

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216354Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 112975

MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Randy Thear, MBA
Associate Director Global RA
145 Brandywine Parkway
West Chester, PA 19380

Dear Mr. Thear:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TEV-50717 (Austedo tablets).

We also refer to the teleconference between representatives of your firm and the FDA on February 17, 2022. The purpose of the meeting was to share and seek feedback on your new drug application submission content for the once daily formulation and the development strategy to support a sufficient bridge to the Austedo twice daily approved indications.

A copy of the official minutes of the meeting/telecon 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}

Teresa Buracchio, MD
Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

¹We 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: PreNDA

Meeting Date and Time: February 17, 2022; 3:00 PM – 4:00 PM EST
Meeting Location: Teleconference

Application Number: IND 112975
Product Name: TEV-50717 (Austedo tablets)
Indication: Treatment of chorea associated with Huntington’s disease and tardive dyskinesia in adults.

Sponsor Name: Teva Branded Pharmaceutical Products R&D, Inc.
Regulatory Pathway: 505(b)(2)

Meeting Chair: Billy Dunn, MD, ON Director
Meeting Recorder: Stacy Metz, PharmD, Senior RPM

FDA ATTENDEES

Billy Dunn, MD, ON Director
Teresa Buracchio, MD, DN1 Director
Laura Jawidzik, MD, Deputy Director (Acting)
Sally Yasuda, MS, PharmD, Safety Team Lead
Natalie Getzoff, MD, Clinical Team Lead
Kenneth Bergmann, MD, Clinical Reviewer
Ami Mankodi, MD, Clinical Reviewer
Bilal AbuAsal, PhD, Clinical Pharmacology Team Lead
Adarsh Gandhi, PhD, Clinical Pharmacology Reviewer
Atul Bhattaram, PhD, OCP Pharmacometrics Lead
Martha Heimann, PhD, CMC Team Lead
Luning Zhuang, PhD, Clinical Pharmacology Team Lead, DP
Praveen Balimane, PhD, Clinical Pharmacology Reviewer, DP
Heidi Wehring, Clinical Analyst, DP
Stacy Metz, PharmD, Senior RPM

SPONSOR ATTENDEES

Mark Gordon, MD, Sr Dir, Global Specialty Clinical Development
Andrew Ahn, MD, PhD, VP, Global Specialty Clinical Development
Yasser Abdel Gawad, Assoc Dir, R&D Project Leadership
Eva Maria Sunzel, PhD, Dir, Clinical Pharmacology
Giulia Ghibellini, PhD, Sr Dir, Clinical Pharmacology
Laura Rabinovich-Guilatt, PhD, Sr Dir, Clinical Pharmacology & Pharmacometrics
Rajendra Singh, PhD, Sr Dir, Pharmacometrics

Leonard Alansky, R.Ph., Dir, Regulatory Affairs, CMC
Parag Shah, PhD, Sr Dir & Site Head, Drug Development
Malini Iyengar, PhD, Sr Dir, Head Respiratory, Oncology & Clin Pharm Statistics
(b) (4) Consultant Statistician

Alexander F J Send, PhD, Assoc Dir, Global Patient Safety and Pharmacovigilance

Mikhail Zeygarnik, MD, PhD, Dir, Global Patient Safety and Pharmacovigilance

Douglas Harnish, PhD, VP, Global Regulatory Affairs

Khalid Yousif, Dir, Global Regulatory Affairs

Randy Thear, MBA, Assoc Dir, Global Regulatory Affairs

Valerie Mulligan, VP, Global Regulatory Affairs

Lauren O'Neill, Global Regulatory Affairs

1.0 BACKGROUND

Austedo (deutetrabenazine), also known as TEV-50717 or SD-809, has been approved for the treatment of tardive dyskinesia and chorea associated with Huntington's disease, and is under development for the treatment of dyskinesia in cerebral palsy in children and adolescents. TEV-50717 was also investigated for treatment of tics associated with Tourette syndrome in children and adolescents.

Austedo is commercially available as 6, 9, and 12 mg tablets administered twice daily. Teva is developing a new formulation to allow once daily (QD) administration to be utilized in all indications for which Austedo is currently approved. The proposed commercial QD formulation would be available in 6, 12, and 24 mg strengths.

