CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215423Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 136844

MEETING MINUTES

Veru Inc.
c/o Camargo Pharmaceutical Services, LLC
Attention: Catherine Gatza, Ph.D.
Director of Regulatory Strategy
2505 Meridian Parkway, Suite 175
Durham, NC 27713

Dear Dr. Gatza:

Please refer to your pre-investigational new drug application (PIND) file for tadalafil/finasteride combination oral capsules.

We also refer to the meeting between representatives of your firm and the Agency on May 23, 2019. The purpose of the meeting was to discuss plans to submit an NDA via the 505(b)(2) pathway for tadalafil/finasteride combination oral capsules.

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 outcome.

If you have any questions, call George Lyght, Pharm.D., Senior Regulatory Project Manager at 301-796-0948.

Sincerely,

{See appended electronic signature page}

Suresh Kaul. M.D., M.P.H.
Medical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 23, 2019, 10:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415,
Silver Spring, Maryland 20903

Application Number: PIND 136844
Product Name: tadalafil/finasteride combination oral capsules
Indication: Benign Prostatic Hyperplasia (BPH)

Sponsor: Veru Inc.
c/o Camargo Pharmaceutical Services, LLC

Meeting Chair: Suresh Kaul, M.D., M.P.H.

Meeting Recorder: George Lyght, Pharm.D.

FDA ATTENDEES

Division Of Bone, Reproductive, and Urological Products (DBRUP)
Audrey Gassman, M.D., Deputy Director, Division of Bone, Reproductive, and Urologic Products
Suresh Kaul, M.D., M.P.H., Medical Team Leader
Jordan Dimitrakoff, M.D., Ph.D., Clinical Reviewer
Martin Kaufman, D.P.M., M.B.A., Sr. Clinical Analyst
Mukesh Summan, Ph.D., D.A.B.T., Pharmacology/Toxicology Supervisor
Leslie McKinney, Ph.D., Pharmacology/Toxicology Reviewer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
George Lyght, Pharm.D., Sr. Regulatory Health Project Manager

Office of Transitional Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III,
Yanhui Lu, Ph.D., Clinical Pharmacology Scientific Lead
Peng Zou, Ph.D., Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ), Office of New Drug Products
Mark Seggel, Ph.D., Chemistry, Manufacturing, and Controls (CMC) Lead
Kalpana Paudel, Ph.D., Biopharmaceutics Reviewer

Office of Surveillance and Epidemiology (OSE)
Liu Wei, Ph.D., Reviewer
Oyinlola Fashina, Pharm.D., OSE Safety Regulatory Project Manager
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SPONSOR ATTENDEES
K. Gary Barnette, Ph.D., Chief Scientific Officer, Veru, Inc.
Mitchell Steiner, M.D., FACS-Chairman, CEO, President, Veru Inc.

BACKGROUND
Veru Inc, has developed a tadalafil/finasteride combination oral capsule for the treatment of the signs and symptoms of BPH.

The purpose of this Pre-New Drug Application (pre-NDA) meeting is to discuss and gain agreement on the following:

- the continued suitability of the 505(b)(2) pathway for approval of the proposed product including the acceptability of the proposed listed drugs (LDs), Cialis (tadalafil) tablets, for oral use (5 mg; NDA 021368, Eli Lilly and Co.) and Proscar (finasteride) tablets (5 mg; NDA 020180, Merck and Co., Inc.)
- the adequacy of the scientific bridge between the tadalafil/finasteride combination oral capsule and the proposed LDs to support the NDA
- the adequacy referenced of clinical and nonclinical information to support the NDA
- any concerns that the Division may have with regard to other filing issues specific to the referenced product

FDA conveyed preliminary responses to Veru on May 21, 2019. Veru responded to the FDA preliminary responses on May 22, 2019, informing the FDA that responses to questions 1, 2, 7, 8, 10, and 11 were understood and that no discussion was required. Veru wanted to discuss the response to Question 3 and how this response was related to the responses to Questions 4, 5, 6, and 9. Veru also wanted to discussion the response to Question 12. **Veru's response is attached**. Additional meeting discussion is shown below in *italicized* font.

