CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211367Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111347

MEETING MINUTES

Laboratorios Leon Farma S.A.
c/o Exeltis USA, Inc.
Attention: Sandy Suh, Pharm.D.
180 Park Avenue
Florham Park, NJ 07932

Dear Dr. Suh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LF111 (drospirenone) 4 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2017. The purpose of the meeting was to discuss the content and structure of your planned NDA submission.

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 Leader
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: Tuesday, December 19, 2017 2:00 PM – 3:00 PM
Meeting Location: White Oak Building 22, Conference Room 1311

Application Number: 111347
Product Name: LF111 (drospirenone) 4 mg tablets
Indication: Prevention of pregnancy
Sponsor/Applicant Name: Laboratorios Leon Farma S.A.

Meeting Chair: Catherine Sewell, M.D.
Meeting Recorder: Jennifer Dao

FDA ATTENDEES

Division of Bone, Reproductive and Urologic Products (DBRUP)
Audrey Gassman, M.D. – Deputy Director
Catherine Sewell, M.D, M.P.H. – Acting Clinical Team Lead
Caren Kieswetter, M.D., M.P.H. – Medical Officer
Mukesh Summan, Ph.D. – Pharmacology/Toxicology Supervisor
Kimberly Hatfield, Ph.D. –Pharmacology/Toxicology Team Leader
Jennifer Mercier – Chief, Project Management Staff
Jennifer Dao – Regulatory Project Manager

OFFICE OF CLINICAL PHARMACOLOGY; Division of Clinical Pharmacology 3 (DCPIII)
Li Li, Ph.D. – Clinical Pharmacology Reviewer
Doanh Tran, Ph.D. – Clinical Pharmacology Team Leader

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
Moo Jhong Rhee, Ph.D. – Branch Chief
James Laurenson, MS – Toxicologist/Environmental Assessment Reviewer
Division of Biopharmaceutics, Branch II
Tapash Ghosh, Ph.D. – Chief
Vidula Kolhatkar, Ph.D. – Team Leader

Bryan Ericksen, Ph.D. – Biopharmaceutics Reviewer

OFFICE OF BIOSTATISTICS; Division of Biometrics III (DBIII)
Kate Li Dwyer, Ph.D. – Statistical Reviewer
Mahboob Sobhan, Ph.D. – Team Leader

SPONSOR ATTENDEES
Belen Liebana, Pharm.D. – Clinical Operations, Exeltis (Spain)
Marta Gomez Burgaz, Ph.D. – CMC Manager, Exeltis (Spain)
Enrico Colli, M.D. – Chief Scientific Offier, Exeltis (Spain)
Sandy S. Suh, Pharm.D. – Regulatory Affairs (US Agent), Exeltis USA, Inc.

1. BACKGROUND

The purpose of this pre-NDA meeting is to discuss the content and structure of the proposed application to adequately support an NDA filing per section 505(b)(2).

Laboratorios León Farma S.A., a Division of CHEMO S.A. France, (the Sponsor) is developing (b) (4) drospirenone (DRSP) 4 mg (LF111) as a Progestin-Only Pill (POP) to be taken daily for 24 days followed by a placebo tablet taken daily for four days for the indication of prevention of pregnancy. DRSP is a fourth-generation progestin derived from spironolactone, a potassium-sparing diuretic used to treat hypertension. The proposed 24/4 dosage regimen is intended to reduce unscheduled bleeding. In addition, the Sponsor believes that LF111 will be more effective than approved POPs, all containing norethindrone.

DRSP (b) (4) is currently approved in the US for use in combination with ethinyl estradiol in Combined Hormonal Contraception (CHC), or with estradiol in menopause hormone therapy (HT).

FDA sent Preliminary Comments to Exeltis USA on December 14, 2017.

2. DISCUSSION

Question 1: The Sponsor has completed the pivotal, multicenter US trial (Protocol CF1111/303). It includes over 5000 cycles. The study included, as previously agreed, about 30 % of women with a BMI > 30. It also included a POP PK analysis (see Section 10.1).

Does the Division consider that these data, in addition to the results generated in the European development program which includes two pivotal European trials for a total of 14 000 cycles (as supportive safety data), are sufficient for the Division's review of a 505(b)(2) NDA for LF111 for contraception?

FDA Response to Question 1:

Yes, we agree that the data from the pivotal, multicenter US trial including over 5,000 cycles and including a proportion of obese subjects, combined with data from the European development program would be sufficient for review of a 505(b)(2) NDA.

Discussion During the Meeting:
The Division asked the Sponsor to clarify which reference YAZ® product was used in Study CF111/103A. The Sponsor clarified that the US-marketed YAZ® was used for the Phase 1 clinical study CF111/103C, but not for the Phase 1 study CF111/103A. The Sponsor could not verify whether their to-be-marketed formulation was used in Study CF111/103C.

- The Sponsor agreed to submit a White Paper to address bridging their product to the US-marketed product, accordingly. Specifically, the Sponsor will provide all the requisite information, i.e., on exposure and food effect, for the Division to conduct a comparative assessment between the to-be-marketed product and the reference drug. The study report and analyses should be submitted to the IND for review. The Division committed to reviewing it in a timely fashion and to sending a separate advice letter on this issue.

Question 2: A study of bone mineral density (BMD) in women of all ages, including pediatric users, will be conducted post-approval (see Section 10.1).

Does the Agency agree with conduct of a BMD study post-approval?

