CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214869Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135441

MEETING MINUTES

Riverside Pharmaceuticals Corporation
Attention: Thomas N. Chase, SB, MD
Chief Executive Officer
1825 K Street NW, Suite 520
Washington DC 20006

Dear Dr. Chase:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (carbidopa 25 mg/ levodopa 100 mg) tablet.

We also refer to the teleconference between representatives of your firm and the FDA on June 11, 2020. The purpose of the meeting was to discuss the (b) (4) 505(b)(2) NDA submission.

A copy of the official minutes of the meeting/teleconference 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 Stacy Metz, PharmD, Senior Regulatory Project Manager, at stacy.metz@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Director (acting)
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting 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.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 11, 2020; 3:00-4:00 PM EST
Meeting Location:	Teleconference
Application Number:	IND 135441
Product Name:	(b) (4) (carbidopa 25 mg/levodopa 100 mg) tablet
Indication:	Treatment of Parkinson's Disease and Syndrome
Sponsor Name:	Riverside Pharmaceuticals Corporation
Regulatory Pathway:	505(b)(2)
Meeting Chair:	Eric Bastings, MD
Meeting Recorder:	Stacy Metz, PharmD

FDA ATTENDEES

Eric Bastings, MD, Director (Acting) DN1
Teresa Buracchio, MD, Deputy Director (Acting) DN1
Dave (Gerald) Podskalny, DO, MPHS, Clinical Team Leader
Len Kapcala, MD, Clinical Reviewer
Martha Heimann, PhD, CMC Team Lead
Mariappan Chelliah, PhD, CMC Reviewer
Gaetan Ladouceur, PhD, CMC
Julia Pinto, PhD, CMC
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Lead
Mariam Ahmed, PhD, Clinical Pharmacology Reviewer
Luann Mckinney, DVM, DACVP, Nonclinical Reviewer
Stacy Metz, PharmD, Senior RPM, DN1

SPONSOR ATTENDEES

Thomas N. Chase, SB, MD, Chief Executive Officer
Kathleen Clarence-Smith, MD, PhD, Chief Medical Officer
(b) (4)

1.0 BACKGROUND

Riverside Pharmaceuticals has developed a redesigned tablet of the immediate-release carbidopa/levodopa 25/100 mg tablet for the treatment of Parkinson's disease and syndrome. The redesigned tablet is oblong in shape and has 3 (b) (4) scores for ease of tablet splitting and to enable precise dosing. They have conducted a Phase 1 study in healthy volunteers to determine the bioequivalence of (b) (4) compared to reference drug (FDA approved generic CD/LD 25/100 mg tablet). The study also examined the effect of food on the pharmacokinetics of (b) (4)

The purpose of this meeting is to discuss the (b) (4) 505(b)(2) NDA submission.

Specific objectives expected from the meeting include the following:

- Discuss the CMC package
- Identify any deficiencies with the current proposed NDA package

FDA sent Preliminary Comments to Riverside Pharmaceutical Corporation on June 9, 2020. The sponsor provided a response document on July 10, 2020, that is both incorporated into these minutes and attached at the end of these minutes.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls

Question 1:
The Sponsor plans to rely on reference to the (b) (4) Drug Master File (DMF (b) (4)) for (b) (4) for all CMC information regarding this drug substance.

Are the specifications for (b) (4) drug substance acceptable to FDA?

FDA Response to Question 1:
USP monograph tests are the minimum standards and are not sufficient to control the quality of the drug substance. However, it is acceptable if the drug substance specification matches the one from the vendor and the referenced DMF is found adequate. Provide a Letter of Reference to the DMF when the NDA application is filed. It is expected that you provide the following drug substance information in the NDA:

- General information
- Physicochemical properties
- Specifications and a Certificate of Analysis of the drug substance.

Meeting Discussion:
The Sponsor proposes to update the (b) (4) drug substance specifications for related substances to match that from the manufacturer. Physical test specifications will

not be added as they are not critical quality attributes. (In the manufacturing process, drug substance is [redacted] (b) (4)).

The Agency agrees.

Question 2:
Carbidopa drug substance is synthesized [redacted] (b) (4) . Details of the synthesis can be found in DMF [redacted] (b) (4) .