DISCUSSION
Questions and Responses

REGULATORY/MEDICAL

Question 1: Veru plans to submit a NDA for Tadalafil/Finasteride Combination (b) (4) via the 505(b)(2) regulatory pathway. An application submitted under Section 505(b)(2) contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference. Veru proposes to establish a scientific bridge through demonstration of bioequivalence (BE) between the proposed product and the approved LDs, Cialis (tadalafil) Tablets, for oral use (5 mg; NDA 021368, Eli Lily and Co.) and Proscar (finasteride) Tablets (5 mg; NDA 020180, Merck and Co., Inc.) administered together. The establishment of this bridge will allow reliance on the

findings of safety and efficacy for the LDs. The Sponsor proposes to rely on the following information to support product approval:

a. The findings of nonclinical and clinical efficacy and safety for the LDs, Cialis (5 mg; NDA 021368, Eli Lily and Co.) and Proscar (5 mg; NDA 020180, Merck and Co., Inc.) as listed in the approved labeling

b. Information from the published literature and public databases pertaining to the safety and efficacy of tadalafil and finasteride

Does the Agency continue to agree that the 505(b)(2) regulatory pathway is appropriate for submission of the proposed Tadalafil/Finasteride Combination (b) (4) NDA?

FDA Response to Question 1:
Yes. Refer to the **505(b)(2) Regulatory Pathway** section for additional information about submitting a 505(b)(2) NDA.

Veru Response to Question 1
No further discussion required.

Question 2: The Sponsor intends to rely upon the Agency's previous findings of safety and efficacy from the approved labeling of the proposed LDs, Cialis (tadalafil) Tablets, for oral use (5 mg; NDA 021368, Eli Lily and Co.) and Proscar (finasteride) Tablets (5 mg; NDA 020180, Merck and Co., Inc.) The Sponsor proposes to conduct a pivotal, single-dose, bioavailability/bioequivalence (BA/BE) study (similarity of the area under the concentration-time curve [AUC] and peak serum concentration [C_{max}]) to establish a scientific bridge between Tadalafil/Finasteride Combination Oral capsules (5 mg/5 mg) and the LDs, Cialis (5 mg) and Proscar (5 mg), in healthy subjects, to allow reliance on the information in the approved labeling of the LD (Question 4).

Does the Agency continue to agree that for the proposed Tadalafil/Finasteride Combination (b) (4) product, Cialis (tadalafil) Tablets, for oral use (5 mg; NDA 021368, Eli Lily and Co.) and Proscar (finasteride) Tablets (5 mg; NDA, 020180, Merck and Co. Inc.) are the appropriate LDs?

FDA Response to Question 2:
Your selection of Cialis (tadalafil) tablets and Proscar (finasteride) tablets as the listed drugs upon which to rely for approval of your 505(b)(2) NDA appears reasonable. However, a sponsor interested in submitting a 505(b)(2) application that relies upon FDA's finding of safety and/or effectiveness for a listed drug(s) should make the final determination of which listed drug(s) is/are the most appropriate for their development plan.

Veru Response to Question 2
No further discussion required.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

Question 3: Veru has conducted a comparative bioavailability study of Tadalafil/Finasteride Combination (b) (4) (5 mg tadalafil and 5 mg finasteride) and the LDs (Cialis and Proscar) administered at the same time.

1. Bioequivalence (BE) was established for Cmax, AUC0-t, AUCinf and a similar Tmax for finasteride from the Tadalafil/Finasteride Combination (b) (4) (test product) compared to the finasteride parameters from the LDs (Cialis and Proscar). BE was assessed using 90% confidence interval of geometric mean ratios for the parameters and the Cis fell between the 80.00-125.00% range.
2. BE was established for AUC0-t and AUCinf for tadalafil from the Tadalafil/Finasteride Combination (b) (4) (test product) compared to the tadalafil parameters from the LDs (Cialis and Proscar).

