CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213586Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 124384

MEETING MINUTES

Teva Branded Pharmaceutical Products, R&D, Inc.
Attention: Levana Volovsky
Director, Regulatory Affairs
145 Brandywine Parkway
West Chester, PA 19380

Dear Ms. Volovsky:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TV-46000 (risperidone extended-release injectable suspension).

We also refer to the teleconference between representatives of your firm and the FDA on March 31, 2021. The purpose of the meeting was to obtain feedback and concurrence on the content and analyses in the planned NDA submission.

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

If you have any questions, contact Eugene Lee, Regulatory Project Manager, at C.Eugene.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 31, 2021 at 11:00AM to 12:00PM
Meeting Location:	FDA Zoom for Government
Application Number:	124384
Product Name:	TV-46000
Indication:	Treatment of schizophrenia
Sponsor Name:	Teva Branded Pharmaceutical Products, R&D, Inc.
Regulatory Pathway:	505(b)(2)
Meeting Chair:	Tiffany R. Farchione, MD
Meeting Recorder:	C. Eugene Lee, PharmD

FDA ATTENDEES

Tiffany R. Farchione, MD	Director, Division of Psychiatry (DP)
Bernard Fischer, MD	Deputy Director, DP
Pamela Horn, MD	Clinical Team Leader, DP
Roberta Rasetti, MD	Clinical Reviewer, DP
Amy Avila, PhD	Nonclinical Reviewer, Division of Pharmacology/ Toxicology for Neuroscience (DPT-N)
Sonia Tabacova, PhD	Nonclinical Reviewer, DPT-N
Julia Pinto, PhD	Branch Chief, Office of Pharmaceutical Quality (OPQ)
Valerie Amspacher, PharmD	Quality Assessment Lead, OPQ
Ada Zhuang, PhD	Team Leader, Office of Clinical Pharmacology (OCP)
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, Division of Biometrics I (DBI)
Kelly Yang, PhD	Biometrics Reviewer, DBI
Mona Khurana, MD	Pediatric Team Leader, Division of Pediatric and Maternal Health (DPMH)
Ramy Abdelrahman, MD	Pediatric Reviewer, DPMH
Doug Warfield, PhD	Associate Director Biomedical Informatics, DP
Denise Johnson-Lyles, PhD	Senior Regulatory Project Manager, Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
C. Eugene Lee, PharmD	Regulatory Project Manager, Division of Regulatory Operations for Neuroscience

SPONSOR ATTENDEES

Douglas Harnish, PhD	Vice President, Regulatory Affairs
Prasad Peri, PhD	Senior Director, Regulatory Affairs CMC
Len Alansky, RPh	Director, Regulatory Affairs CMC
Eran Harary, MD	Vice President, Therapeutic Area Head, Neurology and Psychiatry Clinical Development
Roy Eshet, MD	Senior Director, Neurology and Psychiatry Clinical Development
Helena Knebel, MD	Senior Director, Safety Physician, Global Patient Safety and Pharmacovigilance
Nir Sharon	Associate Director, Statistics
Malini Iyengar	Head of Clinical Pharmacology Statistics
Marjana Durrigl, PhD	Associate Director, CMC Lead
Darka Metličić	Vice President, Generics R&D Site Head Zagreb
Petra Golja Gašparović, PhD	Associate Director, Analytics
James Roberts	Associate Director, Device
Avia Merenlender Wagner, PhD	Senior Manager, Clinical Pharmacology & Pharmacometrics
Anna Elgart, PhD, MBA	Director, Clinical Pharmacology & Pharmacometrics
(b) (4)	Consultant, Clinical Pharmacology & Pharmacometrics
Lilach Golan, DVM, PhD	Nonclinical Development
Alasdair Mackellar	Senior Director, Project Leader
Joël Richard	Chief Development Officer, MedinCell
Levana Volovsky	Director, Regulatory Affairs
Mark Suett, MD	Senior Global Medical Director, Psychiatry, Medical Affairs