Does the Division concur with the choice of [redacted] (b) (4) for carbidopa synthesis?

FDA Response to Question 2:
FDA does not comment on proprietary information found in a DMF unless it is provided by the vendor and all the information is included in the NDA for review. The DMF will be reviewed when your NDA is submitted, and the adequacy determined at that time.

Meeting Discussion:
No further discussion at the meeting.

Question 3:
Levodopa drug substance was produced via [redacted] (b) (4) Details of the manufacturing process will be provided in a DMF to be submitted by [redacted] (b) (4) prior to NDA filing.

Does the Division concur with the [redacted] (b) (4) process used for the manufacturing of levodopa and the established specifications?

FDA Response to Question 3:
As per the response to Question 2, FDA does not comment on proprietary information found in a DMF unless all the information is provided by the vendor and is included in the NDA for review. It is noted that [redacted] (b) (4) of the drug substance specification in line with the ICH Q3C (R6) limit, and provide residual [redacted] (b) (4) data on the drug substance batches. We note your plan to cross-reference a DMF for API information. Please be advised that the DMF should be submitted at least 30 days prior to a cross-reference to allow adequate time for it to be evaluated for conformance with guidelines for electronic submission. Refer to the following information on DMFs: *https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs#Enviro*

Meeting Discussion:
The Sponsor has been notified by the levodopa drug substance manufacturer that a limit of (b) (4) exists as a control for the (b) (4) used in the process. Additionally, the manufacturer has tested 3 batches of drug substance for (b) (4) and found that (b) (4) is below ICH Q3C (R6) limits in each batch. The Sponsor proposes that based on this information (and sufficiency of Agency review of DMF), no additional controls for (b) (4) will be required.

The Agency commented that the information will review the information with the NDA. If the Sponsor's information is correct the proposal is acceptable.

Question 4:
The Sponsor plans to manufacture the (b) (4) tablet and perform all testing of the tablet.

Does the Division concur with the proposed manufacturing plan and specifications?

FDA Response to Question 4:
Include tests for (b) (4) in the specification or provide adequate justification for their omission. Otherwise, the proposed specification appears reasonable for the NDA. The final determination on the acceptability of the release and stability specifications is deferred to the submission review, when all the data may be evaluated in its totality.

We acknowledge the master batch records that you have submitted in the briefing package. However, we are unable to review this information in the context of this meeting - it will be reviewed based on totality of data when the NDA is submitted.

Meeting Discussion:
The Agency stated that a test for (b) (4) is usually part of the drug product specification. However, if the Sponsor chose to omit this test, adequate justification should be provided that demonstrates that (b) (4) is not a critical quality attribute of the drug product.

If there is adequate data supporting the justification, for example, (b) (4), the Agency may consider accepting either skip lot testing for the (b) (4) or omitting this testing from the specification.

Question 5:
The Sponsor proposes to continue with (b) (4) for each of three batches to be manufactured for process validation. Provided acceptable results are obtained for (b) (4) (i.e., specifications are met for (b) (4)) in each validation batch, and given the demonstration of functional scoring in the registration

batches, the Sponsor proposes removing [redacted].

Does the Agency agree?

FDA Response to Question 5:
Your proposal may be acceptable, if adequate testing data is provided to show that additional testing is not required for [redacted] the scored tablet. This will be determined during the NDA review.

Meeting Discussion:
As process validation data will not be provided in the NDA, the Sponsor proposes not including [redacted] based on adequate testing data provided for registration batches. [redacted]

The Agency stated that the Sponsor's proposal is reasonable; however, the final determination will be made during the NDA review.

Question 6:
The Sponsor has developed the [redacted] tablet to be functionally scored. Data is provided in the meeting package to demonstrate the effectiveness of the tablet design in ensuring consistency in scoring and stability of the split tablets.

Does the Division agree the [redacted] tablet meets the requirements for functional scoring and, hence, can refer to the term functional scoring in the product labeling?

FDA Response to Question 6:
You have not adequately demonstrated that the tablets meet the requirement of functional scoring per the FDA Guidance "Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation". You have performed the [redacted]. Provide this data in the NDA submission.