The purpose of this Type B meeting is to share and seek feedback on Teva's new drug application submission content for the once daily formulation and the development strategy to support a sufficient bridge to the Austedo twice daily approved indications.

FDA sent Preliminary Comments to Teva on February 15, 2022.

2.0 DISCUSSION

2.1. Clinical/Clinical Pharmacology Questions

Question 1:

Does the Agency concur that Teva's registration strategy, consisting of:

- Study TV50717-BE-10179 demonstrating BE between the BID and QD formulations at steady state for TEV-50717 (C_{max} , AUC) and metabolites (AUC, individually and as a sum)
- Study TV50717-PK-10175 demonstrating dose linearity across the dosage strengths as well as the clinical dose range for the QD formulation (TEV-50717 and metabolites individually and as a sum),

- A single dose relative BA of QD formulation vs. the commercial BID tablet and food effect characterization of the QD tablet formulation (Study TV50717-BE-10165),
- Along with supplementary PK/PD modeling (based on deuterated total ($\alpha+\beta$)-HTBZ) to support a bridge to the shown efficacy in patients with HD and TD for the BID tablet,

is adequate to support the bioequivalence of the QD formulation for a NDA submission as a 505(b)(2) application?

FDA Response to Question 1:

The adequacy of the proposed approach to support the approval of your product will be a matter of review of the NDA submission, and will depend on the capability of the exposure response analysis to delineate the effect of the differences in the shape of the PK profiles on the efficacy of deutetrabenazine. In addition, you should include justifications to show that the differences in the shape of the PK curves do not materially impact efficacy and safety.

We refer you to our responses in previous communications (particularly the meeting minutes dated December 17, 2020 and April 28, 2020) for more details.

Sponsor's February 16, 2022, Pre-meeting Response

We seek the Division's clarification on the use of "deutetrabenazine" and the intent as well as the analysis to address the differences in the shape of the PK profiles.

Meeting Discussion:

The Agency clarified that the sponsor should try to use all available data for both the parent and metabolite in their analysis when feasible. The Agency also acknowledged that the sponsor could use metabolite data for exposure-response analysis as parent drug data was not available in the Phase 3 studies. The Agency reiterated that the adequacy of the development program will depend on the adequacy and reliability of the PK/PD model and the reliability of the data used to develop the model. The Agency commented that the sponsor should use available PK/PD data from different dosing regimens tested in previous studies. The sponsor confirmed that the proposed product is bioequivalent to the reference for both C_{max} and AUC. The sponsor inquired about the criteria to evaluate the effect of the difference in shape of the PK profiles on efficacy and safety in patients. The Agency clarified that since the test and the reference product are bioequivalent for both C_{max} and AUC, the sponsor can use the PK/PD model to delineate the relevance of the shape of the PK profile. If C_{max} is not the PK metric correlating with efficacy, this can be used to justify that the difference in the shape is not expected to affect the efficacy. The sponsor commented that the proposed product is titrated to effect and there is a wide therapeutic concentration range. The Agency recommended the sponsor to include this rationale in their NDA submission.

The Agency noted that if the test and reference are bioequivalent to the parent compound, they should also be bioequivalent for the metabolite, if both the test and the reference are administered through the same route of administration. Therefore, the Agency recommended that the sponsor confirm the bioanalysis for the parent and metabolite in the pivotal PK bridging.

Question 2:

The safety data summaries from healthy subjects enrolled in all Phase 1 QD formulation studies are complete and will be included in the NDA submission. There are no additional data to be reported on the QD formulation after this submission. Does the Agency agree that a 120-day safety report is not required?

FDA Response to Question 2:

If no clinical safety data are generated after submission of the NDA, a 120-day Safety Update is not necessary.

Meeting Discussion:

None.

Question 3:

Teva proposes to provide a Summary of Clinical Safety (SCS) for the three Phase 1 registration studies along with supportive pilot study data (briefly presented in Appendix A) and does not plan to include an Integrated Summary of Safety (ISS). Teva also does not plan to provide a Summary of Clinical Efficacy (SCE) or Integrated Summary of Efficacy (ISE) in the NDA. Does the Agency agree with this approach?

FDA Response to Question 3:

We do not agree. The Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) are required under 21 CFR 314.50(c)(2)(viii). Similarly, the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS) are required by 21 CFR 314.50(d)(5)(v) and (vi), respectively.