1.0. BACKGROUND

Teva Branded Pharmaceutical Products R&D, Inc. is developing TV-46000, risperidone extended-release injectable subcutaneous suspension (SC), for the treatment of schizophrenia. TV-46000 contains risperidone and two copolymers as excipients dissolved in dimethyl sulfoxide that form a depot under the skin to deliver therapeutic levels of risperidone over periods of 1 to 2 months. TV-46000 is intended to be administered by SC injection from a pre-filled syringe (PFS) at dosages of 50, 75, 100, or 125 mg monthly or 100, 150, 200, or 250 mg every 2 months. There are currently two marketed long-acting injectable (LAI) formulations of risperidone: Perseris (also SC) and Risperdal Consta (intramuscular injection). The proposed 2-month dosing interval is less frequent than Risperdal Consta (every 2 weeks) and Perseris (monthly). The Sponsor hypothesizes that the use of a smaller needle size, lower injection volume, and the lack of reconstitution compared to other existing products may provide a well-tolerated and convenient delivery of risperidone and facilitate treatment. The Sponsor

plans to seek approval via the 505(b)(2) pathway, relying on Risperdal tablets (NDA 20272) as the listed drug (LD).

To date, the Sponsor has conducted the following phase 1/phase 3 studies:

- *SRISPE1ZG15EU* (completed): A phase 1, single ascending dose (12.5 and 25 mg; in arm or abdomen) pharmacokinetic study conducted in 50 healthy subjects

- *TV46000-SAD-10055* (completed): A phase 1, single ascending dose (50, 75, 100, and 150 mg in abdomen; 225 mg in arm) and multiple ascending dose (75 and 150 mg; administered on Days 1, 29, and 57 in abdomen) pharmacokinetic study conducted in 99 patients with schizophrenia or schizoaffective disorder

- *TV46000-BA-10148* (completed): A phase 1, parallel-design, single-dose (100 mg in abdomen) study to assess the relative bioavailability (BA) of TV-46000 in PFS compared to vials in 120 patients with schizophrenia or schizoaffective disorder.

- *TV46000-CNS-30072* (completed): A phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of TV-46000 administered every 1 to 2 months at doses of 50 to 250 mg (arm or abdomen) as a maintenance treatment in 544 adult and adolescent patients with schizophrenia. The primary endpoint was impending relapse rate over time between TV-46000 and placebo-treated patients.

- *TV46000-CNS-30078* (ongoing): A phase 3, multicenter, double-blind, uncontrolled, parallel-group study to evaluate the long-term safety and tolerability of TV-46000 administered every 1 to 2 months at doses of 50 to 250 mg (arm or abdomen) for up to 56 weeks in adult and adolescent patients with schizophrenia (107 de novo subjects, 277 roll-over subjects from Study 30072 thus far).

In the agreed initial pediatric study plan, the Sponsor described their intent to recruit adolescent patients with schizophrenia in their proposed phase 3 studies because of the lack of pediatric data in LAI schizophrenia trials. However, due to the anticipated challenges in enrolling adolescents, there was no target number for enrollment. Only eight adolescent patients were screened, and only two were randomized to receive TV-46000. (b) (4)

The Sponsor's stated purpose for this meeting is to obtain feedback and concurrence on the content and analyses in the planned NDA submission.

2.0. DISCUSSION

2.1. CLINICAL PHARMACOLOGY

Question 1: The Sponsor has characterized the PK and exposure-response relationship of TV-46000 following subcutaneous (SC) administration in 5 clinical studies, including 3 Phase 1 clinical studies and 2 Phase 3 clinical studies (RISPE1ZG15EU, Study 10055, Study 10148, Study 30072, and Study 30078).

Does the Agency agree:

a) With the proposed presentation of the PK summary documents – all available PK and exposure-response analyses in the Summary of Clinical Pharmacology (Module 2.7.2)?

b) That all PK and exposure-response analyses in the Summary of Clinical Pharmacology (Module 2.7.2) are based on the total active moiety (TAM), the sum of plasma concentrations of risperidone and 9-hydroxy-risperidone (9-OH-risperidone), with the individual analytes being displayed in individual CSRs, appendices, and population pharmacokinetic (PopPK) report in NDA Module 5 and referenced in NDA Module 2.7.2?

