CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211855Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120446

MEETING MINUTES

Alkermes, Inc.
Attention: Valmik Doshi
Senior Associate, Regulatory Affairs
852 Winter Street
Waltham, MA 02451

Dear Mr. Doshi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALKS 8700.

We also refer to the meeting between representatives of your firm and the FDA on June 19, 2018. The purpose of the meeting was to discuss the content and format of your proposed NDA.

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

If you have any questions, call Sandra Folkendt, Regulatory Project Manager, at (240) 402-2804.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4289458

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 19, 2018, 9 am
Meeting Location: Teleconference

Application Number: IND 120446
Product Name: ALKS 8700 (diroximel fumarate)

Indication: Relapsing forms of multiple sclerosis
Sponsor/Applicant Name: Alkermes, Inc.

Meeting Chair: Billy Dunn
Meeting Recorder: Sandra Folkendt

FDA ATTENDEES
Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Associate Director
John Marler, MD, Clinical Team Leader
Paul Lee, MD, PhD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Melissa Banks-Muckenfuss, PhD, Pharmacologist
Sandra Folkendt, Regulatory Health Project Manager
Susan Daugherty, Regulatory Health Project Manager
Office of Biostatistics
Kun Jin, PhD, Biometrics Team Leader, Biometrics I
Office of Clinical Pharmacology
Kevin Krudys, PhD, Pharmacometrics Team Leader
Hristina Dimova, PhD, Clinical Pharmacology
Office of Surveillance and Epidemiology
Charlotte Jones, MD, PhD, MSPH, DRISK Medical Officer
Monique Killen, PharmD, Regulatory Project Manager
Division of Biopharmaceutics
Om Anand, PhD, Biopharmaceutics Reviewer

Reference ID: 4289458

SPONSOR ATTENDEES

Craig Hopkinson, MD, Chief Medical Officer /Sr. VP, Medicines Development and Medical Affairs
Georgianna Harris, PhD, Sr. VP, Regulatory Affairs
Lisa von Moltke, MD, VP, Head of Clinical Development
Bhaskar Rege, PhD, VP, Clinical Pharmacology and Translational Medicine
Gary Bloomgren, MD, VP, Drug Safety and Pharmacovigilance
Aine Miller, PhD, Sr. Director, Regulatory Affairs
Richard Leigh-Pemberton, MD, Sr. Director, Clinical Research
Tammy Phinney, VP, US Regulatory Sciences (Biogen)

1.0 BACKGROUND

ALKS 8700 (diroximel fumarate) is being developed by Alkermes for the treatment of relapsing-remitting multiple sclerosis. Diroximel fumarate is a prodrug that converts to monomethyl fumarate, the active metabolite in the approved reference listed drug, Tecfidera. The sponsor plans to submit a 505(b)(2) application with pharmacokinetic bridging studies to Tecfidera. An End of Phase 2 meeting was held between the sponsor and FDA on August 4, 2015. On April 27, 2018, Alkermes requested a pre-NDA meeting with the Division to discuss the content and format of their 505(b)(2) application with a target submission date of December 2018.

A chemistry only pre-NDA meeting was held on April 11, 2018. FDA sent preliminary comments to Alkermes on June 15, 2018.

2. DISCUSSION

2.1. Regulatory and Administrative

Question 1: Does the Agency agree that the proposed format and content of the NDA submission is adequate for filing the diroximel fumarate NDA?

FDA Response to Question 1:

All previously submitted clinical, pharmacological, and nonclinical studies submitted under IND 120446 that support NDA 211855 should be included in the submission, and not merely cross-referenced.

In addition, we have the following requests:

a) Provide an analysis that identifies all opportunistic infections.
b) Clarify the criteria for reporting MS relapse as an adverse event rather than an outcome event.
c) Provide a table of all known cases of malignancy and pre-malignant conditions that have occurred in subjects who participated in the clinical development program. The table should include the study, subject number, event Preferred Term, cumulative drug dose received at the time of the event, latency from first dose to malignancy diagnosis, subject's age at the time of diagnosis, subject's country of origin, subject's sex, duration of follow-up for that subject, and a link to the narrative.

