CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216655Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 216655

REFUSAL TO FILE

Xiamen LP Pharmaceutical Co., Ltd.
C/O LP Pharmaceuticals, Inc. (USA)
Attention: Matthew Nieder, PhD
President
LP Pharmaceuticals, Inc
1633 Bayshore Hwy, Suite 280
Burlingame, CA 94010

Dear Dr. Nieder:

Please refer to your new drug application (NDA) dated and received August 24, 2022, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for aripiprazole oral soluble film.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d)) for the following reasons:

Chemistry, Manufacturing, and Controls

The proposed product does not include imprinting. The drug product must be marked or imprinted with a code as per 21 CFR 206.10, which states that "no drug product in solid oral dosage form may be introduced or delivered for introduction into interstate commerce unless it is clearly marked or imprinted with a code imprint, that, in conjunction with the product's size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product." See the guidance for industry, *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016), for more information on imprinting for solid oral dosage forms.

To support the change in the product the following information is required at a minimum:

- Provide adequate information about composition and safety of the imprinting/marking ink solution with respect to the total daily intake.

- Include acceptance criteria for the imprinting/marking on the film in the Appearance test of the proposed product specification.

- Update the 356(h) and all relevant sections of the application to include the manufacturing facility(ies) responsible for imprinting. Ensure that all facilities remain ready for the commercial production and inspection.

- Manufacture a minimum of one batch for each strength (no less than 1/10 of the commercial scale) of imprinted/marked films using the commercial manufacturing process and control strategy and provide the following information:

  - The batch records in 3.2.R of the NDA application as the representative of commercial batch production.

  - At least 6 months of long-term and accelerated stability data of the above mentioned batches of imprinted/marked films of each strength and commit to continue stability testing of these batches up to the proposed expiry and submit the remainder of the stability data in the annual reports.

- Data demonstrating that the imprinted/marked films meet the proposed drug product specification at release and on stability

- Data demonstrating that the imprinted/marked film has comparable drug release, film strength, and film integrity to the non-imprinted/non-marked film at release and on stability

Clinical

Under the Food and Drug Administration Safety and Innovation Act (FDASIA), any sponsor who submits a marketing application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an initial Pediatric Study Plan (iPSP) no later than 60 calendar days after the date of an EOP2 meeting, or such other time as may be agreed upon between the Secretary and the applicant [505B(a) and (e) of the FD&C Act]. In the absence of an EOP2 meeting, and in cases where a phase 3 study or a combined phase 2/3 study will not be conducted, sponsors should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted.

We note that you failed to submit an iPSP prior to the submission of your marketing application. Submit your iPSP to your IND with a cross-reference letter to the IND to which you have submitted your protocol(s) and clearly mark your submission as **"INITIAL PEDIATRIC STUDY PLAN"** in large font, bolded type at the beginning of the cover letter of the submission.

The iPSP must include 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 [505B(e)(2)(B)]. In addition, FDA has published the guidance for industry *Pediatric Study Plans: Content of*

and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans available on FDA.gov.[1] A PSP template is available on FDA's website.[2] If you have questions regarding the process for submission of an iPSP submission, you may contact the Division of Pediatric and Maternal Health at 301-796-2200. If you have questions about other clinical development issues, you may contact the Division of Psychiatry.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted:

- A preliminary review identified several items in your proposed Prescribing Information (PI) that are inconsistent with labeling regulations and guidances.

  For example, the PI must contain a summary of the essential scientific information needed for the safe and effective use of the drug being labeled (the "subject drug") [see 21 CFR 201.56(a)(1)]. However, we note that:

  - Your product is only available in 5-mg and 10-mg dosage strengths while the starting dosage for some of the proposed indications or populations is 2 mg. There are no instructions regarding how to initiate your product in those circumstances.

  - There are no administration instructions included in the Dosage and Administration section.

