CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216285Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 146207

MEETING REQUEST-
WRITTEN RESPONSES

Laboratorios León Farma S.A.
c/o Exeltis USA, Inc.
Attention: John C. Kim, RPh, JD
SVP Regulatory Affairs
180 Park Avneue, Suite 101
Florham Park, NJ 07932

Dear Mr. Kim:

Please refer to your pre-investigational new drug application (PIND) file for drospirenone 3.5 mg chewable tablets.

We also refer to your submission dated January 29, 2021, containing a meeting request. The purpose of the requested meeting was to discuss the content and structure of the planned submission as a supplement to your existing NDA 211367 Slynd (drosperinone) 4 mg tablet, or as a new NDA submission.

Further reference is made to our Meeting Granted letter dated February 3, 2021, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 26, 2021, background package.

If you have any questions, call Jeannie Roule, Chief, Project Management Staff (acting) at 301-796-3993.

Sincerely,

{See appended electronic signature page}

Gerald Willett, M.D.
Medical Team Leader
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

WRITTEN RESPONSES

Meeting Type: **B**

Meeting Category: **Pre-NDA**

Application Number: **PIND 146207**

Product Name: **Drospirenone 3.5 mg chewable tablets.**

Indication: **Prevention of pregnancy**

Sponsor Name: **Laboratorios León Farma S.A.**

Regulatory Pathway: **505(b)(2)**

BACKGROUND

This development program intends to provide a new dosage form for a new drospirenone chewable tablet that can be chewed and swallowed without water.

NDA 211367, Slynd (drospirenone) 4 mg tablet for oral administration (swallowed whole) was approved on May 23, 2019. The proposed product and the Slynd product contain drospirenone and are indicated for the prevention of pregnancy.

On January 10, 2020, the Sponsor received pre-IND meeting Written Responses from the FDA and that advice included in the responses is incorporated into the current development program.

Recently, the clinical trial Protocol (b) (4) (b) (4) (b) (4) showed that (b) (4) (b) (4) (b) (4) the proposed chewable drosperinone product and the approved drosperinone product were not bioequivalent.

The Sponsor re-developed their drosperinone chewable tablet to be bioequivalent to the approved drosperinone product. (b) (4) 3.5 mg and 4 mg dosage strengths, both with mint flavor (b) (4)) were tested in a bioavailability comparability clinical study.

Three clinical trials have been conducted to support product development of the new chewable tablet: 1) a comparative bioavailability of drospirenone chewable tablets and drospirenone oral tablets to demonstrate biosimilarity, 2) an oral irritation study to

evaluate the safety of drospirenone chewable tablets following daily use by female subjects, and 3) a food-effect study to evaluate the bioavailability of drospirenone chewable tablets in the presence of food.

Results from the bioavailability study (Study No. 2020-FLE1-SLINC-PK-04) showed that their drospirenone 3.5 mg chewable tablet formulation, after a single dose administration under fasting conditions, was biosimilar. (b) (4) , (b) (4)

Based on the results of the bioavailability study, the Sponsor selected the 3.5 mg strength chewable drosperinone tablet as the to-be-marketed product. As the drospirenone 3.5 mg chewable tablet is shown to be therapeutically equivalent to Slynd (drospirenone) 4 mg tablet, development will rely on the Agency's previous finding of safety and efficacy in the approval of Slynd NDA 211367. No additional clinical or nonclinical studies are planned.

On February 5, 2021, an initial Pediatric Study Plan (iPSP) was submitted to FDA. The Sponsor is preparing an efficacy supplement to NDA 211367 Slynd (drospirenone) tablet 4 mg, if acceptable by the Agency. If not acceptable, a 505(b)(2) NDA cross-referencing the Slynd NDA will be submitted.

Confirmation of the clinical and nonclinical development program is sought by the Sponsor from this meeting. Nonclinical studies were not conducted since the application will rely on the Agency's finding of safety and effectiveness for the approved reference listed drug Slynd.

The clinical development program for the chewable tablet includes two key phase I trials (bioavailability) and one key oral irritation study essential to support the approval of the chewable formulation and administration have been completed. Additionally, one phase I study and two safety studies (oral irritation) have been completed to support the development product. These additional studies are included to provide safety information and were conducted to test either a development formulation or an alternate procedure of use.

The marketing application for Drospirenone 3.5 mg chewable tablet is planned for submission to the Agency in approximately 2Q2021.

The purpose of this meeting is to reach agreement with the FDA that the application's content and structure are adequate to support an efficacy supplement to NDA 211367 Slynd.

QUESTIONS AND RESPONSES

Clinical
Question 1:
The application will cross-reference the Slynd 4mg NDA and rely on the Agency's previous finding of safety and efficacy. Furthermore, due to the limited data from the Phase 1 clinical trials, the application will not include an ISE and ISS. However, the safety and efficacy of Drospirenone chewable tablet 3.5 mg will be summarized in Module 2.7.4 and 2.7.3, respectively.