3. The Cmax from the combination product was approximately 25% lower and the Tmax was approximately 36% delayed for the combination product compared to the coadministration of the LDs. Cmax values did not meet the bioequivalence test and fell below the 80.00% lower limit of the 90% CI for this parameter.

(b) (4)

FDA Response to Question 3:
No, we do not agree. The results of your comparative bioavailability study did not establish a clinical bridge to your proposed listed drug for tadalafil to support the efficacy of your proposed drug product because the Cmax of tadalafil in your combination product is 27% lower compared than that of Cialis and the 90% confidence interval of 68.79-76.97% is below the no effect boundary of an 80-125% range.

Additional comment:
We note that out of 33 dosed subjects, 32 subjects were included in the pharmacokinetic and statistical analysis of finasteride and 30 subjects were included in the pharmacokinetic and statistical analysis of tadalafil. Justify the exclusion of these subjects in your future submission.

Additional meeting discussion
The Division explained to the Sponsor that their current BE study does not establish a clinical bridge necessary to file a 505(b)(2) NDA. The Division offered the Sponsor the following two options as potential paths forward:

1. *Design a new formulation and conduct a new comparative bioavailability study with an adequate number of subjects to establish the bioequivalence between the proposed product and the listed drugs; OR*
2. *If the Sponsor intends to rely on literature or other studies, follow the existing regulatory guideline, and obtain the necessary data to establish that the 27% lower*

Cmax of tadalafil has no clinically meaningful impact on the efficacy of the proposed combination product.

The Sponsor acknowledged that the current formulation was not bioequivalent to Cialis and stated that the product had been originally designed (b) (4) *The Sponsor also stated that they intend to re-formulate the product and conduct a new comparative bioavailability study as requested.*

Question 4:

(b) (4)

FDA Response to Question 4:

No. A final decision will be made upon reviewing all data contained in your NDA submission. In addition, the effect of food on the bioavailability of your drug product should be considered in determining whether the safety can be supported.

Additional meeting discussion

Refer to Question 3 additional meeting discussion.

Question 5: Veru intends to run a comparative bioavailability study to assess the effect of food on the pharmacokinetics of the to-be-marketed formulation of Tadalafil/Finasteride Combination (b) (4) from the combination product prior to the submission of the proposed NDA. Veru intends for the completed bioavailability study and the separate food effect study will be the only clinical pharmacology and biopharmaceutics studies presented in the proposed NDA.

It is recognized that the food effect data are not available at this point. However, does the Agency agree that the two assessments (BE study and Food Effect Study) will be only clinical pharmacology and biopharmaceutics studies required to support the proposed NDA?

FDA Response to Question 5:

No, we do not agree. The results from your relative bioavailability study did not establish an acceptable bridge for your combination product to one of the listed drugs to support the efficacy of your drug product. See Response to Questions 3 and 4.

Additional meeting discussion

Refer to Question 3 additional meeting discussion.

CLINICAL

Question 6: Veru proposes that demonstrated BE in extent of absorption between the proposed Tadalafil/Finasteride Combination Oral capsule product and Cialis and Proscar administered together establishes a scientific bridge to FDA's previous findings of clinical safety and efficacy for tadalafil and finasteride for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH), as reflected in the approved Cialis labeling (Eli Lilly and Company, 2017). Veru intends to rely upon this information for the approval of the proposed Tadalafil/Finasteride Combination (b) (4) product NDA, and the Sponsor does not intend to conduct any additional clinical studies.