- Labeling for a drug submitted under a 505(b)(2) application does not need to be identical to the PI for a listed drug submitted under a 505(b)(1) application. The PI for the 505(b)(2) drug must meet all labeling regulatory requirements, should be consistent with labeling guidance recommendations, and must reflect currently available information needed for safe and effective use of the 505(b)(2) drug. Thus, you should revise your proposed PI for your subject drug accordingly.

- We suggest that you refer to FDA's Labeling Resources for Human Prescription Drugs – For Industry for additional information and guidance in developing your product labeling.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[2] https://www.fda.gov/media/84944/download

this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

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

PROPOSED PROPRIETARY NAME

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

If you have any questions, call Shin-Ye Sandy Chang, at 301-796-3971, or email shinye.chang@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

BERNARD A FISCHER on behalf of TIFFANY R FARCHIONE
10/21/2022 02:06:33 PM

IND 150931

MEETING PRELIMINARY COMMENTS

Xiamen LP Pharmaceutical Co., Ltd.
C/O LP Pharmaceuticals, Inc.
Attention: Matthew Nieder, PhD
1633 Bayshore Hwy, Suite 280
Burlingame, CA 94010

Dear Dr. Nieder:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LP088 (aripiprazole oral soluble film).

We also refer to your correspondence, dated and received June 25, 2021, requesting a meeting to discuss the format and content of a future NDA submission, a biowaiver request for the lower strength (5 mg) of LP088, and the justification for not studying the impact of water on drug absorption with LP088.

Our preliminary responses to your meeting questions are enclosed.

You should provide me with a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

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

If you have any questions, call me at (301) 796-3971, or email shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Shin-Ye Sandy Chang, PharmD
Regulatory Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 25, 2021; 11:00 AM to 12:00 PM (EDT)
Meeting Location: Teleconference

Application Number: 150931
Product Name: LP088 (aripiprazole oral soluble film)
Indication: Schizophrenia, (b) (4) adjunctive treatment of major depressive disorder
Sponsor Name: Xiamen LP Pharmaceutical Co., Ltd.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Tiffany R. Farchione, MD	Director, Division of Psychiatry (DP)
Bernard Fischer, MD	Deputy Director, DP
Jean Kim, MD	Clinical Team Lead, DP
Michelle Horner, MD	Clinical Reviewer, DP
Luning (Ada) Zhuang, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Li Tan, PhD	Clinical Pharmacology Reviewer, OCP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, Division of Pharmacology/Toxicology for Neuroscience (DPT-N)
Sonia Tabacova, PhD	Pharmacology/Toxicology Reviewer, DPT-N
Peiling Yang, PhD	Biometrics Team Leader, Division of Biometrics I (DBI) Biometrics Reviewer, DBI
Ta-Chen Wu, PhD	Biopharmaceutics Team Leader, Division of Biopharmaceutics (DBP)
Kamrun Nahar, PhD	Biopharmaceutics Reviewer, DBP
Richard Ishihara, MEM	Regulatory Policy Advisor, Office of New Drugs Policy
Shin-Ye Chang, PharmD	Senior Regulatory Project Manager, Division of Regulatory Operations for Neuroscience (DRON), Psychiatry Group

SPONSOR ATTENDEES

Dr. Ying Ye	CEO
Dr. Haijian Zhu	President

Dr. Linhui Cai	Clinical Director
(b) (4)	Clinical Pharmacology and Regulatory Consultant
Dr. Matthew Nieder	US Regulatory Agent for Xiamen LP Pharmaceutical Co., Ltd.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 25, 2021, 11:00 AM, teleconference between Xiamen LP Pharmaceutical Co., Ltd. and the Division of Psychiatry. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0. BACKGROUND

The Sponsor is developing LP088, an oral soluble film (OSF) formulation of aripiprazole, and plans to submit a new drug application (NDA) using the 505(b)(2) pathway relying on Abilify tablets (NDA 021436) as the listed drug (LD). Aripiprazole is an atypical antipsychotic indicated for: (1) schizophrenia; (2) acute treatment of manic and mixed episodes associated with bipolar I disorder; (3) adjunctive treatment of major depressive disorder; (4) irritability associated with autistic disorder; and (5) Tourette's disorder. The Sponsor believes that an OSF would provide an alternative formulation of aripiprazole for the elderly and patients who have difficulty swallowing the tablet.