Is it acceptable for filing the application without an ISE and ISS?

FDA Response to Question 1:
Yes. We agree that your NDA does not need an ISS or an ISE for filing. Provide a comprehensive safety update of drospirenone contraceptive products that includes current published references and global post-marketing data.

Nonclinical
Question 2:
Module 4 will not contain any original nonclinical studies. With the exception of the flavoring agent, the active and inactive ingredients in Drospirenone 3.5 mg chewable tablets have been adequately qualified in SLYND® NDA 211367). The flavoring agent is PEPPERMINT FLAVOR (b) (4) NF, consisting of peppermint oil and suitable carriers (like maltodextrin, and modified starch). It is considered GRAS (generally recognized as safe) and supported by literature. Therefore, the application will cross-reference the SLYND 4mg NDA and rely on the Agency's previous finding of safety.

Is this acceptable?

FDA Response to Question 2:
Yes, provided that you establish an adequate scientific bridge between your product and the drospirenone component of one or more US approved listed drug products, then reliance on the Agency's previous findings of safety, as reflected in the approved drug product labeling, is appropriate to support the nonclinical section of your NDA and additional nonclinical studies are not anticipated.

Limited information was provided in your briefing package for the excipient components of the PEPPERMINT FLAVOR (b) (4) NF (i.e., peppermint oil and suitable carriers like maltodextrin, and modified starch). Provide additional information to justify the use of this excipient in your formulation, including but not limited to a quantitative listing of the excipient components that make up this flavoring, excipient specifications, and a certificate of analysis. Pending review of this information for the PEPPERMINT FLAVOR (b) (4) NF excipient, additional nonclinical studies may not be needed to qualify this flavoring excipient.

Chemistry, Manufacturing, and Controls
Question 3:
If a separate NDA is required, the CMC section will cross reference Slynd NDA drug substance information with appropriate references to DMFs. A Quality Overall Summary will also be included in Module 2 of the eCTD.

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

FDA Response to Question 3:
Complete drug substance information should be provided either in your application or cross-referenced to your NDA 211367 or in a DMF with the appropriate Letter of Authorization provided. If information is provided in a cross-reference NDA or DMF, we request that the following information be provided in the NDA for ease of review: General information, physico-chemical properties, and Specifications. We remind you to submit a Certificate of Analysis for your drug substance.

We have the following comments regarding the proposed "Intended Drug Product Documents in Module 3" outlined on pages 50 – 54 of the background package. The comments apply to both the active tablet and the placebo tablets:

- To support use of 'Peppermint Powder Flavor' (PEPPERMINT FLAVOR (b) (4) (b) (4) NF) in the drug product, provide chemistry, manufacturing and controls (CMC) information, including the components and composition of the flavor, specifications for the components, reference to any relevant regulatory or compendial standards, copies of relevant certifications, the specification for the peppermint flavor, and a representative Certificate of Analysis. If possible, identify any other FDA-approved drug products that contain PEPPERMINT FLAVOR (b) (4) NF. Alternatively, if the flavor manufacturer has a Drug Master File (DMF) covering the peppermint flavor, provide a Letter of Authorization (LOA) to cross-reference the DMF.
- Information on the White Coating (b) (4)) should include the components and composition. Provide a Letter of Authorization to cross-reference the applicable DMF.
- We recommend inclusion of information about the film-coating (b) (4) in Modules 3.2.P.1 and 3.2.P.4 rather than in 3.2.A.3
- Provide Certificates of analysis for all clinical and primary and supporting stability batches in 3.2.P.5.4.
- Detailed information on the packaging materials should be included in 3.2.P.7 of the new NDA, rather than by cross-reference to NDA 211367. The submission should include LOAs for all packaging material DMFs.

The suitability of the proposed specification, including acceptance criteria, will be evaluated based on the totality of information submitted in the NDA.

Note that all facilities should be ready for inspection at the time of submission. All manufacturing, packaging and testing facilities for both the drug substance and drug product should be identified on the FDA Form 356h, and in Modules 3.2.S.2.1 and 3.2.P.3.1, respectively.

Question 4:

Based on the in vivo results from bioequivalence studies, Drospirenone Chewable Tablet was re-developed, according to FDA's Guidance for Industry: Quality Attribute Considerations for Chewable Tablets (August 2018). From the two "optimized" candidates tested, only drospirenone 3.5 mg chewable tablets showed bioequivalence. A specific dissolution test for this drug product was developed and accordingly, new specifications for dissolution test were proposed. A description of the method and specification to be included in the NDA will be provided in the briefing information package.

