CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212895Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124947

MEETING MINUTES

CSPC Ouyi Pharmaceutical Company, Ltd.
c/o Conjupro Biotherapeutics, Inc.
Attention: Xi-De Wang, PhD, MS, RAC
Senior Director, Regulatory Affairs
302 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Dr. Wang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for levoamlodipine maleate.

We also refer to the meeting between representatives of your firm and the FDA on October 11, 2018. The purpose of the meeting was to discuss your plan to submit an NDA for levoamlodipine maleate for the treatment of hypertension.

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

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 11, 2018, 1:00 PM – 2:00 PM
Meeting Location:	White Oak Building 22, Conference Room: 1309
Application Number:	IND 124947
Product Name:	levoamlodipine maleate
Proposed indication:	Treatment of hypertension
Sponsor Name:	CSPC Ouyi Pharmaceutical Company, Ltd.
Meeting Chair:	Norman Stockbridge, MD, PhD
Meeting Recorder:	Sabry Soukehal

FDA ATTENDEES

*Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Martin Rose, MD, JD	Clinical Team Leader
Maryann Gordon, MD	Clinical Reviewer
Xuan Chi, PhD	Acting Non-Clinical Team Leader
Philip Gatti, PhD	Non-Clinical Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Sabry Soukehal	Regulatory Health Project Manager

*Office of Clinical Pharmacology

Martina Sahre, PhD	Clinical Pharmacology Team Leader (Acting)
Xiaolei Pan, PhD	Clinical Pharmacology Reviewer

*Office of Pharmaceutical Quality

Mariappan Chelliah, PhD	CMC Reviewer

*Office of Management, Division of User Fee Management and Budget Formulation

Chaltu Wakijra, PharmD	Prescription Drug User Fee Staff

SPONSOR ATTENDEES

Xi-De Wang, PhD, RAC	Senior Director, Regulatory Affairs, CSPC-Conjupro Biotherapeutics
Simon Li. MD, PhD	CMO, CSPC
Ronald Walls, MD	VP, Clinical Development, CSPC-Conjupro Biotherapeutics
Tao Wang	President, CSPC Ouyi Pharmaceutical
Yinlian Li	CMC, CSPC Ouyi Pharmaceutical
Li Zhang	Clinical project manager, CSPC
Lan Lan, PhD	Clinical project manager, CSPC-Conjupro Biotherapeutics
(b) (4)	Regulatory Strategist, CSPC Consultant
(b) (4)	Biostatistician, CSPC Consultant
(b) (4)	CMC, CSPC Consultant
(b) (4)	Clinical Pharmacology, CSPC Consultant
(b) (4)	Clinical Pharmacology, CSPC Consultant

1.0 BACKGROUND

CSPC Ouyi Pharmaceutical Co., Ltd, (the Sponsor) is developing levoamlodipine maleate, the purified (S) isomer of the calcium channel blocker amlodipine for the treatment of hypertension, (b) (4) However, in the initial NDA, the Sponsor is seeking the hypertension indication only. The planned tablet strengths are 1.25, 2.5, and 5 mg, to be given once daily. The Sponsor intends to submit a New Drug Application under the 505(b)(2) pathway, where NORVASC® (amlodipine besylate – NDA 019787) is the reference listed drug.

To support a marketing application in the US, the Sponsor completed one pilot relative bioavailability study (Protocol No. 73912) and is conducting a pivotal relative bioavailability study entitled "A Pilot, Open-Label, Randomized, Single Dose, Two-Way Crossover Relative Bioavailability Study of Levoamlodipine Maleate Tablet, 2.5 mg Compared to NORVASC® Tablet, 5 mg in Healthy Subjects under Fasting Conditions" (Protocol No. LAM-US-101). The primary objective of the study is to assess the relative bioavailability of the 2.5 mg levoamlodipine maleate tablet compared to the 5 mg NORVASC® tablet in 8 healthy adult subjects under fasted conditions.