Combination Therapy of the LDs

a. **Efficacy**: For the indication of treatment of signs and symptoms of BPH, tadalafil initiated together with finasteride was evaluated in a 26-week, double-blind, parallel-design study and was shown to be effective in treating the signs and symptoms of BPH in men with an enlarged prostate. Patients were treated with either 5 mg tadalafil + 5 mg finasteride (n = 345), or placebo + 5 mg finasteride (n = 350).

b. **Safety:** A total of 548 subjects received the combination of tadalafil + finasteride in clinical trials that were reported in the prescribing information for the LD (Cialis). Three hundred forty-five (345) of these patients were from the 26-week efficacy study outlined above, and 203 patients were from a separate study in patients who had erectile dysfunction and BPH at baseline. It is important to note that the Sponsor is not seeking an erectile dysfunction indication. However, the safety information from this study, in which tadalafil + finasteride (n = 203) was compared with placebo + finasteride (n = 201), is included in the prescribing information of the LD (Cialis) and will be included in the NDA.

Monotherapy of the LDs

c. The use of tadalafil alone in the treatment of BPH was evaluated in three 12-week, randomized, multinational, double-blind, placebo-controlled, parallel-design efficacy and safety studies. Two studies were conducted in men who had BPH only; the first study randomized 1,058 patients to receive either tadalafil (at 2.5, 5, 10, or 20 mg) or placebo for qd use; the second study randomized 325 patients to receive either tadalafil 5 mg or placebo for qd use. The third study was in men with BPH and erectile dysfunction; in this study, only a 5 mg tadalafil dose (n = 206, 5 mg tadalafil; n = 193, placebo) (Eli Lilly and Company, 2017) was evaluated.

d. The use of Proscar was evaluated in the Proscar Long-Term Efficacy and Safety Study (PLESS), a double-blind, randomized, placebo-controlled, 4-year, multicenter study. There were 3,040 patients from ages 45 to 78 years, with moderate-to-severe BPH symptoms and an enlarged prostate with digital rectal examination (n = 1524 finasteride, n = 1516 placebo); 3,016 patients were evaluable for efficacy. A total of

1,883 patients completed the 4-year study (1000 in the finasteride group, and 883 in the placebo group) (Merck and Co. Inc., 2013).

e. Adverse events (AEs) related to the use of tadalafil and finasteride in clinical trials and AEs from postmarketing experience have been well-documented in the Cialis and Proscar approved labeling, respectively. In addition, Veru will perform a search of the published literature and the FDA Adverse Event Reports System (FAERS) database to identify any other safety signals.

Does the Agency agree that, the demonstrated BE of rate and extent of absorption of finasteride and extent of absorption of tadalafil and the slower rate of absorption of tadalafil, are an appropriate bridge to the efficacy and safety of the co-administered LDs and that no additional clinical efficacy and safety studies are required to support the NDA of the proposed Tadalafil/Finasteride Combination (b) (4) product for treatment of the signs and symptoms of BPH with up to 26 weeks of treatment?

FDA Response to Question 6:
No. Your BA/BE study did not establish a bridge between your proposed fixed dose combination product and one of the listed drugs. Additionally, your food effect study has not been completed (see our responses to questions 3, 4, and 5).

Additional meeting discussion
Refer to Question 3 additional meeting discussion.

Question 7: Tadalafil has been approved since 2011 and finasteride has been approved since 1992 for the treatment of the signs and symptoms of BPH. The labeling for Cialis was changed to add the coadministration of tadalafil and finasteride in October 2014. To support the safety of the proposed Tadalafil/Finasteride Combination (b) (4), in accordance with the Agency's PIND comments, Veru intends to conduct a search of the FDA's FAERS database from October 2014 until 3 months prior to submission of the proposed NDA. The review will focus on the AEs of back pain, headache, dyspepsia, influenza, diarrhea, nasopharyngitis, pain in extremity, gastric pH decrease, and hypertension of tadalafil alone, finasteride alone, and tadalafil + finasteride given in combination. Additionally, a summary of the Serious Adverse Events observed over the time period will also be presented.

Does the Agency agree that the proposed analysis of postmarketing safety information is sufficient to support the proposed NDA for Tadalafil/Finasteride Combination (b) (4) for review?

FDA Response to Question 7:
Yes. We also request that your 120-day safety update include an additional search of the FAERS database for the time period starting after the data lock date for the original search.