FDA Response to Question 2:
Per the advice letter dated March 4, 2015, we find that your plan to conduct a postapproval study of BMD in women of all ages, including pediatric users, acceptable at this time. As previously conveyed, your study should provide comparator-controlled data on changes in bone mineral density (BMD) with use of your product. We re-iterate our prior recommendations:

- Analysis of BMD data should be stratified by age to account for the differences in bone metabolism among adolescents. Specifically, adolescent girls should be accruing BMD, so plateauing of BMD in this population may indicate an adverse effect.
- If adverse effects on BMD are demonstrated following one-year of treatment, subjects will need to be followed to determine the time off-treatment required for resolution of this effect. Such finding might also result in a labeled limitation on the duration of use.

Please also see Additional Comments for further recommendations about the BMD study.

Environmental Risk Assessment

Question 3: The environmental risk assessment studies will be listed in Section 10.2 and Appendix B.

Does the Agency agree with the Sponsor's Environmental Risk Assessment studies and respectively report?

FDA Response to Question 3:
Yes, assuming the planned submission of the referenced environmental risk assessment will be to support a claim for a categorical exclusion from an environmental assessment, presumably per 21 CFR 25.31(b), which is for applications that would result in an increased use of the active moiety, but where the expected introduction concentration (EIC) is less than 1 ppb. The required statement of no extraordinary circumstances also must be present. FDA recommends that the applicant review and reference USFDA, 2016, Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity, available at https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf

Chemistry, Manufacturing, and Controls (CMC)

Question 4: A full Module 3 section is planned for inclusion in the NDA (see Section 10.3 and Appendix C).

Does the FDA agree with the content, structure, and electronic Common Technical Document (eCDT) format for presenting Chemistry Manufacturing and Controls (CMC) information provided for Module 2.3 and Module 3?

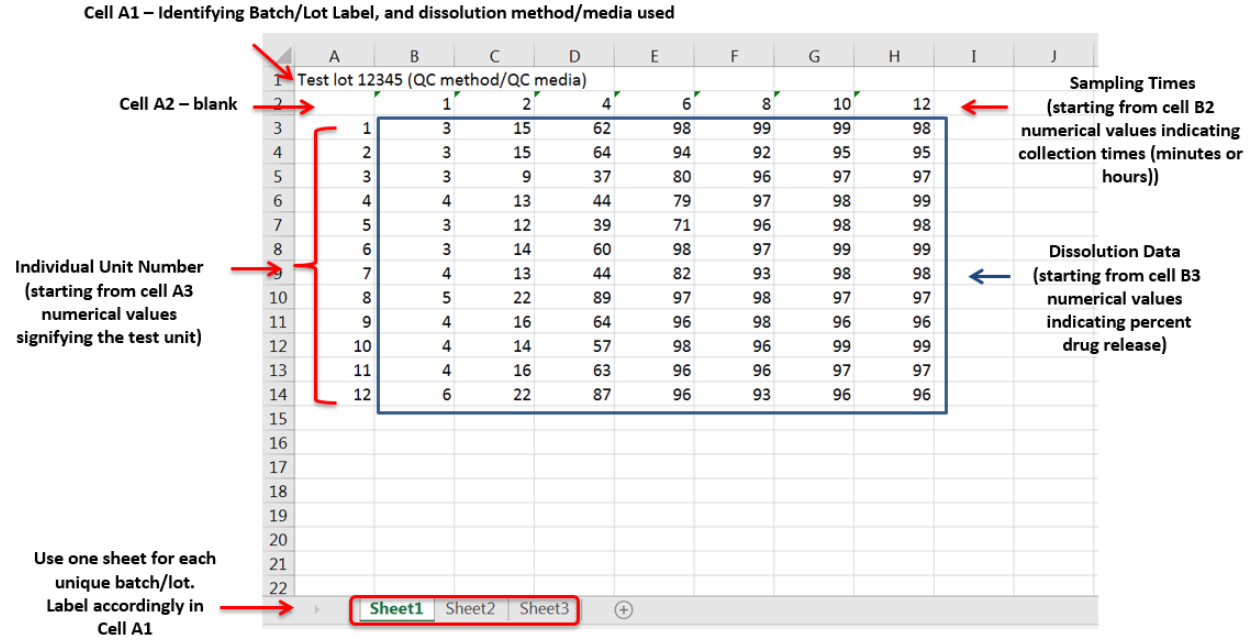
FDA Response to Question 4:
No. While, the drug substance sections of Modules 2.3 and 3.2.S appear reasonable for submission of the NDA, we have the following recommendations regarding the drug product information:

- Include a complete 3.2.P.2 Pharmaceutical Development section covering formulation development and manufacturing process development (P.2.1 – P.2.6; see ICH M4Q: CTD – Quality);
- Provide film-coat information under 3.2.P.4 Control of Excipients rather than under 3.2.A.3 Novel Excipients;
- Include executed packaging records in 3.2.R; and
- Provide the proposed master production record in 3.2.R.

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 submission the dissolution data as described in the example below.
Example - Reporting of individual vessel dissolution data



	1	2	4	6	8	10	12
1	3	15	62	98	99	99	98
2	3	15	64	94	92	95	95
3	3	9	37	80	96	97	97
4	4	13	44	79	97	98	99
5	3	12	39	71	96	98	98
6	3	14	60	98	97	99	99
7	4	13	44	82	93	98	98
8	5	22	89	97	98	97	97
9	4	16	64	96	98	96	96
10	4	14	57	98	96	99	99
11	4	16	63	96	96	97	97
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
Please see additional comments regarding dissolution method and acceptance criteria.

Discussion During the Meeting:
The Sponsor needed clarification on individual data or batch data. FDA clarified that one sheet per batch is acceptable.

Question 5: ICH stability studies are ongoing for the drug product. A description of the stability to be included in the NDA is provided in Section 10.3 and Appendix C.