Additionally, based on the Agency's feedback provided on April 28, 2017 (see minutes dated 05/16/2017, reference ID 4098978), the Sponsor is conducting a study entitled "A Randomized, Open-label, Single-Dose, Two-Way Crossover Study to Assess the Relative Bioavailability of 5 mg of Levoamlodipine Maleate Tablets versus 10 mg of Amlodipine Besylate Tablet (NORVASC®) in Healthy Subjects Followed by a Phase to Study Food Effect on the PK Profile of Levoamlodipine". The objectives of this study are (1) to assess the relative bioavailability of a single oral dose of either 5 mg of Levoamlodipine Maleate tablets or 10 mg of Amlodipine Besylate tablet (NORVASC®) under fasting condition in male and female healthy subjects; and (2) to evaluate food effect on the PK profile of Levoamlodipine Maleate tablets.

To address the safety and efficacy of Levoamlodipine Maleate tablets, the Sponsor plans to rely on the Agency's previous findings of safety and efficacy for NORVASC®.

The stated objectives of this meeting were to:

1. Gain Agency's concurrence and feedback on the PK Analysis Plan for the ongoing BA study which will be the pivotal data of the 505(b)(2) NDA.
2. Gain Agency's concurrence on the content and format of the NDA for levoamlodipine to support an indication mirroring the hypertension claims of NORVASC®, using the 505(b)(2) pathway.
3. Seek Agency's guidance on an expanded safety claim for levoamlodipine, whether data from legacy studies and literature will support inclusion in the initial NDA, or what additional information would need to be included in an sNDA supporting this label expansion.

FDA sent Preliminary Comments to CSPC Ouyi Pharmaceutical Company, Ltd. on October 5, 2018.

2.0 DISCUSSION

2.1. CHEMISTRY, MANUFACTURING, AND CONTROLS

Question 1: To support the NDA in the US, we have added a new manufacturer facility of (b) (4) for the active pharmaceutical ingredient amlodipine base. (b) (4) has an active DMF (# (b) (4)) with the Agency and per manufacturer this DMF has supported a US NDA (or ANDA) for amlodipine besylate. (b) (4) confirmed the regulatory starting material for amlodipine base (b) (4) and the manufacturing from the starting material to amlodipine base are all in compliance with GMP. The Sponsor Ouyi Pharmaceutical will submit a Letter of Authorization from (b) (4) permitting reference to DMF# (b) (4) for manufacturing of Amlodipine, in our NDA. Does the Agency agree with this plan?

FDA Response: We agree with your plan to reference DMF # (b) (4) for the manufacture of the (b) (4) amlodipine base. Your application should include the specification (b) (4) In addition, provide in your application comparative impurity profiles (numerical results and chromatograms) of three batches of (b) (4) amlodipine base (b) (4) and three batches (b) (4) from the previous manufacturer (i.e., that was used to produce the drug substance formulated in pivotal biobatches supporting your application). The impurity comparison should include impurities covered by ICH M7, ICH Q3C, and ICH Q3D. Any new impurity above the ICH Q3A (current revision) reporting threshold should be evaluated and its control strategy discussed in your application.

***Sponsor Response**: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

Question 2: At the NDA submission, the Sponsor plans to include 9 months stability data (at 25^{0}C/60%RH) and 6 months accelerated stability data (at 40^{0}C/75%RH) and a stability protocol. At day 90 after submission, 12 months stability data (at 25^{0}C/60%RH) will be submitted for review. 24 months stability data will be submitted when they become available. Does the Agency

agree that the proposed stability programs of drug product are sufficient to support the NDA of levoamlodipine maleate tablet?

FDA Response: We do not agree. In accordance with ICH Q1A(R2), provide at least 12 months of long-term and 6 months of accelerated stability data for the drug product at the time of NDA submission.

***Sponsor Response**: The Sponsor agrees to provide 12-month long term (LT) and 6-month accelerated stability for NDA review. As was discussed in Sep 2017 (Ref ID: 4146158), 9-month LT and 6-month accelerated stability data for the clinical batch will be provided upon NDA submission. At 3 months post-NDA submission, the outstanding 12-month LT stability will be submitted for review. Additionally, 36-month LT stability data generated in China will be provided at the time of submission for 3 batches manufactured with the same formulation, same manufacturing process, same production line in support of the stability of the product.*

Does the Agency concur that the aforementioned stability data plan complies with our past discussion and expectations?

