose PK studies, the investigational drug will be taken under a fasting condition and trough plasma concentrations will be measured on a daily basis to confirm the attainment of steady-state.

3. *Estetra believes that the proposed Phase 3 clinical trials design will fulfill the regulatory requirements and the objective to comprehensively assess the safety and efficacy of the COC in terms of sample size, length of exposure and selected primary endpoint as well as secondary parameters. Does the Agency concur?*

DIVISION RESPONSE:
In general, the Division concurs; however, the Sponsor is strongly encouraged to submit the revised phase 3 protocol for review and comment prior to initiating the study.

The Division has the following preliminary comments on the draft protocol:

- From the description provided in the protocol, it appears that 75% of subjects will be randomized to study drug. This is anticipated to provide over 12,000 28-day cycles and 300 women completing 13 cycles of study drug exposure per study. If these goals are met, the total exposure requested over the phase 3 program (20,000 28-day cycles, including 400 women who complete thirteen 28-day cycles of study drug exposure), is likely to be adequate to assess the safety and efficacy of the product.
- Women older than 35 years of age may be included in the 20,000 28-day cycles requested for safety and efficacy. Overall, the Sponsor is encouraged to enroll 200-300 women older than 35 years of age per study (or about 10% of the study drug sample).

- Although (b) (6) .

Additional Discussion at the Meeting:
The Sponsor may consider submitting the phase 3 protocol under a Special Protocol Assessment (SPA).

General Considerations: Primary Efficacy Analysis

- The Division defines the principal analysis cohort for pregnancy evaluation as all women who were 18 to 35 years of age at the time of study enrollment and who were evaluated for pregnancy. Subjects in this group should not be censored on their 36th birthday in the pregnancy assessment.
- Efficacy should also be evaluated for all women who are ≤ 35 years of age.
- The Pearl Index (PI) should be calculated based on 28-day cycles of exposure, (b) (6) .
- The Division defines "on-drug" pregnancies as all conceptions that occur from Day 1 (the initiation of taking study drug) to seven days after the final tablet is taken (whether active or inactive and regardless of whether the final tablet is taken at the end of the pill pack or prior to completing the pill pack).
- Cycles in which subjects used a condom or alternative method of birth control for any reason should not be counted in the calculation of the PI unless a conception is documented during that cycle. The subject diary should record all use of any back-up contraception (not just condoms) or emergency contraception use.

General Considerations: Cycle Control

- The bleeding data should be analyzed in the manner recommended by Mishell et al. Contraception 2007, 75: 11-15 using the 28-day cycle equivalents.
- The definition of evaluable cycles for assessment of bleeding data appears unduly restrictive; the Division recommends imputing missing bleeding data rather than (b) (6)

General Considerations: Inclusion Criteria

- The Division discourages the use of a BMI restriction as an inclusion criterion. If there is a restriction on the basis of BMI in the phase 3 trials, it is likely to be described in labeling.
- Inclusion criteria should state that subjects who enter the study must have a negative serum pregnancy test.

General Considerations: Exclusion Criteria

- The restriction on women (b) (6) should be removed.
- The Division recommends that the hypertension exclusion criterion reflect current combined oral contraceptive (COC) labeling (uncontrolled hypertension).
- The Division recommends that the diabetes exclusion criterion reflect current COC labeling (diabetes mellitus with vascular disease).

General Considerations: Safety

- Endometrial biopsies should be conducted in a subset of participants at study entry and at the end of the study (after at least 9 months on treatment). A total of 100-200 women should be included in this subset.

Additional Discussion at the Meeting:
The Sponsor plans to enroll 100 subjects for endometrial biopsies at baseline and cycle 10 (see slide 12). The Division stated that subjects should have their final biopsy at Cycle 13 or last visit. The sample size is expected to be adequate as long as the Sponsor accounts for study dropouts and is able to obtain at least 100 paired biopsies on women treated for at least nine months.

General Considerations: Clinical Pharmacology

- Clarify the purpose of the PK measurement and analytes of interest in the phase 3 studies.
- Consider using population PK sparse sampling in the phase 3 studies to explore the effect of body weight on drug exposure as well as the exposure-response (contraceptive efficacy and safety) relationship.