The Sponsor submitted two IND-opening bioequivalence (BE) protocols (Studies LP088-20-09 and LP088-20-10) on August 11, 2020. The Division recommended that the Sponsor conduct a three-arm crossover design study to test the impact of water on drug absorption, because the Sponsor planned to give water before drug administration. The Division also recommended that the Sponsor monitor for acute dystonic reactions and describe their plan for treating them during the studies. Additionally, the Division suggested that severe mouth or tongue lesions occurring in any patient after

administration of aripiprazole OSF should result in stopping of the study and submission to FDA of a 15-Day IND Safety Report. The chemistry, manufacturing, and controls (CMC) team asked the Sponsor to develop and implement a control strategy for elemental impurities or provide justification for why such strategies are not needed.

The Sponsor states that their study results demonstrate that LP088 at 10 mg has comparable bioavailability to the LD at 10 mg under both fasting and fed conditions and that they intend to file a 505(b)(2) application. The Sponsor requested this Type B pre-NDA to seek the Division's concurrence that no further studies are needed, including the previously requested studies for potential water impact on drug absorption. Additionally, the Sponsor wishes to pursue a biowaiver for in vivo BE studies for approval of the lower strength (5 mg) of LP088.

2.0. DISCUSSION

2.1. CLINICAL

Question 1: Based on the results of two bioequivalence studies, Aripiprazole Oral Soluble Film 10 mg is bioequivalent to ABILIFY® Aripiprazole Tables 10 mg under fasting and fed conditions based upon the finding that the 90% confidence intervals for T: R for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} are contained within the range of 80.00% - 125.00%. A single oral dose of aripiprazole 10 mg was generally safe and well-tolerated in healthy adult male and female population. All AEs reported during the study were mild or moderate in intensity. There were no serious or unexpected adverse events reported during the study.

The goal of LP088 (Aripiprazole Oral Soluble Film) is to achieve bioequivalence to ABILIFY® (aripiprazole) Tablets which was demonstrated to be safe and effective for the approved indications.

Pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, LP088 will be a 505(b)(2) application for aripiprazole with a new formulation. We intend to rely on the safety and effectiveness findings of ABILIY® (aripiprazole) Tablets. No further clinical studies would be needed for the approval of LP088 505(b)(2) NDA.

In principle, does the Division concur that satisfactory outcomes of two bioequivalence studies of LP088 warrant clinical evidence to support the LP088 505b(2) NDA for the same indications as ABILIY® (aripiprazole) Tablets for the adult indications?

> ***FDA Response to Question 1:*** *If your results indicate that criteria are met for comparative bioavailability between LP088 and the LD under both fasted and fed conditions, we agree that your two studies could be used to support a 505(b)(2) NDA submission for LP088. However, Division concurrence would be a matter of review*

after submission; see our responses below for additional comments about your planned 505(b)(2) submission.

2.2. CLINICAL PHARMACOLOGY

Question 2: LP Pharma's Aripiprazole Oral Soluble Film is formulated in two strengths, 5 mg and 10 mg. The in vivo bioequivalence study was performed on 10 mg strength and LP product was found to be bioequivalent to the corresponding Reference Listed Drug of ABILIFY® 10mg Tablets.

We would like to request a biowaiver for in vivo bioequivalence studies of a low strength (5 mg) Aripiprazole Oral Soluble Film.

The justification of this biowaiver is based upon the identical composition/formulations between the two strengths, bioequivalence of the LP Pharma's Aripiprazole Oral Soluble Films 10 mg and ABILIFY® 10mg Tablets and results in a comparative pH dissolution study of 5 mg with 10 mg (bio-strength) of LP Pharma's product.

Does the Division concur with the rationale for the biowaiver request?