Does the Agency agree on the adequacy of the available stability data to support the NDA filing?

FDA Response to Question 5:
The proposed stability package appears adequate to support filing of the NDA. We remind you that at the time of submission the NDA should include at least 12-months long-term data and 6-months accelerated data on three primary stability lots. Also, see response to Question 4 and submit all available long-term stability data obtained using both dissolution methods (method during development and the proposed QC method) in the appropriate format.

Discussion During the Meeting:

The Sponsor requested clarification on the stability package, and specifically about the inclusion of 6-months of accelerated stability data for a fourth pilot scale batch manufactured and packaged consistent with the product batches reported in Table 9, page 17 of Appendix C. The FDA asked the Sponsor to identify which batches they considered the primary registration stability batches. The Sponsor indicated that the three batches listed in Table 9 are the primary registration stability batches. The FDA stated that the proposal to submit data from a fourth pilot scale batch was acceptable.

Post-Meeting Comment: FDA agrees with the stability package described in Appendix 3 of the briefing document, including the proposal to provide a minimum of 3-months long term and accelerated data from three commercial scale batches at the time of NDA submission.

Nonclinical

Question 6: Module 4 will not contain any original nonclinical studies since none were performed. Nonclinical safety will be based on the referenced listed drug and also summarized in Modules 2.4 and 2.6. Appropriate literature references will be provided in Module 4 (see Section 10.4).

Does the Agency agree on the adequacy of the safety (reference listed drug and literature) to support the NDA filing?

FDA Response to Question 6:
If an adequate bridge is established to the drospirenone component of one or more US approved listed drug products, then reliance on the Agency's previous findings of safety to support the nonclinical section of your NDA is appropriate. The adequacy of the literature references to support safety will be a review issue.

We also remind you that your final product labeling will need to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Refer to Section 5.0 Prescribing Information below. We ask that you ensure that the nonclinical aspects of Section 8 of labeling are supported with appropriate nonclinical information from listed drug labeling or submitted relevant published literature.

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.

You are proposing to reference information from FDA reviewers' public summaries to support the safety of your 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.

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.

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 Sponsor relies.

Clinical

Question 7: An Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) will be included in the NDA. The ISS will include all clinical studies* conducted using LF111. Phase 1 (and other single dose or short term studies) will be pooled and the Phase 2 / Phase 3 (longer term studies) will be pooled separately. *All clinical studies will be included for safety; some clinical studies included comparators that are not approved in the US (i.e. studies conducted in Europe). However, the MedDRA dictionaries used in the clinical trials vary. The Sponsor proposes to pool the safety for the Phase 1 trials using MedDRA version 15.1 and for Phase 2/3 use MedDRA 17.0. The ISE will include pooled results from the two Phase 3 clinical studies (Protocols CF111/301 and CF111/302) conducted in Europe along with the results of the pivotal Phase 3 trial conducted in US (Protocol CF111/303). The results from the US trial will not be pooled with the European trials. A detailed list of clinical studies is provided in Section 10.5 and Appendix D.

Does the Agency agree on the pooling strategies for the studies in the ISS (including the MedDRA version) and ISE?

FDA Response to Question 7:

For the ISE, it is acceptable to pool data from two of the Phase 3 trials conducted in Europe (Protocols CF111/301 and CF111/302). Data from the Phase 3 trial conducted in the US (Protocol CF111/303) should not be pooled with the European studies; significant differences in study design and results could confound efficacy assessment. As well, data from Protocol CF111/304, conducted on adolescent subjects, should not be pooled for efficacy.

For the ISS, we do not agree with your proposed strategy for pooling data. The differences in study designs (e.g., use of a comparator, doses, duration of dosing, and age range of subjects) and analysis tools (e.g., MedDRA dictionaries) preclude pooling data from all the Phase 1 studies, or pooling all the Phase 2/3 studies.

Discussion During the Meeting:

- ISE: The Division reiterated concurrence with the Sponsor's plan to pool data from European Phase 3 trials as described above. The Sponsor conveyed that three different MedDRA

dictionaries were used for the Phase 3 protocols CF111/301, CF111/302, and CF111/303: MedDRA v15, v16, and v17, respectively. The Sponsor agreed to align all data sets with the MedDRA v17.0 dictionary and provide a reference table for the term conversions used to recode terms in MedDRA v17.0, as requested by the Division. It will be important for the table to convey how broader terms addressing pain are converted.

- ISS: For the ISS, The Sponsor agreed that the studies will not be pooled for the reasons delineated by the Division. However, the Sponsor agreed to similarly align data from safety studies with the MedDRA v17.0 dictionary to allow comparisons if indicated.
- The Division conveyed ongoing concerns regarding increased risks of thromboembolic events associated with use of some progestins. Therefore, the Division requested the Sponsor ensure that safety analyses will be conducted using terms inclusive of the broad spectrum of symptoms potentially associated with thromboembolic events (e.g., shortness of breath and lower extremity pain/swelling) and of diagnoses with potentially similar presentations (e.g., myocardial infarction).

Post meeting Comment: See Additional Comments regarding safety concerns. Apart from bone mineral density and thromboembolic events, the Division does not have other specific safety concerns that should be addressed at this time. If safety concerns arise during the review process of an NDA submission, these will be conveyed to the Sponsor in information requests.

Question 8: ADaM datasets will only be provided for the US pivotal Phase 3 clinical Protocol CF111/303, ISE, and ISS.

Does the Agency agree that no other ADaM datasets will be submitted other than for Protocol CF111/303, ISE, and ISS?