Does the Division agree with the proposed dissolution test (water with 0.6% tween, 100 rpm and paddles) and the proposed specification for this test in the finished dosage product (L(30 min) = (b) (4)% and Q(4h) = (b) (4)%)

FDA Response to Question 4:

No. We cannot agree at this time with your dissolution test parameters because the necessary information has not been submitted for review. Include Report Code ID0433 "Development of Dissolution Method (Tween and 100 rpm) for drospirenone 3.5 mg Chewable Tablets" in Module 3.2.P.2 of your NDA application. Your report should adequately justify the use of detergent and high rotation speed. Drospirenone has been reported to be sparingly soluble in aqueous buffers. If your solubility study over physiological pH concludes that this is a low solubility drug substance, the discriminating ability of your method must also be demonstrated in this report.

If the drug product is a slow dissolving product, your proposal to establish acceptance limits at two sampling time points may be appropriate. The dissolution acceptance criteria will be evaluated when complete dissolution data are submitted in your NDA.

Question 5:

ICH stability studies are ongoing for the drug product. A description of the stability to be included in the NDA will be provided in the briefing information package.

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

FDA Response to Question 5:

No. As noted in FDA Written Responses dated January 10, 2020 and August 12, 2020, your NDA should include at least 12-months long-term and 6-months accelerated stability data for at least three (3) registration batches/primary stability batches

packaged, with placebo tablets, in the same container closure system intended for marketing, at the time of submission. See ICH Q1A(R2) for recommendations on the selection of stability batches.

In addition to long-term and accelerated stability testing, photostability testing of the drug product should be conducted in accordance with ICH Q1B.

Question 6:

Drospirenone chewable tablet, 3.5 mg is a different strength than Slynd 4mg tablets, but has the same active ingredient, container closure, indication, and excipients. The formulation between the two strengths are essentially the same with the exception of added flavoring (b) (4).

Does the Division agree that this marketing application can be submitted as a supplement to the original Slynd NDA 211367?

FDA Response to Question 6:

No. A different dosage form should be submitted as a separate original application. Refer to the guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*.[1] Slynd is a 4 mg tablet swallowed whole once a day. You are proposing a 3.5 mg tablet, chewed. Per the Orange Book, Appendix C (updated December 2020), tablet and tablet chewable, are two different dosage forms.

Question 7:

A comparative bioavailability of Slynd 4 mg tablet, Slynd 4 mg chewable tablet and Drospirenone 3.5 mg chewable tablet (2020-FLE1-SLINC-PK-04), a food effect study (2020-FLE1-SLINC-PK-06) and an oral irritation study (2020-FLE1-SLINC-CE-07) were conducted to support the filing of an efficacy supplement to Slynd NDA 211367.

In the exclusivity summary for NDA 203667 Minastrin, Study PR-10007, an oral irritation study was identified as the new clinical investigation essential to the approval of the NDA.

Based on the previous assessment in NDA 203667, does the Agency agree that the oral irritation study 2020-FLE1-SLINC-CE-07 is a new clinical investigation essential for marketing application approval?

FDA Response to Question 7:

Yes. We agree that your oral irritation study 2020-FLE1-SLINC-CE-07, is considered a new clinical investigation.

[1] https://www.fda.gov/media/72397/download

We remind you that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application.

Question 8:

It is the Sponsor's position that submitting this application as an efficacy supplement to NDA 211367 is consistent with the Agency's bundling policy. If however a separate marketing application is required, then the NDA submission will cross-reference the Slynd NDA 211367 for which the Sponsor will have the right of reference to support application approval.

Does the Division agree with this approach?

FDA Response to Question 8:

A separate original marketing application is required. Refer to FDA Response to Question 6. We agree you may cross-reference your NDA 211367.

If the cross-referenced portions of your previously approved 505(b)(2) application (NDA 211367) involve reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or published literature (as distinguished from any cross-referenced investigations that were conducted by or for you or for which you have obtained a right of reference or use), then the new NDA should be submitted pursuant to section 505(b)(2) of the FD&C Act. Your new 505(b)(2) application should identify this listed drug(s) or published literature as relied upon for its new 505(b)(2) application in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification/statement and notification), apply to each listed drug upon which an applicant relies.

Question 9:

USP recognizes and differentiates between two types of chewable tablets: (1) those that may be chewed for ease of administration, and (2) those that must be chewed and/or crushed before swallowing to avoid choking and to ensure the release of the active ingredient. These two types of chewable tablets are differentiated by the way they are named and labeled. It has been shown that Drospirenone 3.5 mg chewable tablet must be chewed and swallowed to be therapeutically equivalent to Slynd 4 mg tablet, which is swallowed whole.

Does the Division agree that the words "chewable tablet" should be used in the established name and that principal display panel of the container label and the carton labeling should prominently state "Chew completely before swallowing"?