Meeting discussion: The Agency accepted the Sponsor's proposal to submit the NDA with 9-month long-term and 6-month accelerated stability data provided the remaining long-term stability data is submitted 3 months after receipt of the NDA.

2.2. NONCLINICAL

Question 3: Levoamlodipine maleate is designed to be equipotent to the reference listed drug NORVASC, with the inactive enantiomer removed, for hypertension. As indicated by the Agency in the Type C meeting conducted with the Sponsor on April 28, 2017 that "Years of post-marketing experience with amlodipine have confirmed its safety profile and removing one enantiomer is unlikely to result in new safety concerns, and that "no-further nonclinical pharmacology and toxicology studies are necessary for 505(b)(2) application", our NDA would rely on Agency's prior findings for the safety of the reference listed drug. Supportive of the antihypertensive effect of levoamlodipine, two legacy pharmacology reports that were previously submitted to the IND (#124947) will be submitted with the NDA. One safety pharmacology study, one single-dose acute toxicity study and one 6-week repeat-dose toxicology study previously submitted to the IND will be submitted with the NDA. No other PK and toxicology study reports will be included. Does the Agency agree with the plan regarding nonclinical study reports?

FDA Response: Yes, we agree with the plan regarding nonclinical study reports. Please include the study report of the repeat-dose toxicology study of levoamlodipine in dogs that you performed.

***Sponsor Response**: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

2.3. CLINICAL PHARMACOLOGY/CLINICAL

Question 4: Following discussion with the Agency on April 28, 2017 and subsequent correspondences regarding protocol amendment, we have finalized the protocol for the pivotal BA study including food effect and have initiated the pivotal study. The study is expected to complete by the end of September 2018. This is the pivotal study intended to support this 505(b)(2) NDA submission. The PK Analysis Plan (PKAP) for the pivotal BA study including statistical analysis for BE assessment is included in the Briefing Document for the Agency's review. As a note, the original China BA study legacy report and US pilot BA study report will be also included as supportive evidence for the NDA but datasets will not be included. Does the Agency agree with the submission plan and the PKAP for the pivotal study to demonstrate the BE between the administration of levoamlodipine and equipotent dose of racemic amlodipine?

FDA Response: Yes, your PK analysis plan appears to be adequate.

Sponsor Response*: Thank you for this response. The Sponsor understands that this includes concurrence with the current pharmacokinetic analysis plan including the statistical analysis for bioequivalence assessment. No discussion is requested at the meeting.*

Meeting discussion: The Agency confirmed its concurrence with the Sponsor's PK analysis plan.

Question 5: Regarding the pivotal BA study, datasets will be built in SAS, and both SDTM and ADaM will be submitted as SAS datasets. Do you agree with this plan?

FDA Response: Yes, we agree with your plan for dataset submission. In addition, please submit the SAS code. If PK parameters are estimated in another program other than SAS (e.g. WinNonlin), please also provide the report for that analysis.

Sponsor Response*: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

Question 6: Regarding antihypertensive efficacy, in this 505(b)(2) NDA, we rely on the Agency's prior finding that the reference listed drug NORVASC as a calcium channel blocker is efficacious in treating hypertension. Per FDA Guidance for Industry: Applications Covered by Section 505(b)(2), changes in racemate or enantiomers of an active ingredient do not require review of information other than BA or BE studies. As supportive evidence, legacy summary reports of two Chinese post-marketing studies and one manuscript summarizing a Phase 4 outcome study will be included. Due to the historic nature of these studies, we do not plan to submit full clinical study including datasets. Six published literature showing comparable efficacy between levoamlodipine and racemic amlodipine (Hu et al., 2002; Pathak et al., 2004; Kim et al., 2008; Oh et al., 2012; Liu et al. 2010, and Chai et al., 2015) will be included. According to this plan, we intend to provide a brief Clinical Overview, without integrated efficacy analysis and without Summary of Clinical Efficacy. Does the Agency agree with our plan?