Additional Discussion at the Meeting:
The Sponsor intends to obtain population PK data (Cmin) for the active moieties in a subset of 100 subjects participating in the phase 3 program. These data will be used to explore the effects of various factors (e.g., race, BMI, smoking) on the PK parameters (see slide 12). This will be correlated with exposure-response. The Division concurs with this plan.

General Considerations: Statistics

- The contraceptive failure rate and the associated 95% confidence interval should also be calculated by the life table method.
- The planned sample size may not be adequate to obtain a difference of ≤1 between a point estimate of the PI and the associated 95% upper limit at the end of the first 13 cycles if the true PI is close to 2.0; in such a case, at least 1,283 women-years would be needed to provide power of 0.8, or at least 1,351 women-years to provide power of 0.9.
- Provide an estimate of the PI based on the phase 2 study if possible.

Additional Discussion at the Meeting:
The Sponsor stated that there were no pregnancies during or up to 14 days after stopping active treatment during phase 2 studies. Estetra is targeting a PI ≤ 1.

4. *Estetra plans to evaluate the effects of Estelle on coagulation, lipids, carbohydrate metabolism and endocrine functions in addition to pivotal Phase 3 and PK studies. The program will also include a study to assess contraceptive effects (ovary and pituitary functions, cervical mucus, endometrial thickness, bleeding patterns, etc.) and the time to return to fertility. Does the Agency agree with this approach and the proposed timing for the different studies?*

DIVISION RESPONSE:
The Division generally agrees with this approach but the timing and the location of these two proposed studies is unclear. Will these studies be conducted concurrently with the US phase 3 study?

Additional Discussion at the Meeting:
The Sponsor plans to conduct these studies in Europe in parallel to the US pivotal phase 3 trial.

5. *Does the Agency agree* [redacted]

DIVISION RESPONSE:
No. [redacted]

Additional Discussion at the Meeting:
[redacted]

6. *Estetra is planning* [redacted]

DIVISION RESPONSE:
[redacted]

7. *Does the Agency agree that the ADME studies (both completed and planned) are adequate to support future a New Drug Application (NDA)?*

DIVISION RESPONSE:
Yes, the completed and planned nonclinical ADME studies appear adequate, pending review of the final study reports.

8. *Does the Agency agree that the package of nonclinical repeat-dose toxicity studies performed (ongoing and planned) is adequate to support the start of the planned Phase 3 trials as well as the NDA of the new COC?*

DIVISION RESPONSE:
Yes, the package of nonclinical repeat-dose toxicity studies is appropriate to begin phase 3 clinical trials. They also appear adequate for NDA submission, pending review of the final study reports.

9. *Does the Agency agree that the program of completed and ongoing genotoxicity studies is appropriate to support the initiation of Phase 3 clinical trials as well as the NDA of the new COC?*

DIVISION RESPONSE:
Yes, the completed and ongoing genotoxicity studies are appropriate to begin phase 3 clinical trials. They also appear adequate for NDA submission, pending review of the final study reports.

10. *Does the Agency agree that the overall nonclinical program is adequate to support the NDA of Estelle as a combined oral contraceptive?*

DIVISION RESPONSE:
Yes, the overall nonclinical program appears adequate to support the NDA submission, pending review of the final study reports.

11. *Estetra has planned* (b) (6)

DIVISION RESPONSE:
The proposal appears to be reasonable. (b) (4) The Division has the following comments:

- Complete drug substance information should be provided either in the application or in a Drug Master File (DMF) with the appropriate Letter of Authorization provided. If information is provided in a DMF, the Division requests that the following information be provided in the application for ease of review: General information, physicochemical properties, and Specifications. Please submit a Certificate of Analysis of the drug substance.
- (b) (4)

(b) (4)

In the original NDA submission, at least 12 months of stability data (ICH long term and accelerated storage conditions) should be provided on the primary stability batches of drug product. Other drug product batches can be used as supportive data for expiry determination.

If not already designated, before the NDA is submitted, the Sponsor is encouraged to obtain a United States Adopted Name (USAN) from the USAN Council for the drug substance as per 21 FR 299.4.

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

- Meeting minutes to issue to the Sponsor within 30 days.

ATTACHMENTS AND HANDOUTS

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

/s/

LISA M SOULE
11/21/2012