Your proposed plan to submit only a SCS is acceptable, provided that the SCS contains details sufficient to allow it to serve as the narrative portion of the Integrated Summary of Safety (ISS) while still being concise enough to meet the suggested size limitation for Module 2. Analyses presented in the SCS (Module 2.7.4) should be linked to relevant analyses in Module 5. Links should function from the SCS to the appropriate information in Module 5.3.5.3 and there should be a link back to the corresponding original section in the SCS. We refer you to the Agency's Guidances Industry *M4E(R2): The CTD — Efficacy²* and *Integrated Summaries of Effectiveness and Safety: Location Within the*

² <https://www.fda.gov/media/93569/download>

*Common Technical Document*³ for additional details including limitations on the size of the Module 2 clinical summaries.

Your proposed plan to submit neither an SCE nor ISE is not acceptable. You may submit only an SCE, provided that it contains details sufficient to allow it to serve as the narrative portion of the ISE while still being concise enough to meet the suggested size limitation for Module 2. The format of the SCE or ISE is flexible but should provide information necessary to describe the full extent of effectiveness of TEV-50717 as demonstrated by the bioequivalence studies. This information, for example, may include, but is not limited to, clinical pharmacology studies (e.g., pharmacokinetic [PK], pharmacodynamic, and in vitro studies) that describe dose-response, concentration-response, and drug-drug and drug-disease (e.g., renal dysfunction) interactions; and in vitro studies that clarify drug activity. More information regarding the content and function of the ISE may be found in its procedural guidance⁴.

Sponsor's February 16, 2022, Pre-meeting Response

Teva would like to clarify that if the narrative portion of the ISS are adequately included in the SCS, there would be no ISS, therefore no 5.3.5.3 and ultimately no linking between these two sections (2.7.4 and 5.3.5.3).

Meeting Discussion:

As noted in the premeeting response, both SCS and ISS are required under the CFR, even considering the narrow scope of the studies in this application. For applications of this size, the Module 2.7.4 SCS should follow the outline of the usual Module 5 ISS. It is acceptable for the SCS to include all of the application's safety information, provided it does not exceed the 400-page limit. If the SCS is under the page limit, provide a short informational document in Module 5.3.5.3 that states that the Module 2.7.4 SCS is complete with no further information in Module 5.3.5.3 and also includes a link back to the SCS in Module 2.

2.2. Regulatory and Electronic Submission Questions

APPEARS THIS WAY ON ORIGINAL

Question 4:

An outline of the Table of Contents for the NDA is provided in **Error! Reference source not found.** Does the Agency agree with this content, as well the cross-referencing proposed, and placement of information for NDA submission?

FDA Response to Question 4:

See our response to Question 3 above. The NDA submission should follow technical specifications as presented in the eCTD Technical Conformance Guide in order to

³ <https://www.fda.gov/media/75783/download>

⁴ <https://www.fda.gov/media/72335/download>

ensure that information is easily located within the electronic submission⁵. The Comprehensive Table of Contents Headings and Hierarchy for the eCTD is available to guide you⁶, Note that because this is a comprehensive listing, not all headings are applicable to all submissions.

Meeting Discussion:

None.

Question 5:

Teva proposes to include the three Phase 1 registration studies in Module 2.7.2, along with dose proportionality data pertaining to AUSTEDO (study TV50717-SAD-10132), and the popPK/ and PK/PD modeling data, to provide one concise summary. (Note: All pilot studies [briefly presented in **Error! Reference source not found.**] leading to the three Phase 1 registration studies will be included in Module 2.7.1.) Does the Agency agree with approach?

APPEARS THIS WAY ON ORIGINAL

FDA Response to Question 5:

This approach appears reasonable.

We refer you to the following website, which outlines the Agency's general expectations for submission of pharmacometric data and models:

<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format>.

Meeting Discussion:

None.

2.3. Chemistry, Manufacturing and Controls Question

Question 6:

Teva plans to include 12 months of long-term stability data (25°C/60% relative humidity [RH]) and 6 months of data at the accelerated condition (40°C/75% RH) on three batches of each strength packed in high-density polyethylene (HDPE) bottles in the NDA. In addition, Teva plans to include 9 months of long-term stability data (25°C/60% RH) and 6 months of data at the accelerated condition (40°C/75% RH) on three batches of each strength packed in blisters in the NDA. Is it acceptable for Teva to amend the NDA with the 12 month (25°C/60% RH) blister stability data within the first four months post NDA submission?