FDA Response to Question 1a: *The proposal appears reasonable. Please note the general expectations for submitting pharmacometric data and models can be found at the Agency's website for Model/Data Format.*

FDA Response to Question 1b: *The proposal appears acceptable. Please ensure data and rationale are provided to support the use of the TAM (sum of risperidone + 9-OH-risperidone) in your analysis, and the original data sources are correctly hyperlinked in the document. Please perform AUCtau, Cmax,ss, Cmin,ss comparison for oral risperidone and TV-46000 in PFS and/or vial presentations to support intended dosing conversion between the two dosing routes (oral versus sc). Please ensure any analysis done for TAM is performed for each active moiety separately as well.*

Discussion: *No further discussion.*

Question 2: The Sponsor performed separate Phase 3 studies generating clinical use data for both the PFS (Study 30078) and vials (Study 30072). Both dosage forms were previously evaluated together in a Phase 1 relative BA study (Study 10148). The Sponsor also performed PopPK analysis of pooled data from all Phase 1 and Phase 3 studies to further support comparability of these 2 presentations.

a) Does the Agency agree with the Sponsor position that, given the strong scientific rationale supporting this oral risperidone exposure adjustment, this analysis correctly

characterizes the exposure of risperidone following administration of TV-46000 from vial or PFS presentations, indicating comparability of the product presentations?

b) Does the Agency agree that the clinical experience from the PFS Phase 3 study and the PopPK analysis, together with data from the already provided Phase 1 relative BA study, can be used to support the acceptability of the PFS for commercial use?

FDA Response to Question 2a and 2b: *This would be a matter of review.*

Discussion: *The Sponsor noted in the meeting package that heterogeneity of the study population may contribute to the exposure difference between PFS and vial presentations. The relative BA analysis demonstrated ~16% to 17% higher exposure ($AUC_{0\text{-}84\ days}$) of TAM following administration of PFS compared to vial. Additionally, in the oral dosing period, patients in the vial treatment group were found to have lower exposure levels compared to patients in the PFS treatment group. The exposure difference between the between PFS and vial presentations becomes smaller after exposure adjustment from the oral dosing period.*

The Division explained that we usually do not recommend use of a post-hoc analysis to support comparability evaluation. However, we do consider the totality of information contained in the application package when making the final decision. For example, phase 3 efficacy and safety data, and popPK analysis, as listed in Teva response to FDA preliminary comments, would all be taken into consideration when making final conclusions.

Additional Comments from Clinical Pharmacology

You should perform modeling and simulation for both every month and every 2 month dosage regimens to determine an acceptable dosing window, strategies to address missed doses, when and under what scenarios oral supplementation might be needed, dosing recommendations for short-term and long-term concomitant medications, and for patients with renal or hepatic dysfunction. Please also perform a simulation for scenarios when dose dumping occurs.

We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA guidance for industry, Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format *(December 2016). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.*

Discussion: *No further discussion.*

2.2. CLINICAL

Question 3: An overview of the proposed clinical data package to support the 505(b)(2) NDA is provided in Section 6.1. This package includes 1 successful Phase 3 efficacy and safety study (Study 30072), an interim data cut for the ongoing Phase 3 long-term safety study (Study 30078), and 3 previously submitted Phase 1 studies (RISPE1ZG15EU, Study 10055, and Study 10148).

a) Does the Agency agree that the proposed clinical data package is acceptable for the NDA filing and review for the proposed indication of TV-46000 for the treatment of schizophrenia?

b) Does the Agency agree with the proposed safety database for the NDA filing?

FDA Response to Question 3a: *The results of Study 30072, interim safety data from Study 30078, and the results of Studies RISPE1ZG15EU, 10055, and 10148 appear adequate for NDA submission. Acceptability for filing would be a review issue after the NDA is submitted.*

FDA Response to Question 3b: *The overall exposure numbers by dosing regimen appear adequate to support NDA submission. Your plan to submit safety data for 133 patients with exposure for at least 1 year (65 for the monthly regimen and 68 for the every-2-month regimen) at the time of NDA submission is consistent with past discussions with the Agency. You have not provided a detailed summary of patient exposure by dose and dosing regimen in your briefing document, and the adequacy of exposures to the highest doses tested would be a matter of review.*

Discussion: *No further discussion.*

Question 4: The Sponsor plans to provide an interim data cut for the ongoing Phase 3 long-term safety study (Study 30078) in the initial NDA (also included in this briefing package; see *TV46000-CNS-30078 Interim CSR*), which includes data from new patients enrolled to the study. Data from patients who rolled over into this study from the Phase 3 efficacy and safety study (Study 30072) will be incorporated into the 120-day safety update. Is this proposal to provide the data from ongoing Phase 3 long-term safety study acceptable to the Agency?