Meeting Discussion:
The Sponsor stated that the hardness specification for tablets tested in-process is [redacted] kp. [redacted]

The subsequent slide graphically depicts the distribution of tablet hardness as a function of registration batch.

Additionally, the (b) (4) scored, (b) (4) design of the product provides for (b) (4) (b) (4)

Given this information, the sponsor asked if we agreed that the tablets met the requirements for functional scoring and no additional work is needed.

The Agency explained that because only a small portion of the tablets from the primary batches fall under the lower and upper ends of the proposed tablet hardness range, the data from the split tablets study does not meet the requirements of the FDA Guidance "Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation". The Agency recommends the Sponsor manufacture batches (smaller non-GMP batches are acceptable) that are intentionally (b) (4) (b) (4)

Question 7:

The Sponsor plans to initially file three registration batches manufactured at a scale of (b) (4) tablets each with (b) (4) months long term/6 months accelerated stability. All scheduled stability studies will continue to completion and the subsequent data will be provided during NDA review or as a post marketing commitment.

Stability data obtained to date (6 months accelerated and long term) for the three registration batches show no evidence of degradation under both long term and accelerated conditions. There is no change in the (b) (4) impurity level ((b) (4)%) from T=0 and all other impurities remain below (b) (4)%.

Does the Division agree that this stability program and commitment is sufficient to permit the filing of the NDA?

FDA Response to Question 7:

We do not agree with your proposal to submit only (b) (4) months of long-term and 6 months of accelerated stability data for the registration batches. As previously communicated in the Written Response dated July 17, 2017, and in accordance with ICH Q1A(R1) Guideline, we expect the NDA to contain at least 12 months of long-term and 6 months of accelerated stability data at the time of submission. Any additional data provided

during the review cycle may or may not be reviewed depending on the resources available.

Meeting Discussion:
Given the significant body of information on the stability of solid oral dose products containing carbidopa and levodopa, Sponsor proposes submitting the NDA with (b) (4) months of long-term stability data and 6 months of accelerated data from each of three registration batches, and providing the 12-month long-term data at the time of the 120-day safety update.

The Agency stated that per the current policy, the application is expected to be complete when it is submitted. Therefore, in accordance with ICH Q1A(R2) Guideline, at least 12 months of long-term and 6-months of accelerated stability data should be provided in the NDA.

2.2. Regulatory Questions

Question 8:
The Sponsor proposes to submit a 505(b)(2) NDA for the novel redesign tablet (b) (4). The Sponsor will rely on the Agency's previous findings of safety and efficacy of Sinemet® (carbidopa 25 mg/levodopa 100 mg) (NDA 17555). A table listing 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 will be provided in the meeting package.

The Sponsor has conducted one bioequivalence/food effect study in support of the 505(b)(2) NDA. No other clinical studies are planned to be conducted.

In addition, no nonclinical studies have been conducted or are planned to be conducted. The Sponsor plans to rely on the nonclinical data presented in the Sinemet® labeling.

Does FDA concur that no additional clinical and nonclinical studies are needed?

FDA Response to Question 8:
On face, based on the results you presented in your briefing package for the Phase 1 study, (b) (4) is bioequivalent to Sinemet under fasting condition. However, the Phase 1 study results suggest that administration of high-fat high-calorie meal with (b) (4) resulted in a 25% reduction in the Cmax for levodopa, while the exposure (both Cmax and AUC) of carbidopa decreased by approximately 60%. Therefore, you will need to address in your NDA whether administration of (b) (4) in the fed state would affect its efficacy. The need for additional studies will be a matter of review of your NDA.

Meeting Discussion:
No further discussion at the meeting.

Question 9:
The Sponsor has conducted one bioequivalence/food effect study in support of the NDA. The Sponsor plans to submit the full study report for the above bioequivalence/food effect study as well as electronic study data in CDISC format. The Sponsor plans to provide a summary of safety in the 48 healthy volunteers in this study in the Summary of Clinical Safety (CTD Section 2.7.4). Since this is the only study, the Integrated Summary of Safety (in Module 5) would likely be identical to both the study report and the Summary of Clinical Safety (CTD Section 2.7.4). Therefore, the Sponsor does not plan to submit an Integrated Summary of Safety in Module 5.