FDA Response to Question 8:

No. All available datasets should be submitted, including the European ADaM datasets. In general, you should submit both raw and analysis datasets in CDISC format along with the SAS program(s) used to duplicate the analysis datasets derivation from these raw datasets. Please refer to the Guidance Providing Regulatory Submissions In Electronic Format — Standardized Study Data at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf

If source datasets are not available, please provide an explanation as to why not. Legacy data may be submitted. Additionally, TS domain is required for submissions after 12/16/2016. For the legacy data, the TS domain can only include 3 variables: study id, TSPARMCD = SSTDTC, and TSVAL = XXXX-XX-XX (year/month/day) so that we can see the study start date.

In addition to the ADaM datasets, please provide the following information:

- Executable SAS program(s) with adequate document(s) to duplicate the analysis datasets derivation from raw datasets.

- SAS programs as well as format library files used to duplicate your primary and secondary efficacy results. If the SAS programs use any SAS macro, please provide all necessary macro programs.

For more technical requirement on the submitted datasets, please refers to FDA Study Data Technical Conformance Guide: https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm384744.pdf

Question 9: In the completed pivotal US trial (Protocol CF1111/303), a high withdrawal rate is noted. The majority of the discontinuations appear to be from "lost to follow-up". We propose to list and describe all of the discontinuations however we will only include CRFs (case report forms) for discontinuation due to death and adverse events (serious or adverse events of interest). All CRFs will be available for submission upon request.

Does the Agency agree with our proposal of presenting and analyzing the reason for subjects withdrawn from the study?

Does the Agency agree that only CRFs for discontinuations from death and serious adverse events or adverse events of interest will be included in the NDA?

FDA Response to Question 9:

- We agree with your proposal to present and analyze the reasons for subjects withdrawn from the study.

- We do not agree that only CRFs for discontinuations from death and serious adverse events (SAEs) or adverse events of interest (AESI) should be included in the NDA. In addition to those for SAEs and AESIs, you should provide CRFs for the following subjects:
  - Patients who discontinued treatment
  - Patients who reported any type of pregnancy

ADDITIONAL COMMENTS:

Clinical Pharmacology Comments:

1) Clarify if the reference drug (YAZ®) used in Study CF111/103A is the US approved product. If not, justify how LF111 is bridged to the listed drug that you intend to rely upon FDA's finding of efficacy and safety.
2) Provide relative bioavailability (BA) of LF111 compared to YAZ® following single-dose administration measured by $AUC_{0-\infty}$ for Study CF111/103A.
3) For NDA submission:
   a) Submit pharmacokinetic (PK) analysis dataset and PK parameter dataset in SAS Transport (.xpt) format.

b) Provide a summary of formulations used in each clinical study. If the to-be-marketed (TBM) formulation is different from that used in the pivotal Phase 3 study, bioequivalence study may be needed.
c) Include all bioanalytical method validation and study (performance) reports and provide links to them in Section 2.7.1 Summary of Biopharmaceutics and Analytical Methods.
d) Provide a rationale for dose-selection.

4) As per our Advice Letter dated January 6, 2015, we continue to have reservations as to whether your selected 4 mg dose of (b) (4) DRSP has been established as the lowest effective dose. We remind you that dose selection will be a significant review issue if the safety profile of the 4 mg dose demonstrated in Phase 3, including endometrial safety, raises concern.

Discussion:
The Sponsor clarified that Study CF111/103A did not use the US marketed YAZ® product. Only Study CF111/103C used the US approved YAZ® product. See discussion under Question 1 for additional details.

Clinical Comments:

5) After a preliminary review of your meeting package, the reported high discontinuation rate in the US trial will be a review issue. The discontinuation rate in your US trial is higher than that of any recently approved combined hormonal contraceptive.

6) Identified potential safety issues for your product:

a) Bone Mineral Density (BMD) safety:

The scope of this meeting precludes detailed discussion of a postmarketing BMD study design. This safety concern will be a review issue. If your product is approved, you will be required to conduct a postmarketing BMD study. Briefly, we provide the following preliminary recommendations on the design of this study for your consideration:

- Include adolescents and adult women on no hormonal contraception in your comparator arms.
- Propose a hypothesis and power your study to take into account the expected rate of accrual of BMD in adolescents, the expected decline in BMD in adult women, as well as the expected differences between BMD for your product and the control arm. The study should be powered to account for drop-outs.
- The study population in trials assessing BMD should be comprised of approximately 50% US subjects. The Division recognizes that intrinsic and extrinsic factors that differ across the world can affect BMD measurements. These include, but are not limited to, sun exposure, underlying illnesses/concomitant therapies, consistency of medical practice, baseline nutrition, underlying calcium and vitamin D nutrition, and calcium and vitamin D supplementation in food products. If an adequate US population is not included, these factors should be evaluated to ensure that the BMD changes are applicable to the intended US population and US medical practice.