FDA Response to Question 4: *Your plan to submit safety data for at least 300 patients with exposure for at least 6 months from the ongoing long-term safety study, 30078, by the 120-day safety update, is acceptable.*

Discussion: *No further discussion.*

Question 5: Both q1m and q2m TV-46000 dosing regimens have demonstrated statistically significant efficacy in the Phase 3 Study 30072. In addition, the safety profile of both dosing regimens in the 2 Phase 3 studies (Study 30072 and Study 30078) is consistent with the known safety profile of other risperidone formulations. Aiming to provide patients convenience, acceptance, and flexibility for their treatment options, the Sponsor plans to apply for approval of both dosing regimens (q1m and q2m) for the treatment of schizophrenia. Does the Agency agree with the Sponsor's proposal to license TV-46000 injection for both q1m and q2m dosing regimens for the treatment of schizophrenia?

FDA Response to Question 5: *The adequacy of the data to support labeling of both dosing regimens will be a matter of review following NDA submission. As previously noted in the December 2017 EOP1 meeting, the 2-month dosing interval is associated with a large fluctuation in PK parameters, and the data will be reviewed for potential lack of efficacy and increased risk for relapse prior to the next injection.*

Discussion: *The Sponsor proposed to conduct an exploratory analysis of the exposure-response relationship to describe the correlation between plasma TAM exposures and risk of relapse and to conduct a Kaplan-Meier survival analysis on the injection regimen-level to evaluate the risk of relapse for q2m for all doses over time in the inter-dose interval. The Sponsor asked whether their proposal would suffice to address the Division's concern. The Division indicated that, at a high level, the Sponsor's approach appears reasonable, but from a statistical standpoint the Sponsor's analysis proposal to evaluate the risk for relapse lacks sufficient detail. The Sponsor should include the detailed algorithm used in the NDA submission. The Division may ask for additional information when reviewing the NDA in the future and would make an effort to evaluate and communicate with the Sponsor on this issue early in an NDA review.*

Question 6: Comparable efficacy, safety, tolerability, and PK characteristics have been demonstrated for TV-46000 injected in the abdomen and the upper arm. This was demonstrated with subtherapeutic doses of TV-46000 in Study RISPE1ZG15EU, with therapeutic doses in Study 10055, and in the Phase 3 studies (Study 30072 and Study 30078). Does the Agency agree that this information is sufficient to assess whether both injection sites (abdomen and upper arm) may be used for the administration of TV-46000?

FDA Response to Question 6: *The adequacy of the data to support use at both injection sites will be a matter of review.*

Discussion: *No further discussion.*

Question 7: Data from the clinical development program, encompassing 2 Phase 1 studies in patients with schizophrenia or schizoaffective disorder and 2 Phase 3 studies in patients with schizophrenia, will be integrated for the ISS. Data from the 2 Phase 3 studies will also be integrated for the Integrated Summary of Efficacy (ISE). Only data from new patients in the Phase 3 long-term safety study (Study 30078) will be included in these analyses.

For the integrated safety and efficacy analyses, 2 analysis sets will be applied to the 2 defined patient cohorts: the safety analysis set will be applied to both cohort 1 (which includes the patients from the Phase 3 studies) and cohort 2 (which includes the patients from the Phase 1 studies). The efficacy analysis set will be applied to cohort 1 only.

Does the Agency agree with the proposed analyses and presentation of data as described in the ISS/ISE Statistical Analysis Plan (SAP):

- Is this plan acceptable?
- Does the Division have any feedback or advice on the proposed SAP for the ISS/SCS?

FDA Response to Question 7: *We do not agree with your proposed treatment groups for Cohort 1. Patients on monthly and every-2-month dosing regimens should not be grouped together as the PK profile differs between these regimens. We recommend the following groups for Cohort 1: placebo, 50 mg q1m, 100 mg q2m, 75 mg q1m, 150 mg q2m, 100 mg q1m, 200 mg q2m, 125 mg q1m 250 mg q2m, TV-46000 q1m all doses pooled, TV-46000 q2m all doses pooled, and all TV-46000 doses and dosing intervals pooled.*

Your proposed plan for Cohort 2 appears acceptable.

In addition to groupings by dose and dosing interval, include summaries of adverse events by injection site.