FDA Response to Question 6:

⁵ <https://www.fda.gov/media/93818/download>

⁶ <https://www.fda.gov/media/76444/download>

We recommend submission of 12 months long-term stability data for the blister configuration in the original NDA. Whether we review information submitted to the NDA after the original submission will be determined based on the timing of the submission and available Agency resources. The expiration dating period assigned during the review will be commensurate with the extent and quality of the available stability data. Refer to ICH guidance “Q1E Evaluation of Stability Data.”

Sponsor’s February 16, 2022, Pre-meeting Response

Teva has further refined the timelines associated with the availability of the 12-month stability data on the blisters to supplement the NDA. The 12-month blister stability data will be submitted within 60 days post NDA submission. With the stability data received within 60 days of submission, will the Agency agree to accept and review this data within the NDA review timelines?

Meeting Discussion:

The Agency confirmed that it will accept the 9 months of long-term stability data on the blisters to be submitted in the original NDA for review. However, the Agency cannot commit in advance to review amendments received later than 30 days after NDA submission.

2.4. Nonclinical Question

Question 7:

Aligned with the feedback received during an FDA Type B meeting in March 2020 that no additional nonclinical studies are needed, Teva intends to cross-reference any prior studies submitted, as appropriate. Does the Agency agree with this approach?

FDA Response to Question 7:

We agree it is acceptable for you to provide nonclinical studies by cross-reference to another application you hold.

Meeting Discussion:

None.

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*.⁷ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.⁸

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 Information⁹ and Pregnancy and Lactation Labeling Final Rule¹⁰ 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.

⁷ 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>.

⁸ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁹ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

¹⁰ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).¹¹ 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).¹²

¹¹ 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>.

¹² <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)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>(4)</i>	

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*.¹³

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

On February 16, 2022, the sponsor provided a response document. Those responses have been incorporated within these minutes.

¹³ <https://www.fda.gov/media/85061/download>

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

/s/

TERESA J BURACCHIO
03/18/2022 04:16:29 PM



IND 112975

MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Xuan-Tien Huynh, MS
Manager, Global Regulatory Affairs
145 Brandywine Parkway
West Chester, PA 19380

Dear Ms. Huynh:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TEV-50717 tablets.

We also refer to the telecon between representatives of your firm and the FDA on March 31, 2020. The purpose of the meeting was to obtain feedback on the requirements to register a new QD formulation for Austedo.

A copy of the official minutes of the meeting/telecon 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

¹We 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: EOP2

Meeting Date and Time: March 31, 2020; 3:00-4:00 PM EST
Meeting Location: Teleconference Meeting

Application Number: IND 112975
Product Name: TEV-50717 tablets
Indication: Treatment of chorea associated with Huntington's disease (HD) and tardive dyskinesia (TD) in adults.
Sponsor Name: Teva Branded Pharmaceutical Products R&D, Inc.

Meeting Chair: Eric Bastings, MD
Meeting Recorder: Stacy Metz, PharmD

FDA ATTENDEES

Eric Bastings, MD, Director (acting) DN1
Gerald (Dave) Podskalny, DO, MPHS, Clinical Team Lead
Ken Bergmann, MD, Clinical Reviewer
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Lead
Mariam Ahmed, PhD, Clinical Pharmacology Reviewer
Stacy Metz, PharmD, RPM DN1

SPONSOR ATTENDEES

Douglas Harnish, PhD, VP, Specialty Regulatory Affairs
Laura Rabinovich, PhD, Sr. Dir, Clinical Pharmacology
Frank Schneider, PhD, Assoc Dir, Clinical Pharmacology
Eva Maria Sunzel, PhD, Assoc Dir, Clinical Pharmacology
Micha Levi, PhD, Sr Dir, Pharmacometrics
J E Hamer-Maansson, Assoc Dir, Pharmacology Statistics
Parag Shah, PhD, Sr Dir, Drug Analysis & Formulation
Leonard Alansky, RPh, Dir, Regulatory Affairs CMC
Mark Gordon, MD, Sr Dir, Specialty Clinical Development
Keith Earle, DVM, MSc, Dir, Nonclinical Development

1.0 BACKGROUND

TEV-50717 is marketed under the brand name AUSTEDO as 6, 9, and 12 mg tablets. Teva is developing a QD formulation tablet for TEV-50717 and is planning to bridge to the current twice daily AUSTEDO marketed product. Teva is requesting a meeting to

discuss Teva's plan for registration of this new QD formulation that will be marketed as an alternative to the AUSTEDO tablets given BID.