- Procedures for longitudinal evaluation of BMD machine performance and cross-calibration of instruments, as well as the plan for centralized analysis, should be detailed in proposed protocols. In designing the plan for longitudinal evaluation of BMD machine performance and cross-calibration of instruments and the plan for centralized analysis of BMD scans, consider the relevant quality control concerns described in the following article: *Faulkner KG, McClung MR. Quality control of DXA instruments in multicenter trials. Osteoporosis Int. 1995;5:218-227.*
- Measuring BMD at all sites (lumbar spine, hip, and femoral neck) and providing these data for review is recommended.
- Study objectives should include characterizing the time at which loss of BMD plateaus and characterizing the time to resolution of any clinically significant changes in BMD on treatment; this may require additional months of post-treatment follow-up.
- Be advised that if there is an adverse impact on BMD at one year, follow-up DXA scans for the evaluation of time to resolution would be required.
- Proposed labeling needs to address the risk of BMD loss and respective mitigation strategies. Therefore, design the trial(s) so that monitoring and treatment decisions reflect those prescribed in labeling.
- In trials assessing the risks of compromised BMD in adolescents, the control group may enroll adolescents who are using non-hormonal contraception or are sexually abstinent.

b) Risk of Thromboembolic Events (TE):
   - Products containing DRSP have been associated with an increased risk of thrombotic events as compared to other progestin hormonal contraceptive products. This safety concern may be a review issue. Unique characteristics of the coagulation pathway in adolescents (particularly those <17 years of age) may impart a greater relative risk of TE compared to adult women. Additionally, the increased risk of thrombotic events in first-time users of HC poses greater concern in adolescents because they are more likely to be first-time users. A postmarketing study may be required to address this safety concern.

Additional CMC Comments:

7) Provide three samples of the finished drug product.

Discussion During the Meeting:

The Sponsor will submit three sample blister packs to the Agency, through Jennifer Dao, for review at the time of NDA submission.

8) Submit complete dissolution method development report as outlined in the preliminary comments dated September 5, 2013.

9) Your proposed dissolution method contains (b) (4) data supporting

discriminating ability of the method and a list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.

In Silico PBPK Modeling Supporting DS and/or DP Attributes

To aid in the regulatory-decision making in terms of setting the appropriate acceptance criterion(a) for drug substance (DS) or drug product (DP) attributes (e.g., drug substance particle size, drug product hardness, drug product dissolution) based on in silico physiologically-based pharmacokinetics (PBPK) modeling, provide the following information/data (if available):

10) Relevant *in vivo* data (e.g., BA/BE, PK data) to demonstrate that drug product-batches with your proposed acceptance criterion(a) for drug substance or drug product attributes have a similar systemic exposure compared to that of the pivotal bio-study drug product-batch.

11) Available supportive data from *in silico* physiologically-based pharmacokinetics (PBPK) modeling and simulation demonstrating the *in vivo* impact at the extremes of the proposed drug substance and/or drug product attributes. For this purpose, the submission of the following information is recommended:

    a. A modeling summary report, providing an overview of the modeling strategy, and details the modeling procedures including model development, verification/validation, as well as, application in a step-wise manner. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.

    b. Detailed information on the inputs used in the development, optimization and verification/validation of the model(s). All the physiological and physicochemical parameters, as well as, their sources should be clearly specified. It is understandable that some input parameters are estimated (optimized). However, when the parameters are optimized, the initial value selection, the estimation method, the justification for the optimization algorithm, and the assumption(s) used should be provided. For simulation, provide the input values/ranges of parameters, single or population simulation (number of simulated subjects) along with the output report.

    c. The definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt,.xls).

    d. Although the FDA does not request the use of a specific software, due to substantive differences in software/versions, clear identification of software parameters is critical, which should include: name and version of the software, and (for custom modeling software) schematics of model structure and differential equations.

    e. The methodological approach for model verification/validation, verification/validation results, as well as, sensitivity analyses to interrogate the robustness of the model should be clearly presented. Note that it is expected that PK data may contribute to establish confidence in model appropriateness when addressing the study question(s).

f. The generated data from the verified/validated model to address the study question(s) should be presented using tables, figures and text where appropriate.

g. The complete PBPK modeling and simulation report, definition files, and datasets in module 5.3.1.3 of the eCTD.

The FDA's final decision regarding the acceptability of the acceptance criterion(a) of the drug substance and/or drug product attributes will be made during the review of your submission based on the totality of the supportive data and relevant information, including quality demonstration of submitted PBPK modeling and simulation work.

Discussion During the Meeting:
The Sponsor asked if it was a requirement to submit data from in silico physiologically-based pharmacokinetics (PBPK) modeling and simulation. FDA encourages all applicants to develop a PBPK model, however this is not a filing or approval requirement.

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).

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

5. ABUSE POTENTIAL ASSESSMENT

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

6. 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), 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.

7. 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

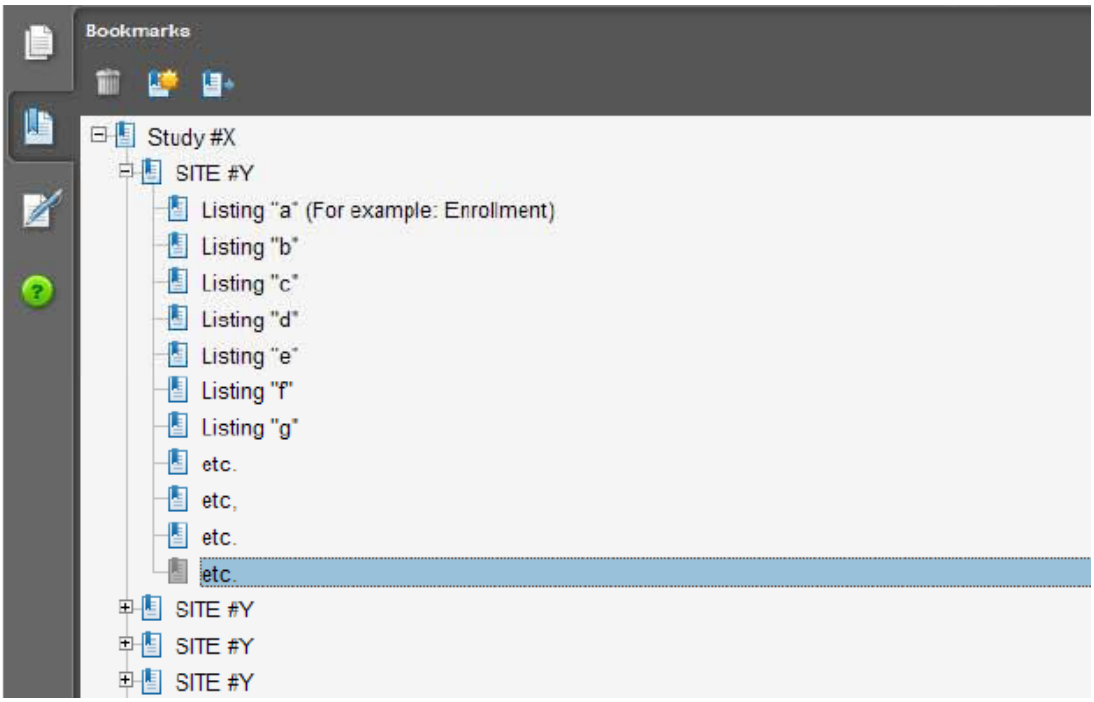
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571,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