Discussion: *No further discussion.*

2.3. STATISTICS

Question 8: The efficacy analysis set for the integrated efficacy analysis complies with while-on-treatment estimand and includes all patients stabilized on oral risperidone (2 to 5 mg/day in adults or 2 to 4 mg/day in adolescents) who received at least 1 dose of test (TV-46000) or placebo IMP according to the treatment group to which they were randomized. This estimand's summary statistics will be the difference between treatment groups in time to relapse (survival) under the treatment to which the patient was initially randomized until his/her relapse or last treatment/early termination. The

primary efficacy analysis in Study 30072, which will also be used for the ISE, is time to impending relapse for all stabilized patients.

The safety analysis set complies with while-on-treatment estimand and includes all patients treated with oral risperidone (2 to 6 mg/day) who received at least 1 dose of test (TV-46000) or placebo IMP. In this analysis set, treatment will be assigned based upon the treatment patients actually received, regardless of the treatment to which they were randomized.

The primary analyses for the ISE and the sensitivity analyses details are provided in the ISS/ISE SAP (Appendix D) and the Company Position below.

a) Is the primary efficacy analysis of the ISE acceptable?

b) Does the Agency confirm that the sensitivity analysis of the tipping-point, as applicable, can support the conclusion of the robustness of the results?

FDA Response to Question 8: *Given that there is only one efficacy trial to support the indication, there is no need to create an ISE. Long-term safety study 30078 should not be included in the ISE.*

> ***Discussion:*** *The Division had no objection to the Sponsor's proposed side-by-side comparison of the two studies in module 2.7.3 in an exploratory manner.*

Question 9: The Study Data Standardization Plan (Appendix B), planned submission format, datasets, and Case Report Form format are provided in this package and are planned to be included in the NDA.

The planned NDA will be prepared according to the electronic common technical document (eCTD) format, and the data will follow the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM). All study datasets from studies conducted in healthy volunteers and patients will be submitted. The Sponsor will provide Statistical Analysis System (SAS) datasets in lieu of classic case report tabulations. Each dataset will be provided as a SAS transport file and a Data Definition Table in accordance with the FDA Guidance ("Providing Regulatory Submissions in Electronic Format - Standardized Study Data"). Both raw and derived data will be provided.

For the multiple imputation used for tipping-point analysis, the Sponsor plans to submit the SAS programs that generate the "complete" datasets and analysis and statistical summary datasets in order to enable the Agency to reconstruct the tipping-point analysis.

a) Does the Agency agree or have any advice on the Study Data Standardization Plan, submission format, and datasets that will be provided?

b) Will the Agency accept receiving the SAS programs that generate the tipping-point analysis without accompanying imputed datasets?

FDA Response to Question 9a: *Please include the following in your future NDA submissions:*

- *All raw as well as derived variables in .xpt format;*
- *Raw data in legacy format if data were not collected in CDISC;*
- *SAS programs that produced all efficacy results;*
- *SAS programs used to generate derived variables from the original clinical database, and detailed descriptions of mappings from the clinical database to derived variables, together with a document of derived variable definitions ('define' file);*
- *A list of IND number with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*

FDA Response to Question 9b: *We have no objection to receiving the SAS programs without accompanying imputed datasets. However, the provided SAS code needs to be executable and accompanied by a detailed algorithm.*

Discussion: *No further discussion.*

2.4. REGULATORY AND ELECTRONIC SUBMISSION

Question 10: Does the Agency agree with the Sponsor's proposed Table of Contents (TOC) and data to be included in the TV-46000 NDA submission?

FDA Response to Question 10: *See the FDA's* Comprehensive Table of Contents Headings and Hierarchy.

Discussion: *No further discussion.*

Question 11: The Sponsor addressed the Agency's request to study TV-46000 in adolescents by applying continuing efforts for enrollment and assessment of the safety and effectiveness of TV-46000 in adolescent patients in the Phase 3 development program (both in the completed Study 30072 and in the ongoing long-term safety Study

30078). [redacted]

FDA Response to Question 11: *Due to the small number of adolescent patients treated so far with TV-46000, it is unlikely that these data would meaningfully contribute to a pediatric assessment* [redacted] *We recommend that you submit the agreed PSP with your application. We will evaluate your efforts to enroll pediatric patients and the data, simulations, and analyses submitted as part of the application review.*

Discussion: [redacted] *The adequacy of the data would be a matter of review.*

The Division stated that to be fileable an NDA application must be complete at the time of submission such that the review team can begin a substantive review. The Division indicated that if the Sponsor intends to enroll new pediatric patients and collect additional data in the ongoing study that could substantially add to the exposure and safety database in pediatric patients, these data should be submitted at the time of NDA submission to allow a substantive review of the application to begin.