The purpose and objectives of this meeting are as follows:

- to discuss whether the proposed clinical development plan aiming to demonstrate comparable systemic exposure is sufficient to allow bridging of safety and efficacy of the QD osmotic tablet with the approved AUSTEDO product, and allow for registration of the QD osmotic tablet for the treatment of chorea associated with Huntington's disease (HD) and tardive dyskinesia (TD) in adult patients
- to discuss the design for the registrational Phase 1 clinical studies
- to discuss the proposed study endpoints to support the QD development program
- to discuss the overall development plan for the QD osmotic tablet

FDA sent Preliminary Comments to Teva on March 26, 2020.

2.0 DISCUSSION

2.1. Clinical Pharmacology Questions

Question 1:

Teva plans to conduct 3 phase 1 studies aimed to show PK bioequivalence and assess relative bioavailability. Does the Agency agree that the proposed clinical development plan would support registration of this new QD formulation?

FDA Response to Question 1:

No, we don't agree. See response to Question 3 regarding the acceptability of PK bridging approach based only on AUC. In addition, we have the following comments:

- Given that AUSTEDO is administered with food, we recommend that you combine the food effect study and the planned single dose bioequivalence study to show within study comparison of the bioequivalence of the proposed ER formulation to AUSTEDO under both fasting and fed conditions.
- Since the ER strengths are not proportionally similar in composition, a single dose fasting dosage strength equivalence assessment study or a dosage strength proportionality study for the ER product should be conducted.
- If the proposed ER product has nonlinear pharmacokinetics (PK) over the therapeutic dose range, a single dose of the highest and lowest strengths of the ER product should be compared to their corresponding IR reference tablets administered over the ER dosing interval. If the relative bioavailability (BA) of intermediate ER strengths cannot be inferred based on the studies described above, bioavailability of a single dose of the intermediate strength(s) of the ER

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product under fasting conditions should be compared to the corresponding IR reference tablet administered over the ER dosing interval.

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See Attached Document

Meeting Discussion:

The sponsor may use the steady state exposure as the primary analysis. C_{max} and AUC parameters following the single dose and C_{max}, AUC_{tau}, and C_{min} following repeated dose will be considered when the agency reviews the application. For decision making, the agency will consider the totality of data. See the agency's response to response to Question 2.

The sponsor asked if the agency would consider their proposal of using only the steady-state exposure as the primary analysis. The agency stated their review will be based on the totality of data from the single- and repeated-dose studies. The sponsor inquired about the weighting and the relevance of the single-dose data in decision making. The agency stated that with only limited information, they would not commit to only considering the steady-state information and excluding the relevance that differences in C_{max} may have on efficacy. The agency would need to understand the difference between fasting and fed conditions for the QD formulation following both single- and repeated-dose administration compared to Austedo taken under fed condition (as described in the Austedo label).

The sponsor asked if they could provide information that might support their position that the difference in the C_{max} between Austedo and the QD formulation does not affect efficacy. The agency stated that the sponsor could provide additional information using data from the Huntington's disease (HD) and tardive dyskinesia (TD) programs, if available. The agency reiterated that the information provided in the meeting package about the PK/PD modeling in the TD population alone does not exclude the relevance of the C_{max} to efficacy in the TD and HD populations. The agency suggested that the sponsor include efficacy data from both programs that confirm that administration of doses that provide similar AUC but differ in C_{max} have a similar response, for example, by showing that patients in the Phase 3 trials who split their total daily dose unevenly and those who split their daily dose equally have a similar response. The agency suggested that the sponsor could develop a PK/PD model using all available data for model-based prediction of exposure for HD patients who participated in the Phase 3 study. The model-based C_{max} could be tested for its relevance to efficacy for HD and TD populations. The agency cautioned that C_{max} and AUC are correlated parameters in general, which may confound the interpretation of the results if the quality and quantity of available data do not support such analyses. Utility of such an approach depends on the quality of available PK data from the HD and TD clinical trials and the acceptability of the modeling and simulation approach. The agency agreed with the sponsor that modeling using the active metabolite levels, instead of the parent drug, is

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acceptable for the exposure-response analyses. The parent drug was not quantified in previous TD and HD trials because of assay reliability issues.