Efficacy was not measured in this study; therefore, the Sponsor does not plan to submit a Summary of Clinical Efficacy (CTD Section 2.7.3) in Module 2 and an Integrated Summary of Effectiveness in Module 5.

Does FDA agree with the above?

FDA Response to Question 9:
If no additional clinical efficacy and/or safety studies are needed because bioequivalence of (b) (4) to Sinemet was adequately demonstrated, you will not need to submit a Summary of Clinical Efficacy or Integrated Summaries of Efficacy or and Safety.

Meeting Discussion:
No further discussion at the meeting.

Question 10:
The Sponsor plans to rely on the Agency's previous findings of safety and efficacy of Sinemet (NDA 17555 approved May 22, 1975) as reflected in the approved labeling. The Sponsor proposes to use the Sinemet prescribing information (PI) document as a template for the development of the (b) (4) PI. We note that the current Sinemet PI does not comply with the Physician Labeling Rule format requirements.

Does FDA agree with the above?

FDA Response to Question 10:
You should use the Sinemet Prescribing Information (PI) as a template for your proposed labeling with respect to the information to include; however, the proposed PI that you submit with your NDA is required to comply with the content and format requirements of the Physician Labeling Rule (PLR) [see 21 CFR 201.56(b)(1)(iii) and (c)(1)]. In addition, the Pregnancy and Lactation Labeling Rule (PLLR) revised the PLR content and format requirements for subsections 8.1 through 8.3, and your proposed PI must also comply with PLLR. We note that Rytary is another oral carbidopa-levodopa product that was approved under Section 505(b)(2) of the FD&C Act with reference to Sinemet, and the Rytary PI was approved in the PLR format. Review of the Rytary PI (last approved December 17, 2019) may be of assistance when you develop your

labeling in PLR/PLLR format. See Section 3 below for more information about PI resources and information you should include in your application with respect to PLLR.

Meeting Discussion:
No further discussion at the meeting.

Question 11:
The Sponsor plans to file a request for a categorical waiver from the requirement to prepare an Environmental Assessment in support of the future NDA based on 21 CFR 25.31(a) "no increased use."

Does FDA concur with this plan?

FDA Response to Question 11:
Submission of a claim for categorical exclusion under 21 CFR 25.31(a) appears reasonable. Please include your rationale for "no increased use" (e.g., alternative to an existing product) and ensure that the claim includes a statement that "no extraordinary circumstances exist. Refer to "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications[2]" for further information.

Meeting Discussion:
No further discussion at the meeting.

Question 12:
(b) (4) is not a CNS-active new molecular entity. The RLD, Sinemet®, does not contain CNS-active substances controlled under the Controlled Substances Act. The Sponsor considers that (b) (4) contains the same active ingredients as the innovator drug product, Sinemet®, and should not be scheduled under the CSA. Therefore, the Sponsor does not plan to submit an abuse potential assessment in the NDA submission.
Does FDA concur with this plan?

FDA Response to Question 12:
We agree with your plan to not submit an abuse potential assessment in your NDA submission. Though we disagree with the statement that the activity of levodopa is not CNS mediated, we agree that levodopa and carbidopa are not controlled substances.

Meeting Discussion:
No further discussion at the meeting.

Question 13:
The proposed indication for (b) (4) is the treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. The labeling for Sinemet states that

[2] https://www.fda.gov/media/70809/download

"Use of the drug in patients below the age of 18 is not recommended." The Sponsor plans to submit a waiver for the requirement to submit the pediatric assessment prior to the NDA submission.

Does FDA concur with this plan?

FDA Response to Question 13:
No further discussion at the meeting.

Your plan to request a waiver for studies required the Pediatric Research Equity Act (PREA) is reasonable. Please refer to the PREA REQUIREMENTS in Section 3.0 just below regarding pediatric waiver requests.

Meeting Discussion:
No further discussion at 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*.[3] In addition, you may contact the Division of Pediatric and

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] 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

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

females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[9]

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

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[9] 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.

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[10] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[11]. 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

[10] https://www fda.gov/media/84223/download
[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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).[12] 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.[13]

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

[12] 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.
[13] http://www.regulations.gov

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*.[14]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The sponsor response document provided on July 10, 2020.

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

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

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/s/

ERIC P BASTINGS
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