FDA Response: Yes, provided we are convinced that the antihypertensive effect of racemic amlodipine resides in the S-enantiomer. We recommend that you submit results from published or original bench research indicating that at relevant concentrations in preparations of cells expressing human L-type calcium channels, the R-enantiomer has no blocking activity, while the S-enantiomer has blocking activity at levels in line with those observed with racemic amlodipine at twice the concentration of the S-enantiomer.

***Sponsor Response**: The Sponsor maintains that the antihypertensive effect of racemic amlodipine resides in the S-enantiomer based on the following:*

1) *Multiple randomized, double-blind, active-control clinical trials have demonstrated that the antihypertensive efficacy is attributed to the S-enantiomer (levoamlodipine).*
2) *In vivo non-clinical studies demonstrated that the antihypertensive effect of the S-enantiomer is comparable to racemic amlodipine.*
3) *In vitro studies confirmed that the S-enantiomer was 1000 times more effective in antagonizing calcium-induced constriction of potassium-depolarized rat aorta compared to the R-enantiomer.*

These data will be summarized and included in the NDA. Does the Agency agree with this plan?

Meeting discussion: The Division emphasized that it needs to be convinced that the R-enantiomer does not contribute to inhibition of L-type calcium channel by racemic amlodipine. The Division encouraged the Sponsor to provide all requested data (nonclinical and efficacy data) along with a comprehensive literature search and seek the Agency's input on its adequacy via a Type C Written-Response-Only meeting request before filing the NDA.

Question 7a: We have described (b) (4)

(b) (4)

FDA Response: No, we would not accept labeling indicating that (b) (4)

***Sponsor Response**: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

Question 7b: Does the Agency agree (b) (4) ?

FDA Response: No, please see answer to Question 7a.

***Sponsor Response**: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

Question 7c: If answer is no for Question 7b, what additional data would be required to support a supplemental NDA for this claim? Since CSPC studies were conducted mostly over 10 years ago and all the data will have to be re-coded with new tools and database rebuilt with FDA required software, only summary reports or manuscript from these studies are planned to be included in the current NDA submission. If database for one or more studies (such as the CV Events Study) need to be submitted to support such a claim, could the Agency provide guidance on how the database should be prepared to enable a potential supplemental NDA submission?

FDA Response: Please see response to Question 7a.

***Sponsor Response**: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

2.4. REGULATORY

Question 8: The proposed USPI for levoamlodipine, representing the base case scenario is included in Appendix B, and the complete table of contents for the corresponding NDA are included in Appendix C. Does the Agency agree with the proposed USPI for the base case scenario?

FDA Response: If approved, your prescribing information will be based primarily on the listed drug upon which your proposed application relies. To the extent you have modeled your proposed USPI on the listed drug for the indications you are seeking, what you propose is appropriate. Please note however, the exact text of a final label will be determined and agreed to in the course of a complete review of your application.

***Sponsor Response**: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

Question 9: Levoamlodipine as the active enantiomer is being developed for the same hypertension indication in the same dosage form and given by the same route of administration as NORVASC. In the initial NDA application, we plan to seek antihypertensive indication in adult patients for all doses and in pediatric patients ages 6-17 years for 1.25 to 2.5 mg once daily.

If clinical studies are needed to obtain antihypertensive indication in pediatric patients ages 6-17 years for 1.25 to 2.5 mg once daily, we plan to seek antihypertensive indication in adult patients only in the initial NDA and to include (b) (4) in the initial NDA submission. Does the Agency agree with this plan?

FDA Response: We do not agree (b) (4) Additionally, we note that you have not submitted a pediatric study plan to satisfy the PREA requirement. For more information please see Section 3.0 below. An agreed initial pediatric study plan is needed prior to filing your marketing application.

Sponsor Response*: The Sponsor commits that an iPSP will be submitted prior to NDA submission* (b) (4) *to provide a plan to address the use of the drug in pediatric patients 6-17 years of age.*

(b) (4)

The Sponsor's NDA will also establish the comparability of PK properties between Norvasc and S-amlodipine.

Does the Division agree that the review of the NDA may commence concomitantly with the iPSP review by the Pediatric Division?