The agency emphasized that the relevance of the C_{max} parameter cannot be excluded by the limited data provided in the meeting materials and discussed the limitations of the PK/PD analyses in TD presented in the meeting package. The sponsor inquired if they can submit another package that has additional analyses to show that the C_{max} parameter is not relevant, before they initiate their PK studies. The agency stated that these additional analyses should be included in the NDA.

The sponsor inquired if they can provide the data from the single-dose BE and food effect study and request the agency's guidance on the path forward for developing the QD daily formulation. The agency agreed with this request.

Question 2:

Does the Agency agree with the proposed primary analyte for the Phase 1 clinical studies (b) (4)?

FDA Response to Question 2:

No, we don't agree. Given the ability of your developed assay to reliably measure deutetrabenazine, you should analyze the data for the parent compound using the confidence interval (CI) approach. You should also report the geometric mean ratios and the CI for each active metabolite. The acceptability of the study results will be matter of review. Please refer to the product specific guidance for deutetrabenazine for more information.

<https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm?event=Home.Letter&searchLetter=D#letterSearchBar>

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See Attached Document

Meeting Discussion:

The studies should be powered to provide a precise estimate for the geometric mean ratios (GMR) for all relevant parameters, including the parent and the metabolites.

The sponsor inquired about the agency's position of basing the primary BE analysis on the parent, instead of the metabolites, and questioned the relevance of OGD's product specific guidance in that case. The parent contributes to less than (b) (4) of the total exposure and there is a poor correlation between the parent and the metabolites. The sponsor argued that the parent is not expected to contribute to efficacy. Although the concentration of the parent is relatively low, the variability is higher compared with the metabolite. Thus, the sponsor would like to power the study based on the exposure for the metabolites instead of the parent. The sponsor asked, what if the parent did not meet the BE limits and the metabolite did; how would the agency address such data?

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The agency acknowledged that the parent levels would be low compared to the active metabolites. However, it is important to understand any potential differences in the exposures of parent and the active metabolites from the proposed modified-release QD formulation relative to Austedo. The agency clarified that their review will consider the totality of evidence and it would not be limited to a single measured analyte. The agency stated that it is up to the sponsor to decide how would they like to power their BE study. Ideally the study should be powered for the worst-case scenario with regard to the variability of the analytes to allow for precise estimation of the relevant PK parameters. The agency also clarified that the poor correlation seen previously between the exposure to parent and metabolites was caused by unreliable or insensitive assays.

Question 3:

Does the Agency agree with

(b) (4)

FDA Response to Question 3:

No. You have not provided information that excludes C_{max} as an important contributor to efficacy. You indicated that AUC or C_{ave,ss} is a relevant parameter for the efficacy, based on a PK/PD model in patients with TD. However, this argument does not exclude the relevance of C_{max} for patients treated for TD or HD. We acknowledge your discussion about the flexibility in posology for AUSTEDO, and the titration from 6 mg once daily to twice daily based on tolerability/efficacy. However, on its own, it does not support the notion that C_{max} is not. We also note that food increased the C_{max} by 50% and did not affect the AUC; however, AUSTEDO should be administered with food, as was done in the Phase 3 clinical trials. The dose you chose for the Phase 3 trials of AUSTEDO was based on an attempt to match the AUC for the total active metabolites of tetrabenazine rather than the C_{max}, and that the C_{max} for the total active metabolites was 50% lower than after the administration of tetrabenazine. However, the efficacy of AUSTEDO was supported by information from a controlled clinical efficacy and safety study. It is not clear that further lowering of C_{max} will not impact the efficacy of the proposed once daily formulation.

If the proposed once-daily formulation is not bioequivalent to AUSTEDO (for C_{max} and AUC), additional clinical studies would be needed.

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See Attached Document

Meeting Discussion:

The sponsor should characterize the food effect in a single-dose study, and provide a comparison with a single dose of Austedo administered with food (as per Austedo's dosing recommendation in the label).

The sponsor requested clarification of the agency's response to Question 1, on whether they need to administer the reference (Austedo) with food. The agency confirmed that in the single-dose BE study, the reference should be Austedo administered with food, as recommended in the current Austedo label. The QD formulation should be administered with and without food, as the test. The agency emphasized that the food effect on the QD formulation should be addressed using a single-dose study.