FDA Response to Question 2: *The following should be included in your NDA submission to request a biowaiver for LP088 5 mg:*

- *A formal biowaiver request for the proposed 5-mg strength of LP088*
- *An acceptable comparative bioavailability study with the 10-mg strength of LP088 and the LD*
- *Support that the formulation of the lower strength is proportionally similar in active and inactive ingredients to the corresponding highest strength with which the comparative bioavailability study was conducted*
- *Support that all the strengths are the same dosage form and have the same release mechanism and manufacturing process*
- *Dissolution profile comparisons between the highest and lower strengths meet the f2 similarity requirements in three different pH media (i.e., pH 1.2, 4.5, and 6.8), using the Similarity Factor f2 for the profile comparison*
- *Evidence of PK linear kinetics over the proposed dose range*

Whether to grant the biowaiver request would be determined at the NDA stage based on the totality of the supporting data provided.

In addition, we note that you have not provided sufficient information regarding the in vitro drug release method in the meeting package. We do not believe that the dissolution test condition you employed for the purpose of a biowaiver is justified or clinically relevant. In support of your planned NDA, you should develop a suitable drug release/dissolution method for the proposed drug product as quality control for batch release and stability testing. The selection of the proposed method and test conditions/parameters should be adequately justified and discriminating toward critical bioavailability attributes.

Question 3: We would like to discuss the potential for water impact on drug absorption of LP088. As inquired by the Division in the May Proceed Letter (October 6, 2020), the impact of water on drug absorption needs to be addressed. As we presented the justification that there is little impact of water on the drug absorption of LP088, does the Division concur with our conclusion?

FDA Response to Question 3: *Water impact is a product/formulation specific concern. Water impact on other products/formulations may not be applicable to your product. However, whether an additional water impact study is needed would be determined based on review of the totality of the data —we encourage you provide the justification (in vivo and in vitro data of your product) in the NDA submission.*

2.3. NONCLINICAL

Question 4: The proposed strengths of Aripiprazole Oral Soluble Film are 5 mg and 10 mg, which are consistent with recommended dosage and administration for indications of schizophrenia, bipolar mania, major depressive disorder in adult patients in the ABILIFY® label. The proposed indications for Aripiprazole Oral Soluble Film are treatment of schizophrenia, (b) (4) and major depressive disorder in adult patients. The proposed dosing recommendation is the same as that approved for the tablet formulation.

LP088 (Aripiprazole Oral Soluble Film) achieved bioequivalence to ABILIFY® (aripiprazole) tablets which was demonstrated to be safe and effective for the approved indications.

All impurities and residual solvent(s) in the drug substance and all impurities in the LP088 drug product are below qualification levels as defined in ICH Q3A, Q3B and Q3C guidelines. All excipients used in LP088 are listed as known inactive pharmaceutical ingredients and the quantities do not exceed amounts used in FDA approved oral drug products based on the FDA Inactive Ingredient Database.

We intend to rely on the nonclinical findings of ABILIY® (aripiprazole) Tablets, no nonclinical study is warranted.

Dose the Division concur that no nonclinical study is needed to support the LP088 505b(2) NDA, and reference to the package insert information on the nonclinical findings of ABILIY® (aripiprazole) Tablets to support non-clinical study requirements?

> ***FDA Response to Question 4:*** *Based on the information provided in the briefing package, additional nonclinical studies do not appear to be needed; however, the final determination would be a matter of review after submission of the NDA and assessment of the adequacy of the comparative bioavailability study. Additional nonclinical studies may be needed if new or higher amounts of impurities or degradation products are identified that exceed the specification in drug substance/drug product or contain a structural alert for mutagenicity. Refer to ICH M3(R2), and ICH M7(R1), ICH Q3A, and ICH Q3B for more information.*

3.0. OTHER

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*.[1] 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.[2]

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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,

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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).[1] 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

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[7] http://www.regulations.gov

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring*

(BIMO) Inspections for CDER Submissions (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

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

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/

SHIN-YE CHANG
08/16/2021 01:38:47 PM