Reference ID: 4289458

d) Provide tables with the number of reported malignancies, number of subjects, subject years of exposure, and incidence rates for cases of malignancy in completed and ongoing trials. We also request presentation of these analyses stratified by duration of subject follow-up (less than 1 year, 1 to less than 2 years, 2 to less than 3 years, and more than 3 years). For each subject group, we request the median cumulative dose, the cumulative dose range, and the median duration of treatment exposure.

The adequacy of content is subject to review after receipt of the full submission.

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

Question 2: Does the Agency agree with the Study Data Standardization Plan (SDSP) and the plans for inclusion of completed case report forms and patient narratives to be submitted with diroximel fumarate NDA?

FDA Response to Question 2:
The data plan and Case Report Form submission format appear acceptable. Ensure all hyperlinks within documents and link to the appropriate associated documents are functional. We also have the following requests regarding CRFs and narratives:

a) Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. Narratives should be integrated; that is, for subjects who had more than one event requiring a narrative and whether the event occurred in the same trial or in the core study or an extension study, present a single narrative rather than separate narratives for the various events. After submission of the NDA, you should be prepared to supply rapidly any additional CRFs or narratives upon our request. See also item 2(g) below.
b) Include a MSWord file and Excel spreadsheet that indicates those subjects for whom you submitted a case report form or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
c) Provide reports for any autopsies conducted after study deaths.
d) Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.
e) Note that CRFs should include all clinical documents collected about the patient, regardless of whether you label them "CRFs"; these documents include
f) Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, and data queries.
g) Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including "Lost to follow-up", "Other", "Physician/investigator decision", "Withdrew consent", and "Patient decision", provide more specific information regarding the discontinuation. The Division may request selected narratives or CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA submission. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the

reader to come to a reasonable conclusion regarding the subject and the adverse event. Complete narratives may require additional items, but you should include the following items in all narratives when available:

i. Patient age and gender
ii. Adverse event onset and stop dates presented as relative Study Day number
iii. Signs and symptoms related to the adverse event being discussed
iv. An assessment of the relationship of exposure duration to the development of the adverse event
v. Pertinent medical history
vi. Concomitant medications with start dates relative to the adverse event
vii. Pertinent physical exam findings
viii. Any abnormal vital sign measurements
ix. Pertinent test results such as lab data, ECG data, procedures, biopsy data, and autopsy results
x. Discussion of the diagnosis as supported by available clinical data
xi. For events without a definitive diagnosis, a list of the differential diagnoses
xii. Treatment provided
xiii. Whether re-challenge occurred and any results
xiv. Adverse event outcomes and other post-event follow-up information

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

2.2. Clinical/Safety

Question 3: Does the Agency agree with the proposed approach of safety data analysis plan for the purpose of evaluating the safety of diroximel fumarate? Specifically does the agency agree with:

a) Proposed pooling for Phase 1 and Phase 3 studies;
b) Proposed analyses for the assessment of safety data including adverse events (TEAE, SAE, AEs leading to discontinuation), adverse events of special interest (AESI), laboratory data, vital signs data and ECG data;
c) Proposed adverse events of special interest;
d) Exclusion from the safety population in A301 study of the subjects that are rollovers from the short term blinded A302 study Part B. Significant safety data (SAEs, AEs leading to discontinuation, and AEs leading to death) will only be summarized in this group of patients.
e) Analysis and discussion of blinded safety data (SAEs, AEs leading to discontinuation, and AEs leading to death) will only be summarized for the ongoing A302 Part B Study.

FDA Responses to Questions 3a-e:

a) The proposed pooling for the Phase 1 and Phase 3 studies appears reasonable.
b) The proposed analyses of safety data appear acceptable. We have the following requests for Adverse Event data reporting:

i. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document.[1]
ii. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
iii. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
iv. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
v. Ensure that all adverse events are presented, and not only events deemed "drug-related."
vi. Provide a table of treatment-emergent adverse events reported more frequently in 2% or more, after rounding to the nearest percent, of subjects in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
vii. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

c) The proposed list of adverse events of special interest appears reasonably complete. We recommend adding "pancreatitis" to the AESI list.
d) The exclusion of patients who are "rollovers" from Study A302 Part B is reasonable due to blinding in the ongoing study. Provide a list of these excluded patients in the submission.
e) A summary of safety data from patients in the ongoing blinded A302 Part B Study is acceptable.