The sponsor agreed to the agency recommendations and requested to submit the data following the single-dose BE study to obtain the agency guidance on the development of the QD formulation. The agency agreed to consider this data and provide guidance on the path forward for the development of the QD formulation

Question 4:

Does the Agency agree that

(b) (4)

(b) (4)

FDA Response to Question 4:

See response to Question 1, 2 and 3.

Meeting Discussion:

No further discussion at the meeting.

2.2. Nonclinical Questions**Question 5:**

The sponsor is seeking agreement with the Agency that no additional nonclinical studies are warranted to support the upcoming clinical studies as well as registration of TEV-50717 QD formulation. The Sponsor's position to seek a waiver is based on available nonclinical and clinical data from AUSTEDO marketing application, and from recent clinical PK data demonstrating comparable systemic exposure of TEV-50717 QD formulation to that of marketed AUSTEDO given BID.

FDA Response to Question 5:

Nonclinical studies of TEV-50717 would not be needed if systemic exposure to deutetrabenazine or metabolites does not exceed that following administration of Austedo and there are no formulation-related issues (e.g., impurities) that raise a safety concern.

Meeting Discussion:

No further discussion at the meeting.

Question 6:

The Sponsor is seeking agreement with the Agency that no additional nonclinical safety studies are warranted to support the excipient profile in TEV-50717 24 mg QD

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formulation, since all excipients are within the US FDA IID limits for the oral route of administration. Does the Agency agree?

FDA Response to Question 6:

Based on the information provided in the meeting package, it does not appear that nonclinical studies would be needed to support the safety of the excipients in TEV-50717.

Meeting Discussion:

No further discussion at the meeting.

2.3. Chemistry, Manufacturing and Controls Question

Question 7:

Teva plans on

(b) (4)

(b) (4)

(b) (4) Does the Agency agree that

(b) (4)

(b) (4)

(b) (4) would support registration of this new QD formulation?

FDA Response to Question 7:

We do not agree. Per ICH Q1A(R2) Stability Testing of New Drug Substances and Products,² we recommend that the initial NDA submission include a minimum of 12 months long-term (25°C/60% R. H.) stability data, plus 6 months accelerated (40°C/75% R. H.) data for three primary batches per strength of the same formulation as the to-be-marketed product in the proposed commercial packaging. The Office of New Drug Products (ONDP) may recommend that the Agency refuse to file an NDA that does not include the recommended stability data package. The expiration dating period assigned during the review will be commensurate with the extent and quality of the available stability data. Refer to ICH guidance Q1E Evaluation of Stability Data.³

Whether information submitted subsequent to the original NDA submission will be determined based on the timing of the submission and available Agency resources.

Meeting Discussion:

No further discussion at the meeting.

² <https://www.fda.gov/media/71707/download>

³ <https://www.fda.gov/media/71722/download>

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*.⁴ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.⁵

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁶

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic*

⁴ 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>.

⁵ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁶ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

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Submissions in Electronic Format--- Standardized Study Data. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,⁷ as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards.

Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁸ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at fda.gov.⁹ For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of

⁷ <https://www.fda.gov/media/88173/download>

⁸ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁹ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide¹⁰ (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.¹¹ When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.¹²

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources¹³ and the CDER/CBER Position on Use of SI Units for Lab Tests website.¹⁴

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

¹⁰ <https://www.fda.gov/media/88173/download>

¹¹ <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹² <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

¹³ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹⁴ <https://www.fda.gov/media/109533/download>

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guidance for industry *Assessment of Abuse Potential of Drugs*.¹⁵

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).¹⁶ 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).¹⁷

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

¹⁵ 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>.

¹⁶ 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>.

¹⁷ <http://www.regulations.gov>

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)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>

(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.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

- (1) Study phase
- (2) Statement of whether the study is intended to support marketing and/or labeling changes
- (3) Study objectives (e.g., dose finding)
- (4) Population
- (5) A brief description of the study design (e.g., placebo or active controlled)
- (6) Specific concerns for which you anticipate the Division will have comments
- (7) For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to

endpoint measures, dose, and/or population)

- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

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

/s/

ERIC P BASTINGS
04/28/2020 04:13:49 PM