Meeting discussion: The Sponsor clarified (b) (4) The Division indicated that it will seek the Division of Pediatric and Maternal Health's input regarding the Sponsor's request to review the iPSP concomitantly with the NDA.

DPMH response: Post-Meeting Addendum

We acknowledge receipt of you iPSP on October 19, 2018. We will respond to your proposed iPSP within 90 days of receipt.
You should not file your NDA until you have an Agreed iPSP. Failure to include an Agreed iPSP with your marketing application could be a refuse-to-file issue. As per our Draft Guidance for Industry on Pediatric Study Plans, you should submit your iPSP at least 210 calendar days prior to your NDA submission.

We refer you to the FDA draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

Question 10: Does the Table of Contents for the NDA, including datasets to be submitted (Appendix C), appear complete and appropriate?

FDA Response: Yes.

***Sponsor Response**: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

Question 11: This application will include clinical data from a single BA study. The planned date of NDA submission is Nov 30, 2018. What is the appropriate PDUFA fee to be tendered?

FDA Response: According to section 736(a)(1)(A)(ii) of the Act "A fee established under subsection (c)(5) for a human drug application for which clinical data (other than BA/BE) with respect to safety or effectiveness are not required for approval, such fee shall be half of the amount of the fee established under clause (i)." The fee required by subparagraph (A) shall be due upon submission of the application.

Please be advised that if the published literature (e.g., article that discusses a study beyond BA/BE studies) or a reanalysis of previously submitted data is/are required for review and approval of the application, the literature or reanalysis may be considered clinical data for user fee purposes and would result in a full fee.

FY 2019 user fee rates:

User Fee Type	2019
Application Fee - Clinical Data Required	$ 2,588,478
Application Fee - No Clinical Data Required	$ 1,294,239

Please note that the final determination regarding user fees will be made when the application is submitted in its entirety.

***Sponsor Response**: Thank you. No further discussion required.*

Meeting discussion: This question was not discussed during the meeting.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an

assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Please refer to the meeting discussion under Questions 6 and 9.

5.0 ACTION ITEMS

Please refer to the meeting discussion under Questions 6 and 9.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes. However, the Sponsor provided responses to the Division's Preliminary Comments. The Sponsor's responses can be found in italics font in Section 2.0 (Discussion).

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/

NORMAN L STOCKBRIDGE
11/08/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124947

MEETING MINUTES

CSPC Ouyi Pharmaceutical Company, Ltd.
Attention: Simon Li, MD, PhD
CMO and VP of CSPC Pharma Group
302 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Dr. Li:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for levoamlodipine maleate.

We also refer to the meeting between representatives of your firm and the FDA on April 28, 2017. The purpose of the meeting was to discuss the development plan of levoamlodipine maleate tablets intended to support a 505(b)(2) New Drug Application.

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

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes and Sponsor's slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Pre-NDA

Meeting Date and Time: April 28, 2017, 3:00 pm – 4:00 pm
Meeting Location: White Oak Building 22, Conference Room: 1315

Application Number: IND 124947
Product Name: levoamlodipine maleate
Indication: Treatment of hypertension (b) (4)
Sponsor Name: CSPC OUYI Pharma

Meeting Chair: Norman Stockbridge, MD, PhD
Meeting Recorder: Sabry Soukehal

FDA ATTENDEES

*Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Shari Targum, MD	Clinical Team Leader
Thomas Papoian, PhD, DABT	Non-Clinical Team Leader
Philip Gatti, PhD	Non-Clinical Reviewer
Xi Yang, PhD	Non-Clinical Reviewer
Sabry Soukehal	Regulatory Health Project Manager

*Office of Clinical Pharmacology

Sudharshan Hariharan, PhD	Clinical Pharmacology Team Leader
Xiaolei Pan, PhD	Clinical Pharmacology Reviewer

*Office of Pharmaceutical Quality

Mohan Sapru, PhD	CMC Team Leader

*Division of Biopharmaceutics, OPQ

Ta-Chen Wu, PhD	Biopharmaceutics Team Leader
Joan Zhao, PhD	Biopharmaceutics Reviewer

SPONSOR ATTENDEES

Jiangmin Wang	CMC, CSPC Ouyi
Yinlian Li	CMC, CSPC Ouyi
Hanyu Yang	Non-clinical, CSPC Pharma
Rongduan Wang	VP of CSPC Pharma
Simon Li. MD, PhD	CMO, VP of CSPC Pharma
Charles Wang, PhD	President of International Business, CSPC Pharma

1.0 BACKGROUND

The Sponsor is developing levoamlodipine maleate, the purified (S) isomer of the calcium channel blocker amlodipine, for the treatment of hypertension (b) (4) The planned tablet strengths are 1.25 mg, 2.5 mg, and 5 mg, to be given once daily.