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

Question 4: Does the Agency agree with the proposed presentation of the ISS?

FDA Response to Question 4:

The proposal to place the text portion of the ISS in Module 2 and the appendices and data sets in Module 5 is acceptable. Additionally, we have the following requests for the ISS submission:

a) Submit a table detailing all the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
i. Title of the table or figure in the application
ii. A hyperlink to the location of the table or figure with page number
iii. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)

[1] http://www.meddra.org/how-to-use/support-documentation

b) Format the tables of the ISS according to examples in FDA's "Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review."[2]

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

Question 5: Does the Agency agree with the proposal for the 120 Day Safety Update? Specifically, does the Agency agree with the following:

a) 120 Day Safety Update cut-off date, and

b) Proposed cumulative summaries and data to be included in 120 Day Safety Update?

FDA Response to Question 5a and 5b:

a) The 120 Day Safety Update cut-off date appears acceptable.
b) Your proposal appears reasonable. The "significant safety information" update for Study A302 Part B should include pregnancies as well.

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

2.3. Clinical Pharmacology

Question 6: Does the Agency agree that the clinical pharmacology program for diroximel fumarate is adequate to support the NDA filing?

FDA Response to Question 6:

Your bridging strategy is acceptable, on face. However, there is a concern that patients might not be able to distinguish between high fat and low or medium fat meals. Therefore, diroximel fumarate should be administered in the fasted state. We expect that you will submit the results of the ongoing Thorough QT study (A110) in the NDA.

Discussion:

The discussion focused on the labeling instructions associated with administration conditions for Diroximel fumarate and the sponsor's proposed strategy regarding food. FDA clarified that the main concern was that patients might not be able to accurately determine meal composition. In addition, it appears that the acceptable therapeutic exposure ranges (Cmax) defined by dimethyl fumarate (DMF) were based only on the results of Study 109, while the results from diroximel fumarate bridging study A104 and historical DMF data show different monomethyl fumarate (MMF) mean Cmax values under fed conditions.

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072275.pdf

FDA emphasized that these are only preliminary thoughts based on the sponsor's pre-NDA submission. The sponsor's labeling approach will be a review issue.

Question 6 Sponsor post-meeting request: As a follow-up, we would like to ensure that we have a correct understanding of the data that the clinical pharmacology reviewer was referring to on the call so that we can adequately address the concerns as part of our NDA application. It was our understanding that the reviewer was making a cross study data comparison between historical DMF data in the Summary basis of approval (SBA) and what we have observed in our PK bridging studies for diroximel fumarate under fed conditions (studies A104 and A109). More specifically the reviewer made comments to historical DMF data in particular Cmax value of 1.45 µg /ml from Study C-1903, "A Single-Center, Randomized, Crossover Study to Investigate the food effect on MMF PK". We located this reference within the SBA (page 82 of the pdf file for the clinical Pharmacology and Biopharmaceutics review). Please confirm if this understanding is correct.
We would like to highlight the following aspects that we believe limit the ability to utilize a cross study data comparison to draw conclusions:

- MMF PK is known to be variable, and known to be significantly influenced by formulation changes for DMF. Both diroximel fumarate clinical studies A104 and A109 were conducted with commercial product of DMF, whereas Study C-1093 was not.
- There are considerable differences in study design and conditions between the two studies; in particular the PK sampling times between our studies and Study C-1903 were different. Hence, direct comparisons of PK parameters for diroximel fumarate and DMF can only be made within A103, A104, and A109.
- In response to the reviewer's comment on sample size, we wish to note that we have conducted two independent studies that provide PK data for DMF under high fat conditions (A104 n= 42 and A109 n= 47). Study C-1903 included 33 subjects.