JENNIFER M DAO
01/09/2018

CATHERINE A SEWELL
01/09/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 111347

MEETING MINUTES

CHEMO France
C/o Hyman, Phelps & McNamara, P.C.
Attention: Frank J. Sasinowski
Counsel to CHEMO France
700 Thirteenth Street, N.W., Suite 1200
Washington, D.C. 20005

Dear Mr. Sasinowski:

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

We also refer to the meeting between representatives of your firm and the FDA on September 9, 2013. The purpose of the meeting was to discuss a proposed program for obtaining approval of a new progestin-only pill, drospirenone.

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, please call Pamela Lucarelli, Regulatory Health Project Manager at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Lisa Soule, M.D.
Medical Team Leader
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:	Type B: End of Phase 2
Meeting Date and Time:	September 9, 2013 at 9:30 A.M. to 10:30 A.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room 1313 Silver Spring, Maryland 20903
Application Number:	PIND 111347
Product Name:	Drospirenone (DRSP)
Indication:	Prevention of pregnancy
Applicant Name:	CHEMO France
Meeting Chair:	Lisa Soule, M.D.
Meeting Recorder:	Pamela Lucarelli

FDA ATTENDEES

Hylton V. Joffe, M.D., M.M.Sc. – Director, Division of Bone, Reproductive, and Urologic Products (DBRUP)
Lisa Soule, M.D. – Clinical Team Leader, DBRUP
Ronald Orleans, M.D. – Medical Officer, DBRUP
Krishan Raheja, Ph.D. – Pharmacologist/Toxicologist, DBRUP
Myong-Jin Kim, Pharm.D. – Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCPIII) Office of Clinical Pharmacology (OCP)
Mahboob Sobhan, Ph.D. – Team Leader, Division of Biometrics II (DBII)
Xin Fang, Ph.D. – Statistical Reviewer, DBII
Kareen Riviere, Ph.D. – Biopharmaceutics Reviewer, Office of New Drug Quality Assessment
Jennifer Mercier – Chief, Project Management Staff, DBRUP
Pamela Lucarelli – Regulatory Health Project Manager, DBRUP

SPONSOR ATTENDEES

Philippe Perrin – President Director General, CHEMO France
Dominique Droulin – Director, Development, Endocrinology & Gynecology, CHEMO France
(b) (4) – Director, (b) (4)

Enrico Colli, M.D. – Chief Scientific Officer, CHEMO Research
Marta Gómez Bugraz – CMC Manager, CHEMO Research
(b) (4) – Regulatory Consultant, (b) (4)
(b) (4) – Regulatory Consultant, (b) (4)

BACKGROUND

The Sponsor is developing a progestin-only pill (POP) containing drospirenone (DRSP) for the prevention of pregnancy. Unlike most POPs, which are taken continuously, this POP would be administered in a 24/4 day regimen. The Sponsor also seeks labeling that would allow for some delay in pill-taking without the need for back-up contraception and that will not exclude use by lactating women.

DISCUSSION

The Sponsor's questions are presented below in *italics*, followed by the Division's responses that were provided to the Sponsor on September 5, 2013, in normal text. Additional discussion held during the meeting is summarized below in **bold** text.

1. *Does the Division agree that the results of pharmacokinetic (PK) and pharmacodynamic (PD) trials, the demonstrated contraceptive effectiveness of LF111 and the tolerability of LF111 as evidenced in the already generated data - to be confirmed in the remaining two Phase 3 clinical studies, one of which is currently being conducted in Europe and the other will be conducted the US, respectively - adequately justify the 4-mg dose and the 28-day dosing regimen that includes a 4-day drug-free interval?*

   Division Response:
   The Division notes that the multiple-dose PK study (CF111/103A) showed a lower systemic exposure of DRSP from LF111 compared to YAZ, with relative bioavailability of 77.8% for AUC and 66.8% for Cmax. The results of pharmacodynamic (PD) studies demonstrated that LF111 at 4 mg dose and 24/4 regimen appears to be adequate in suppressing ovulation.

   However, the Division is not convinced that the Sponsor has identified the lowest effective dose. Dose-selection has been based in part in comparison to a combined oral contraceptive (COC) regimen; however, the mechanisms of action for progestin-only contraceptive pills (POPs) include actions in addition to ovulation inhibition. Therefore, the systemic exposure to DRSP may not need to be as high as that in a COC, which targets consistent ovulation inhibition as the primary mechanism of action.