The Sponsor intends to submit a New Drug Application under the 505(b)(2) pathway, where NORVASC® (amlodipine besylate – NDA 019787) is the reference listed drug.

The Sponsor's asserted that clinically, 2.5 mg/day of levoamlodipine besylate demonstrated similar efficacy in treating hypertension as 5 mg/day of amlodipine besylate and showed fewer side effects.

On April 2, 2015, the Division permitted the IND-opening study to proceed. The Sponsor conducted a bioavailability study in healthy volunteers under fasted conditions where a single dose of 2.5 mg of levoamlodipine maleate was compared to a single dose of NORVASC® 5 mg. The Sponsor concluded from that study that 2.5 mg levoamlodipine maleate was bioequivalent to the 5 mg NORVASC®.

The Sponsor is now planning four clinical studies (protocol numbers LAM-US-101, (b) (4)) to support an NDA submission.

The Sponsor sought a meeting with the Division to obtain feedback on the appropriateness of the proposed development plan and receive guidance on the design of studies (b) (4)

FDA sent Preliminary Comments to CSPC OUYI Pharma on April 25, 2017.

2. DISCUSSION

Summary

The Sponsor sent follow up questions about the dissolution test (b) (4) The questions and a summary of the discussion that took place during the meeting can be found below.

1. Dissolution test:

   The dissolution method used for the brand name Norvasc as recommended by FDA was directly used for the development of levoamlodipine maleate tablet. We propose to use this same method as the QC method for product release and long term stability studies. This method will be validated per ICH 2A/B and the validation data will be provided as part of the NDA package. Does the Division agree with this proposal?

The Sponsor acknowledged the Division's preliminary responses and asked whether their plan to use the same dissolution method employed for NORVASC® is acceptable, adding that they do plan to validate the method. The Division of Biopharmaceutics responded that the Sponsor's proposal seems reasonable and advised that:

a) the proposed dissolution method for the proposed drug product should demonstrate discriminating ability for the most relevant critical material attributes and critical process parameters,

b) the dissolution method should be validated (method robustness, etc), and

c) validation data on the analytical method (precision, accuracy, linearity, stability, etc) should be provided, as described in the recommendations in Attachment 1.

The Division referred the Sponsor to the following FDA guidance document: "*Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms and Guidance for Industry*" for detailed recommendations.

The Division of Biopharmaceutics also offered to review the Sponsor's dissolution method for its acceptability prior to NDA submission. If the Sponsor wishes, they may submit the complete dissolution method development report (including complete dissolution data and validation report) to the IND. However, the acceptance criteria will be determined at the NDA stage after review of the data.

The Division of Clinical Pharmacology also agreed to the Sponsor's request to review PK study protocols and provide feedback.

(b) (4)

(b) (4)

[redacted]

2.1. Chemistry, Manufacturing, and Controls

Question 1: Does the Division agree that the proposed specifications for drug substance and drug product are sufficient to support the proposed clinical studies of levoamlodipine maleate tablet?

FDA Response: The proposed specifications for drug substance and drug product appear adequate to support the proposed clinical studies. However, because USP <231> will be eliminated beginning January 01, 2018, we recommend that you develop and implement a control strategy for elemental impurities as described in USP <232> and <233>, and ICH Q3D for both the drug substance and drug product. Furthermore, include a test for microbial enumeration in the drug substance and the drug product specifications and stability evaluations.