Additional Meeting Discussion
No further discussion required.

Question 8: Veru proposes that since no clinical efficacy and safety studies will have been conducted with the Tadalafil/Finasteride Combination (b) (4), an integrated summary of safety (ISS) and an integrated summary of efficacy (ISE) will not be submitted in the NDA.

Does the Agency agree that an ISS and ISE will not be required for the proposed NDA?

FDA Response to Question 8:
No. For an NDA submission, your application must include an ISE and ISS. We recognize that these integrated summaries will be limited due to the data being submitted in the NDA. The ISE may consist of a clinical narrative or a descriptive summary of studies you have conducted that presents study design, clinical outcomes, and other key findings. The ISS should include an integrated assessment of the totality of safety information being submitted (e.g. safety information from the labeling for the LDs, safety data from the studies that you conducted, postmarketing data from the FAERS database search that you conducted, and safety information and/or data available in the literature).

Additional clinical comment:
We note that on page 22 of your meeting package you state that "A total of 548 subjects received the combination of tadalafil + finasteride in clinical trials that were reported in the prescribing information for the LD (Cialis). Three hundred forty-five (345) of these patients were from the 26-week efficacy study outlined above, and 203 patients were from a separate study in patients who had erectile dysfunction (ED) and BPH at baseline." These 203 subjects treated with tadalafil + finasteride referenced above were not treated in a separate study but were a subgroup of the 345 tadalafil + finasteride subjects treated in the 26- week study who reported having ED at baseline. Clarify this apparent discrepancy of information in future submissions.

Veru Response to Question 8
No further discussion required.

NONCLINICAL

Question 9: Veru intends to rely upon the nonclinical information in the approved labeling of the LDs, Cialis (tadalafil) Tablets, for oral use (5 mg; NDA 021368, Eli Lily and Co.) and Proscar (finasteride) Tablets (5 mg; NDA 020180, Merck and Co. Inc.), with nonclinical information from the published literature, to support the approval of the proposed Tadalafil/Finasteride Combination (b) (4) product NDA. Veru proposes that demonstration of BE between the proposed Tadalafil/Finasteride Combination (b) (4) and the LDs, Cialis and Proscar, will establish a scientific bridge to allow reliance on FDA's previous findings of nonclinical safety and efficacy for tadalafil and finasteride, as reflected in the Cialis and Proscar approved labeling (Merck and Co. Inc., 2013; Eli Lilly and Company, 2017). Nonclinical studies conducted for the approval of Cialis included carcinogenesis, mutagenesis, and impairment of fertility; animal toxicology and pharmacology and carcinogenesis, mutagenesis, and impairment of fertility studies were conducted for the approval of Proscar. No additional nonclinical studies are planned. In

addition, no novel excipients will be utilized in the proposed formulation of the Tadalafil/Finasteride Combination (b) (4)

Based on the scientific bridge established with the completed comparative bioavailability study, does the Agency agree that no additional nonclinical efficacy and safety studies will be required to support the NDA for Tadalafil/Finasteride Combination (b) (4)

FDA Response to Question 9:
Pending the establishment of an adequate bridge between your tadalafil/finasteride combination oral capsule and one or more US approved listed drug products, reliance on the Agency's previous findings of safety to support the nonclinical section of your NDA is appropriate. The adequacy of submitted literature in support of your NDA to support safety will be a review issue.

Additional meeting discussion
Refer to Question 3 additional meeting discussion.