   The NDA submission will need to provide a rationale for dose-selection. The Division recommends that the Sponsor be prepared to justify the dose selection by including information on the effect of lower doses of DRSP on ovulation inhibition as well as on parameters that reflect other mechanisms of contraceptive efficacy for a POP.

Discussion at the Meeting:

The Sponsor discussed its findings to date and its rationale for pursuing the 4 mg DRSP dose, noting the lower systemic exposure compared to the 3 mg (b) (4) DRSP dose that is approved in various COCs, along with concern that a lower dose might not provide sufficient contraceptive efficacy for women with high body mass index (BMI) or who do not comply exactly with the dose regimen. The Sponsor is targeting women such as these, as well as women with contraindications to estrogen-containing contraceptives. The inflexible dose regimen of current POPs is believed to be a major reason they are not widely used in the US, and the Sponsor hopes to improve their acceptability by being able to offer a more forgiving regimen. The Division indicated that this appeared to be a reasonable rationale, and encouraged the Sponsor to explore exposure-response analysis in women of high BMI as additional support. The Sponsor plans to conduct a population pharmacokinetic (PK) analysis, including in women of high BMI. The Division cautioned that if venous thromboembolic events (VTEs) were observed in the development program, this might reopen the discussion about whether appropriate dose selection had been achieved.

The Sponsor plans to submit the phase 3 protocol as a Special Protocol Assessment request.

2. *Does the Division agree with the proposed design of the US Phase 3 Study (CF111/303), including selection criteria, sample size and treatment duration?*

Division Response:

Because Pearl Index data from Europe are generally considerably better than that obtained in the US population, the Division will not rely heavily on efficacy data from Study 301. In addition, that study seems to have had somewhat restrictive entry criteria, included very few women (<6%) with a BMI ≥ 30 kg/m^2, and excluded women with some of the conditions that would contraindicate use of a COC but that are not currently listed as contraindications to a POP.

The Division has the following preliminary comments on the Study 303 protocol; further comments are likely when the full protocol is submitted for review:

- Enrollment of women < 18 years is encouraged, as feasible.
- The Sponsor is also encouraged to remove the upper age limit as this product is likely to be a useful option for perimenopausal women. Although women > 35 years at entry will not be part of the primary efficacy population, data on these women will be important in determining the safety profile in patients who are likely to use the product, if approved.
- The Sponsor is encouraged to enroll smokers at a rate representative of their prevalence in the US reproductive-aged female population, as this product may be a useful option for smokers contraindicated from use of COCs.
- The size of the study should be determined so as to provide a reasonably tight 95% confidence interval (CI) around the Pearl Index. The Division assesses both the Pearl Index and the upper bound of the CI in evaluating the acceptability of the contraceptive efficacy.

- As there is no BMI restriction in the proposed phase 3 study, the Division recommends that the Sponsor use population PK analysis to explore the effect of body weight/body mass index on DRSP exposure as well as on contraceptive efficacy and safety parameters.
- It appears that this is the only study that will provide instructions relevant to a 24 hour delay in dosing; it is unclear whether this will provide sufficient data to support labeling that allows for pills to be delayed for up to 24 hours without requiring use of back-up contraception.
- It is unlikely that labeling claims about change in weight or blood pressure would be accepted.

Discussion at the Meeting:
The Sponsor clarified that it had included the 24-hour delay instructions in the open-label European trial. In that study, about 20-25% of the subjects missed one or more pills, although data about pill-taking compliance did not always match pill counts on returned blister packs. In the electronic diary, subjects are prompted to enter the hour at which they took their pill. The Division stated that the acceptability of labeling with respect to delayed pill intake will be a review issue, based on the amount, quality and reliability of data pertaining to delayed doses.

3. *Does the Division agree that the proposed clinical program, including US Phase 3 study CF111/303, depending upon results, will provide the necessary clinical data package required for a 505(b)(2) NDA for the indication to prevent pregnancy in women who elect to use an oral contraceptive? Does the Division concur that this clinical program has the potential, depending on the results, to provide adequate overall exposure to assess safety as well as to provide adequate evidence of efficacy?*

Division Response:
It appears that the overall development program will include appropriate studies to support an NDA. It also appears that the anticipated overall exposure will be sufficient to allow evaluation of safety in the NDA review. However, as discussed at the April 28, 2011 meeting, in order to evaluate rare adverse events like venous thromboembolic events, it is likely that the Division will require a large post-marketing safety study if the product were approved.

4. *Does the Division concur with the adequacy of the sponsor's proposed method of bridging to the Agency's previous finding of safety for DRSP generated in the historical non-clinical investigations with DRSP?*

Division Response:
Yes.

5. *Does the Division agree that the information on endometrial safety, including the planned Phase 2 study (CF111/205), will be adequate to assess the effect of DRSP as a POP on this parameter?*

Division Response:
Yes, the plan to study 20 subjects over one year is acceptable. However, the description of Study 205 on page 22 of 49 says n=12; clarify the number of women to be studied.

Discussion at the Meeting:
The Sponsor clarified that it plans to enroll 20 women in order to obtain 12 women who complete the evaluation at one year. The Division stated that this is acceptable.

6. *Does the Division agree with the methodology for assessing "scheduled" and "unscheduled" bleeding in the LF111 clinical trials since there is no established methodology in the literature for assessing these bleeding patterns in POPs?*

Division Response:
The proposal to define Scheduled Bleeding as any bleeding beginning on Day 25-28 ± 1 day and continuing up to 8 consecutive days is acceptable. Unscheduled bleeding should be defined as any bleeding outside this window.

Discussion at the Meeting:
The Sponsor agreed to implement the Division's definition of "unscheduled bleeding."