With respect to the dissolution test, on face it seems reasonable. However, based on the limited data/information provided in the meeting package, it is premature for us to provide a final recommendation on the acceptability of the proposed dissolution method and acceptance criterion at this point. Please refer to Attachment 1 for detailed recommendations on the dissolution information that should be provided in your NDA submission.

Meeting discussion: Please refer to the discussion summary.

Question 2: Does the Division agree that the proposed stability programs of drug product are sufficient to support the proposed clinical studies of levoamlodipine maleate tablet?

FDA Response: Yes, the proposed stability program appears adequate to support the proposed clinical studies. However, include microbial testing as part of the stability evaluation. Additionally, during stability evaluation, if the level of any individual degradant in the drug

product is found to exceed the ICH Q3B(R2) recommended limits, such degradant impurity will need to be *toxicologically qualified.*

Meeting discussion: This question was not discussed during the meeting.

2.2. Non-clinical

Question 3: Does the Division agree that the available toxicology data is sufficient to support the proposed clinical studies of levoamlodipine maleate tablet in US subjects?

FDA Response: Yes.

Meeting discussion: Please refer to the discussion summary.

Question 4: Does the Division agree that no further nonclinical pharmacology and toxicology studies are necessary for 505(b)(2) application of levoamlodipine maleate tablet?

FDA Response: Yes, we agree that for the hypertension indication no additional nonclinical studies will be needed, as amlodipine's effect as a calcium channel blocker is well established, and this activity appears to be dependent on the S-amlodipine isomer. However, it is not clear whether amlodipine's beneficial effect on the other approved indication of coronary artery disease (CAD) is due entirely to its calcium channel blocking effect, nor whether removing R-amlodipine from the racemic mixture may compromise this clinically beneficial activity. Please refer to the following publications that describe cardiovascular activity of amlodipine unrelated to its direct effect as a calcium channel blocker:

- Stepien O. and Marche P.; Amlodipine inhibits thapsigargin-sensitive CA^{2+} stores in thrombin-stimulated vascular smooth muscle cells; Am. J. Physiol. Heart Circ. Physiol. 2000; 279:H1220-H1227.
- Tulenko T.N. et al.; The smooth muscle cell membrane during atherogenesis: A potential target for amlodipine in atheroprotection; Am. Heart J. 2001; S2-S11.
- Stepien O. et al.; Amlodipine inhibition of serum-, thrombin-, or fibroblast growth factor-induced vascular smooth-muscle cell proliferation; J. Cardiovasc. Pharmacol. 1998; 31:586-793.

Also, please note that additional nonclinical studies may be needed if levels of impurities or degradants are not within acceptable threshold limits (see ICH-Q3A and ICH-Q3B).

Meeting discussion: The Division believes that amlodipine may have pharmacologic activity(ies) in addition to its activity as a calcium channel blocker that contribute to the clinical benefits in patients with coronary artery disease. The three studies cited above in our preliminary answer are just a portion of the extensive published data investigating amlodipine’s actions, other than blocking the L-type calcium channel. We believe additional non-clinical pharmacology studies are not unlikely to be sufficient to obtain approval for the coronary artery disease indication because of the uncertainty about which activities are important. Hence it is the Division’s position that the sponsor would need to conduct a clinical efficacy trial of administering levoamlodipine to patients with coronary artery disease to gain a claim that amlodipine benefits these patients.

However, we agree that your current non-clinical safety data are sufficient to support filing of an NDA. (b) (4)

2.3. Clinical Pharmacology/Clinical

Question 5: Does the Division agree that the proposed clinical studies are adequate to support a 505(b)(2) NDA of levoamlodipine maleate tablets at 1.25, 2.5 and 5 mg for the indications approved for NORVASC®?

FDA Response: We believe that you can sustain the antihypertensive claim based on the data that you have on the blood pressure effects of levoamlodipine.

(b) (4)

Clinical Pharmacology Comments: We generally agree (b) (4)

Moreover, you will not need to conduct the proposed single (SAD, LAM-US-101) (b) (4) studies as they might not generate any novel information about safety/tolerability of your product.

Meeting discussion: Please refer to the discussion summary.

Question 6: (b) (4)

FDA Response: (b) (4)

Meeting discussion: Please refer to the discussion summary.