FDA Response to Question 9:
The established name of the drug product is “drospirenone chewable tablets.” Specific comments on your labeling will be addressed following the submission of the NDA.

Additional Comments:

We have the following recommendations regarding your proposed dissolution information (method and acceptance criterion/criteria).Ensure this information is provided in the submission.

Dissolution Method:
Provide in your submission the dissolution method development report that supports 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. Clearly specify the testing conditions associated with each method development study. 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 min. etc.).

c. Data supporting the discriminating ability of the selected dissolution method. In general, ensure that the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares 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). Report the dissolution data 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 your dissolution acceptance criterion of the proposed drug product, consider the following:

a. Use the multi-point dissolution data (n=12, sampling every 2 hours) from the pivotal clinical/PK drug product-batches and primary registration batches for the setting of the dissolution acceptance criterion of the proposed drug product (i.e., sampling time points and limits). When applicable, include the dissolution profile data to support in-process dissolution acceptance criteria.

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

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

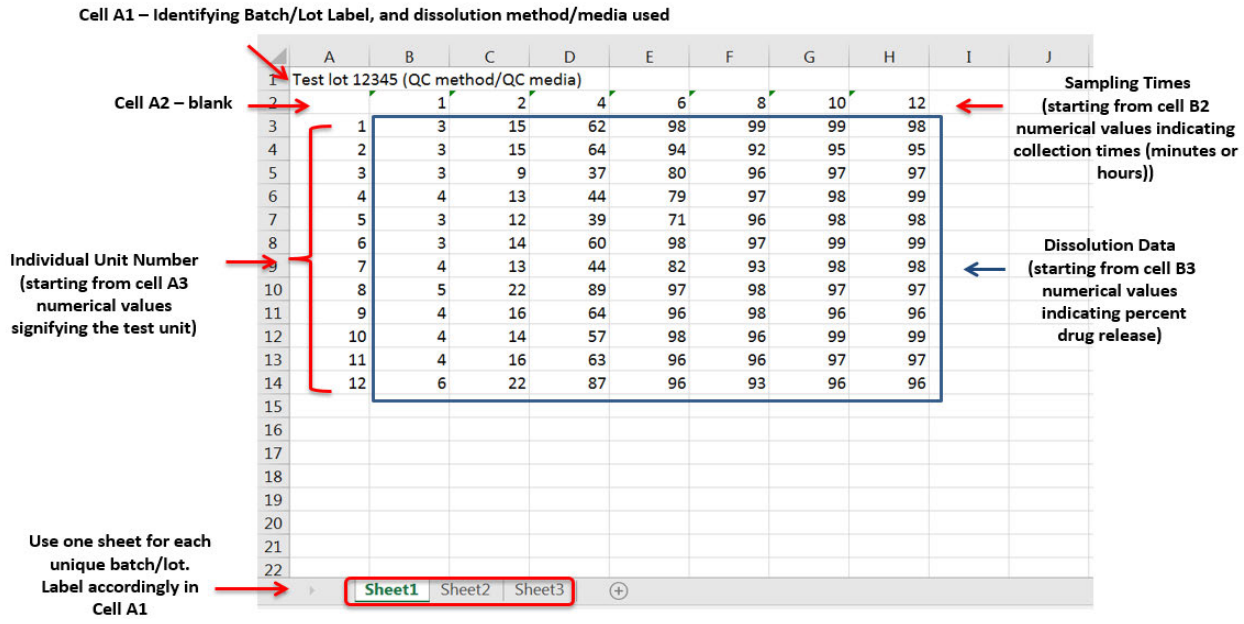
d. Select the sampling time point where Q = (b) (4) % dissolution occurs. However, if the drug product is a slow dissolving product, setting of acceptance limits at two or more sampling time points may be adequate. The first time point should include a dissolution range (e.g. (b) (4) % dissolution at 20 minutes) and the second time point should be where Q = (b) (4) % dissolution occurs.

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

Dissolution Data Presentation:
In your dissolution method development report present detailed experimental dissolution data as follows:

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

<u>Dissolution Acceptance Criterion/Criteria Recommendation</u>:
Note that our recommendation on the adequacy of the proposed dissolution acceptance criterion/criteria for the proposed drug product will be made during the review process based on the totality of the provided dissolution data.

<u>IN SILICO PBPK MODELING SUPPORTING DS and/or DP ATTRIBUTES</u>
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 [redacted] (b) (4) dissolution) based on in silico physiologically-based pharmacokinetics (PBPK) modeling, provide the following information/data (if available):

1. 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.

2. 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 these 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.

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*.[2] 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.[3]

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

[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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 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.

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

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

1999).[6] 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.[7]

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.

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[6] 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.
[7] http://www.regulations.gov

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.

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
03/25/2021 02:52:58 PM