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

Question 10: The Tadalafil/Finasteride Combination (b) (4) is being developed in 5 mg tadalafil and 5 mg finasteride dosage strengths. The final formulation of the Tadalafil/Finasteride Combination (b) (4) is:

Table 1 Formulation

Ingredient/Component	Composition % w/v	Amount/Tablet (mg)
Tadalafil USP (b) (4)	(b) (4)	5.0
Finasteride USP (b) (4)	(b) (4)	5.0
(b) (4) (Silicified Microcrystalline Cellulose, NF)	(b) (4)	
Lactose Monohydrate, NF (b) (4)		
Sodium Starch Glycolate, (b) (4) NF, Ph.Eur, JP (b) (4)		
Sodium Lauryl Sulfate, NF (b) (4)		
Colloidal Silicon Dioxide, NF EP JP (b) (4)		
Magnesium Stearate, NF (b) (4)		
TOTAL	100.0	200.0

The proposed formulation for Tadalafil/Finasteride Combination (b) (4) does not contain any novel excipients, and the levels of the excipients fall within the acceptable ranges of these excipients in the IID. Therefore, Veru proposes that no additional nonclinical studies are required to support the safety of the excipients in the planned NDA. Does the Agency agree?

FDA Response to Question 10:
We agree, provided that there are no further formulation changes and no new impurities identified in the combination product. Impurities should meet the criteria established in ICH Q3A and ICHQ3B guidances. Also, see the response to question 11 regarding specifications.

Additional Meeting Discussion
No further discussion required.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Question 11: The tadalafil and finasteride drug substances used in the Tadalafil/Finasteride Combination (b) (4) conform to United States Pharmacopeia (USP) specifications.

Does the Agency agree that the proposed drug product specifications are appropriate for submission of the Tadalafil/Finasteride Combination (b) (4) NDA for review?

FDA Response to Question 11:
No. The drug product specification should include a test for content uniformity. Each active ingredient should be identified by two complementary or orthogonal methods. Per USP Chapter <1111> Microbiological Examination of Nonsterile Products: Acceptance Criteria For Pharmaceutical Preparations And Substances For Pharmaceutical Use, the requirements for bioburden control should include the absence of *Escherichia coli*. Additional tests such as moisture content may be warranted.

Complete drug substance information should be provided either in the application or in Drug Master Files (DMFs) with the appropriate Letters of Authorization. If information is provided in a DMF, provide the following information in your NDA for ease of review: General information, physico-chemical properties, and Specifications. Submit Certificates of Analysis for each of the drug substances.

As previously stated in the written response only (WRO) correspondence on November, 21, 2017, USP standards are the minimum standards and specifications for both drug substances that should be set based on the ICH Q6A guidance on Specifications: (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q6a-specifications-test-procedures-and-acceptance-criteria-new-drug-substances-and-new-drug-products).

Additionally, your submission should include data demonstrating that the selected dissolution method(s) is/are appropriate for your drug product. Demonstrate the

discriminating/biopredictive ability of the proposed dissolution method(s). Provide the dissolution method development and validation report supporting the selection of the proposed dissolution test(s) and dissolution data for the clinical batches and registration batches in your NDA submission.

For immediate release products, the selection of the acceptance criteria sampling time point should be where Q= (b) (4)% dissolution occurs. Also refer to our additional comments in the written responses only correspondence dated November 21, 2017.

The overall suitability of the drug substance and drug product specifications, including acceptance criteria, will be determined based on the totality of information submitted in the NDA.

Additional Meeting Discussion
No further discussion required.

Question 12: At the time of the NDA submission, Veru proposes to have (b) (4)months (b) (4) stability and 6 months of stability under accelerated conditions. Veru understands that this will only allow for a (b) (4)month expiry to be granted for the product and is willing to accept this expiry for the product.

Does the Agency agree tha (b) (4)months of stability at standard temperatures (25°C/60% RH) and 6 months of stability under accelerated conditions (40°C/75%RH) will support the NDA filing?

FDA Response to Question 12:
No. The NDA should be complete at the time of submission and include at least 12 months of long-term stability data and 6 months of accelerated stability data from three registration batches.

Additional meeting discussion
FDA reiterated that at least 12-months long-term stability data for three registration batches should be provided in the initial NDA submission.

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.

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* (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.

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.

ACTION ITEMS

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Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	June 22, 2019

ATTACHMENTS AND HANDOUTS
Sponsor's Response to FDA's Preliminary Responses.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SURESH KAUL
06/18/2019 12:02:09 PM