3.0 OTHER IMPORTANT INFORMATION

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please

note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site,* in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

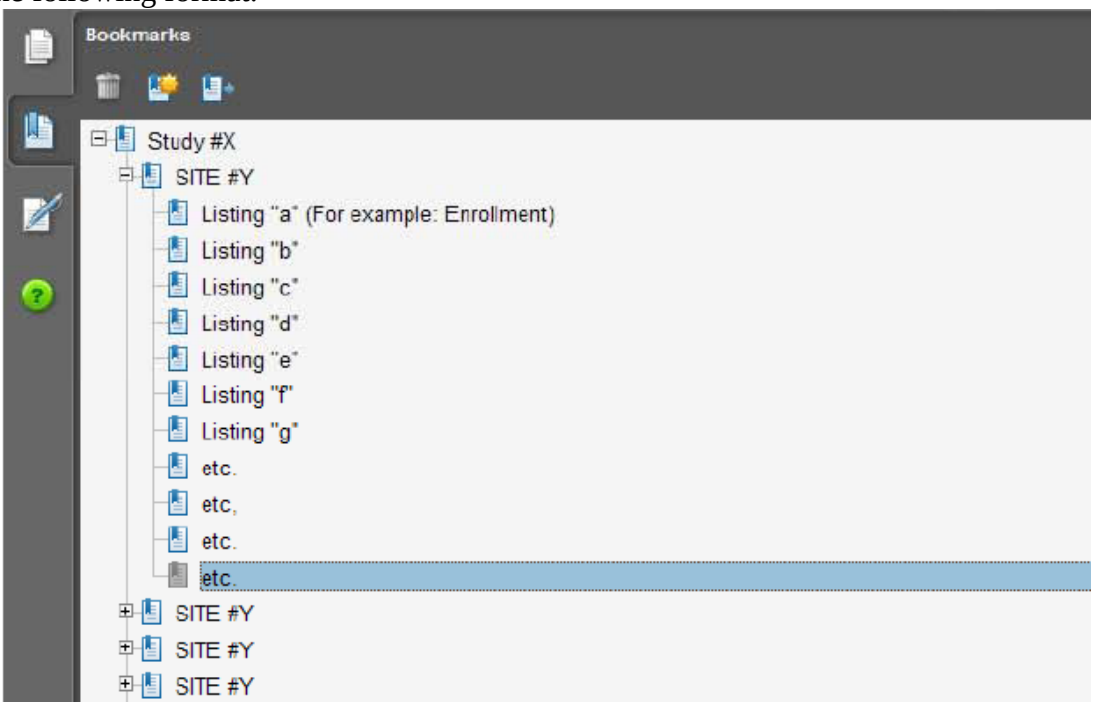
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Recommendations regarding the dissolution information that should be provided in your NDA submission:

1. **Dissolution Method:** Include the dissolution method development report supporting the selection of the proposed dissolution test. Include the following information in the dissolution method development report:

2. **Dissolution Acceptance Criterion:** For the selection of the dissolution acceptance criterion of your proposed drug product, consider the following points:

   a. FDA recommends use of the dissolution profile data (i.e., 15, 20, 30, 45, and 60 min) from the pivotal clinical batches and primary (registration) batches (throughout the stability program) for setting the dissolution acceptance criterion.
   b. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution occurs.
   c. The dissolution acceptance criterion should be based on average in vitro dissolution data (n = 12).
   d. The selection of the specification 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 CTD.

3. **Data Presentation:** In the dissolution method development report, present detailed experimental data as follows:
   a. Include individual vessel data as much as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.
   b. In addition to the mean dissolution data presented in graphical and tabular formats in the dissolution method development report, submit all individual vessel dissolution data for the clinical and registration/stability batches in ".xpt" format. Submit a DEFINE file along with the .xpt files.
   c. Present batch release and stability dissolution data graphically; in the plot(s) of individual vessel data for the clinical and stability batches, include data at release, zero stability time point, and over the duration of stability testing under long-term storage conditions.

Attachment 2

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

Below are the Sponsor's two questions sent on April 27, 2017.

2 Pages have 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 and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
05/16/2017