7. *Does the Division agree that the clinical development plan, including planned Phase 1 study CF111/107, will adequately address the safe use of LF111 in lactating women in order to not exclude in product labeling this population (breastfeeding mothers requiring contraception) as suitable candidates for treatment with LF111?*

Division Response:
No. Unless Study 107 demonstrates very negligible transfer to breast milk, it is unlikely that labeling recommending use by lactating women would be granted in the absence of a neonatal/infant growth and development study. Further discussion will be needed after the results of Study 107 are available.

The Sponsor is referred to the *Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling*, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf

In addition, the Sponsor will need to address the timing of initiating use of LF1111 postpartum, with respect to the increased risk of thromboembolism in the early postpartum period.

Discussion at the Meeting:
The Sponsor plans to begin with Study 107 and proceed in a stepwise manner based on the results of that study. Further discussion is anticipated after that study is complete; the Division noted that this could be achieved by a meeting or by written responses only at the Division's discretion.

8. *CHEMO Group will submit an initial pediatric plan to the Agency no later than 60 days after the EOP2 meeting, as required by the FDA Safety and Innovation Act. Prior to that submission, we would appreciate the Division's comments on our proposed pediatric plan as outlined in this document. With that in mind, does the Division agree that the general design of our proposed pediatric plan appears to be acceptable and adequate?*

   Division Response:
   The overall strategy proposed appears acceptable, but the Division will provide more specific comments when the full Pediatric Plan is submitted. The plan will also need to be reviewed by the Pediatric Research Committee The Division has the following preliminary comments:

   - The lower eligible age of 14 years seems arbitrary; the Division recommends that any adolescent < 18 years who is at risk of pregnancy be allowed to enter the study.
   - The Sponsor is strongly encouraged to enroll a comparator arm to provide a context for any bone mineral density (BMD) changes observed. Adolescent girls should be accruing BMD, so an adverse effect could be present even in the absence of BMD reductions from baseline.
   - The Sponsor is encouraged to specify a hypothesis about the impact on BMD that will be tested and to power the study sufficiently to evaluate the hypothesis.
   - If adverse effects on BMD are demonstrated following one-year of treatment, the Sponsor will need to follow subjects to determine the time off-treatment required for resolution of this effect. Such findings might also result in a labeled limitation on the duration of use.
   - Further statistical and clinical pharmacology comments will be provided upon submission of the full plan.

9. *Does the Division agree with the proposed dissolution test (water with 0.6% tween, 75 rpm and paddles) and the proposed specification for this test in the finished dosage product (acceptance criteria for dissolution test and Q(2h)= 70%)?*

   Division Response:
   There is insufficient information to determine the acceptability of the proposed dissolution method at this time. Specifically, the Sponsor has not provided the pH solubility profile of the drug substance and the solubility of the drug substance in the different media investigated.

   FDA recommends that the Sponsor provide a full dissolution method development report as an amendment to this IND for review by the FDA. This report should include the following information:

   - Solubility data for the drug substance covering the physiological pH range;
   - A detailed description of the dissolution test being proposed for the evaluation of the product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media including choice of surfactant, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for the product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified.

The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. FDA recommends use of at least twelve samples per testing variable;

- The complete dissolution profile data (individual, mean, SD, profiles) for the product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);
- Data to support 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) product and the test products (aberrant formulations) that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent; and
- Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

Additionally, the acceptability of the proposed dissolution acceptance criterion for the product will be made during the NDA review process based on the totality of the provided dissolution data. For the selection of the dissolution acceptance criterion of the product, the following points should be considered:

- The dissolution profile data (i.e., 15, 30, 45, 60, 75, 90, 105, and 120 minutes) from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of the product (i.e., specification-sampling time point and specification value). The criterion should be based on average *in vitro* dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).
- The *in vitro* dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- For immediate release product the selection of the specification time point should be where Q=80 % dissolution occurs.

Discussion at the Meeting:

The Division agreed with the Sponsor's proposal to use the current dissolution method and acceptance criterion to release the clinical trial material until the Sponsor develops a final dissolution method.

The Division also reminded the Sponsor that a dissolution method development report can be submitted as an amendment to this IND for review and feedback by the FDA and that a dissolution method can be accepted prior to the submission of the NDA.

However, the acceptability of the proposed dissolution acceptance criterion for the product will be determined during the NDA review process based on the totality of the provided dissolution data.

The Division noted that it would be best if the specification time point was where Q= (b) (4) % dissolution occurs. If the Sponsor proposed to use two timepoints, i.e., Q=X% and Q= (b) (4) % and provided justification, the Division would consider that as a possibility.

The Sponsor stated that they intend to request a meeting with ONDQA to address some of their additional CMC and Biopharmaceutics questions.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), the Sponsor must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that the Sponsor plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and 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 clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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 the Sponsor intends 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, it 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). The Sponsor should establish a "bridge" (e.g., via comparative bioavailability data) between its proposed drug product and each listed drug upon which it proposes to rely to demonstrate that such reliance is scientifically justified.

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

If the Sponsor intends 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)), it 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 the Sponsor proposes 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.

The Division encourages the Sponsor to identify each section of its proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

In the 505(b)(2) application, 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 the Sponsor is proposing to rely on published literature, include copies of the article(s) in the submission.

In addition to identifying in the Sponsor's annotated labeling the source(s) of information essential to the approval of its proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, the Sponsor is also encouraged to include that information in the cover letter for its marketing application in a table similar to the one below.

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

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 the Sponsor's application is submitted, such that its 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 the 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.

ACTION ITEMS

The Division will provide meeting minutes to the Sponsor within 30 days of the date of the meeting.

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
10/03/2013