Question 12: Does the Agency agree that it would be appropriate to utilize the integrated data from both Phase 3 studies for the adverse drug reaction (ADR) tables, which will include data from both Study 30072 and new patients in Study 30078? Considering that Study 30078 is still ongoing, would the Agency agree to receive Teva's finalized proposed Prescribing Information at the 120-day safety update to reflect the remaining patient data, in case any new signal is observed?

FDA Response to Question 12: *The presentation of adverse drug reactions in the prescribing information would be a matter of review. You may propose changes to the proposed prescribing information during the review cycle, at your discretion.*

Discussion: *No further discussion.*

2.5. CMC

Question 13: Does the Agency agree that the proposed commercial release and stability tests are appropriate for the sterile risperidone drug substance in support of the planned NDA submission?

FDA Response to Question 13: *The proposed specification for sterile risperidone drug substance appears reasonable from an API perspective; however, final determination is an NDA review issue and would incorporate the microbiology and non-clinical perspective.*

Discussion: *No further discussion.*

Question 14: Does the Agency agree that the proposed commercial release and stability tests are appropriate for the release-modifying excipients diblock and triblock co-polymers in support of the planned NDA submission?

FDA Response to Question 14: *The proposed specifications for the diblock and triblock copolymers appear reasonable. However, the adequacy of the specification will be determined during the NDA review in the context of the totality of the data and the adequacy of the DMF that contains the CMC information for these non-compendial excipients.*

Discussion: *No further discussion.*

Question 15: Does the Agency agree that the proposed commercial release and stability tests are appropriate for the TV-46000 in PFS drug product in support of the planned NDA submission?

FDA Response to Question 15: *The proposed specification for the drug product appears reasonable. However, the adequacy of the specification would be determined during the NDA review in the context of the totality of the data.*

Discussion: *No further discussion.*

Question 16: TV-46000 in PFS is intended to be marketed in 7 different product strengths (50, 75, 100, 125, 150, 200, and 250 mg) that have the same qualitative and quantitative composition and differ only in the fill weight provided in PFS. The FDA previously requested that the Sponsor ensure that there is no dose overlap (due to proximity of some strengths) and that a syringe delivers an accurate dose. As a response to these requests, the Sponsor is proposing the introduction of (b) (4) (b) (4) as a parameter in the drug product specification that will address both dose

accuracy and potential dose overlap. Below, the Sponsor presents the testing methodology principles, batch data, and proposed acceptance criteria for (b) (4) In addition, delivered volume, which is an essential performance requirement (EPR), will be tested explicitly in the DV protocol and will confirm the system's ability to deliver the intended volume of product over its shelf life. Delivered volume will be tested implicitly at (b) (4) (b) (4) (b) (4) (b) (4)

Does the Agency agree with the Sponsor's proposal for the testing methodology and approach for the establishment of acceptance criteria for (b) (4) in the drug product specification and for delivered volume in the DV protocol?

FDA Response to Question 16: *The Agency has requested a CDRH consult for this question. We expect to provide a response either during the teleconference or as a post-meeting note.*

Discussion: *No further discussion.*

Post-meeting Comment from CDRH
We recommend that you test delivered volume instead of (b) (4) for your release, stability, and (b) (4) for the syringe as it is the standard method for evaluating prefilled syringe products.

The design verification approach for delivered volume appears acceptable. You proposed 12 months stability testing. Please ensure the design verification covers your proposed shelf life.

3.0. OTHER

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 27, 2021, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

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*.[2] 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.[3]

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[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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).[6] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov).[7]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of 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.

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[6] 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.
[7] http://www.regulations.gov

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*

(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

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

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

process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[9]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic 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*, as well as email access to the eData Team (cder-edata@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 page[10] 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. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical

[9] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of 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 Guide (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. 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.[11]

4.0. ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0. ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's discussion points for Questions 2, 5, 8, 11, and 16.

8 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

[11] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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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/

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