Furthermore, as agreed with the Agency at the EOP2 meeting and a subsequent Type C Interaction, the bridge between DMF and diroximel fumarate would be based on comparative MMF bioavailability data where the objective was to bridge to the MMF exposure information within the DMF label. As per the Tecfidera product label, DMF when coadministered with a high-fat, high-calorie meal resulted in an approximately 40% reduction in MMF Cmax (Tecfidera USPI, 2017). With low and medium-fat meals, the extent of reduction in MMF Cmax values from diroximel fumarate was less than that observed when DMF was administered with a high-fat, high-calorie meal, and Cmax values were within the acceptable therapeutic exposure range defined by DMF administered under labeled conditions. In A109, following co-administration of DMF with a high-fat meal, the mean MMF Cmax was 1.12 µg /mL. Following co-administration of diroximel fumarate with a low fat or medium fat meal in the same study, the mean MMF Cmax values were 1.53 µg /mL and 1.33 µg /mL respectively. Based on the data from our PK bridging studies subjects participating in the Phase 3 studies (A301 and A302) were instructed to take diroximel fumarate with or without food but to avoid a high-fat, high-calorie meal. We will also provide efficacy data (MRI and ARR) in the NDA application from the A301 study that shows the same magnitude of effect as the clinical efficacy seen with DMF pivotal trials.

In summary, we wish to reiterate our concern around using cross study comparisons in the setting of determining relative bioavailability as opposed to including the appropriate control arm within the study for valid comparisons. We would ask the agency to provide any additional concerns/comments in response to the differences outlined above between our data and data from the SBA for DMF.

Question 6 FDA Response to post-meeting request: We confirm that the Cmax value quoted by the reviewer was from Study C-1903 in the summary basis for approval, and we acknowledge your concern about comparing the results from diroximel fumarate bridging study A109 to historical DMF data. However, we also noted that the mean MMF Cmax after administration of DMF with high fat meal was found to be 1.376 µg/ml in another diroximel fumarate bridging study (A104). If these Cmax values were used to define the low range, then the mean Cmax after administration of diroximel fumarate with a medium fat meal would fall below the low range (in addition to the high fat meal). In addition, we note that some of the boxplots in Figure 2 (Boxplot of MMF Cmax by Fed Status Following Administration of DMF or Diroximel Fumarate (DRF)) are likely based on cross-study data comparison, e.g., DRF Fasted and DRF Fed HF. These observations illustrate that defining acceptable therapeutic exposure ranges based on the results of only one study could be misleading. Our main concern continues to be that patients might not be able to accurately determine meal composition. This issue will be a matter for review of any future NDA submission.

Question 7: Does the Agency agree with following:

a) Submission of files and datasets from the PopPK analyses conducted using NONMEM;
b) Submission of the Clinical Pharmacology Summary Highlights in lieu of a Clinical Pharmacology Summary Aid?

FDA Response to Question 7a and 7b:

a) Yes, we agree with your plan, although you do not have to convert files from the .csv format to the .XPT format. You may directly submit the NONMEM datasets as .csv files.

b) Yes, you may submit the Clinical Pharmacology Summary Highlights in addition to the Summary of Clinical Pharmacology Studies document in Module 2.7.2 and Summary of biopharmaceutical studies and associated analytical methods in Module 2.7.1.

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

2.4. Pharmacology

Question 8: Does the Agency agree that the nonclinical development program for diroximel fumarate is adequate to support the NDA filing?

FDA Response to Question 8:

Based on the information provided in the briefing document, the nonclinical development program appears sufficient to support filing of the NDA. The adequacy of the studies will be a matter of review.

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

2.5. Chemistry, Manufacturing and Controls

Question 9: Does the Agency agree that the proposed 106-count configuration is bracketed by the existing registration stability for the 20-count and 120-count configurations?

FDA Response to Question 9: Yes, we agree.

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

Question 10: Does the Agency agree with the proposal to submit the 17 month stability data for the registration batches no later than 30 calendar days after submission of the original application?

FDA Response to Question 10: Yes, we agree.

Discussion: The sponsor acknowledged FDA's response and no discussion occurred.

3.0. OTHER INFORMATION

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

Reference ID: 4289458

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

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

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

Reference ID: 4289458

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

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

Reference ID: 4289458

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

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

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

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

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

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

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the 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 (February 2018) and the associated 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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

See Question 6 and post-meeting question from sponsor

5.0 ACTION ITEMS

No action items were identified

6.0 ATTACHMENTS AND HANDOUTS

Sponsor did not provide any additional handouts for the meeting

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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
07/11/2018