CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210296Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 126454

MEETING MINUTES

Banner Life Sciences, LLC
Attention: Thomas Lategan, PhD
Senior Manager, Regulatory Affairs
4125 Premier Drive
High Point, NC 27265

Dear Dr. Lategan:

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

We also refer to the meeting between representatives of your firm and the FDA on September 5, 2017. The purpose of the meeting was to discuss the content and format of an NDA for monomethyl fumarate.

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, contact Laurie Kelley, Regulatory Project Manager at laurie.kelley@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 5, 2017, 11:00 – 12:00 p.m.
Meeting Location: FDA White Oak

Application Number: 126454
Product Name: Monomethyl fumarate
Indication: Multiple sclerosis
Sponsor/Applicant Name: **Banner Life Sciences, LLC**

FDA ATTENDEES

Billy Dunn, M.D., Director, Division of Neurology Products
Eric Bastings, M.D., Deputy Director, Division of Neurology Products
John Marler, M.D., Clinical Team Leader
Jody Green, M.D., Clinical Reviewer
Martha Heimann, Ph.D., CMC Lead, ONDQA/DNDQA-1
Joan Zhao, Ph.D., Biopharmaceutics Reviewer
Jagan Parepally, Ph.D., Clinical Pharmacology Reviewer
Ann Tobenkin, PharmD., Safety Evaluator, Division of Pharmacovigilance, OSE
Dangela Stojanovic, Ph.D., Epidemiologist, Division of Epidemiology, OSE
Hongliu Ding, Ph.D., Epidemiologist, Division of Epidemiology, OSE
Erin South, Risk Management Analyst, Division of Risk Management, OSE
Corinne Kulick, PharmD., Team Leader, Division of Pharmacovigilance, OSE
David Croteaum M.D., Medical Officer, Division of Pharmacovigilance

SPONSOR ATTENDEES

Frank Rousseau, C.O.O
Jason Vaughn, V.P., Product Development
Tom Lategan, V.P., Regulatory Affairs
Nikki Sprague, Program Management
Laurence Wang, Pharmacokinetics
Joe Quinn, Statistician

1.0 BACKGROUND

Banner Life Sciences, LLC., is developing a delayed-release formulation of monomethyl fumarate for the treatment of relapsing forms of multiple sclerosis. The sponsor plans to submit a 505(b)(2) application using Tecfidera as the reference-listed drug. On May 2, 2017, Banner requested a meeting to discuss the content and format of an NDA to be submitted later this year for monomethyl fumarate.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls

Question 1: The CMC information for the drug substance will be described only by reference to Drug Master File (b) (4) through a Letter of Authorization. Only eCTD sections such as the internal specifications, testing, and methods authored by BannerLS (i.e., 3.2.S.4.1, through 3.2.S.4.5) will be included in the NDA per se. Is this acceptable to the Division?

FDA Response to Question 1:
Your approach is acceptable, provided you identify each CTD module that is incorporated by cross-reference to the DMF. However, we request that you include the following information in the NDA:

- Module 3.2.S.1 General Information,
- Summary table of the manufacturer's release specification in Module 4.2.S.4.1
- Discussion of physical properties of the drug substance that impact on the product in Module 3.2.P.2 Pharmaceutical Development.

Meeting Discussion: There was no discussion during the meeting.

Question 2: The clinical program is complete, and so we would be in a position to submit the NDA including the 9 months data in October 2017. The submission would be amended with the 12 months data for each condition in January 2018. Is this acceptable to the Division?

FDA Response to Question 2:
An initial NDA submission should 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 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." Whether we review information submitted to the NDA subsequent to the original submission will be determined based on the timing of the submission and available Agency resources.

Meeting Discussion: There was no discussion during the meeting.

2.2. Nonclinical

Question 3: Based on the safety and tolerability findings of our clinical program, we have not conducted additional preclinical studies and will rely on the Division's previous comments that no new studies are required. Furthermore, the literature review requested by the Division was conducted and submitted to the IND (Sequence 0011). Neither our studies nor the literature review revealed new findings relevant to the safety or efficacy of DMF/MMF. We therefore assume that no new nonclinical studies are required and as such submission of Module 4 and the corresponding sections of Module 2 are not required. Does the Division concur?

FDA Response to Question 3:
Although we acknowledge that DMF is not quantifiable in plasma following oral administration of DMF, we suggest that you conduct a more thorough literature review to address whether or not DMF may itself contribute to efficacy. The adequacy of the literature search will be a matter of review.

You should address any issue (e.g., impurity or excipient) that would raise a safety concern for which nonclinical studies would be needed. Justification should be provided for the choice and amount of the excipient(s) in the drug product.

Meeting Discussion: Banner asked about the need for additional information about clinical efficacy. FDA explained that a more thorough literature review is necessary to provide a scientific bridge between MMF and DMF (Tecfidera, the intended reference listed drug). Banner should address the potential for DMF to have pharmacological effects not shared by MMF; for example, the potential for DMF to exert local effects in the intestinal tract that could contribute to efficacy in MS patients.

Banner indicated that the literature review conducted to address this issue was more thorough than described in the document submitted to the IND. They intend to provide a comprehensive summary of the literature reviewed and the search terms used to identify the relevant publications. FDA noted that submission of electronic copies of the most relevant publications would facilitate review.

2.3. Clinical

Question 4: The results of the pivotal study (Study BLS-11-104) demonstrates bioequivalence of BLS-11 delayed-release capsules to the Reference listed product and therefore establishes the basis for the assessment of the efficacy of BLS-11 under the 505(b)(2) submission . Does the Division concur?

FDA Response to Question 4:
This will be a matter of NDA review.

Meeting Discussion: There was no discussion during the meeting.

Question 5: We consider a single BannerLS 95 mg capsule to constitute the "corresponding lower dose" for our product. Does the Division concur?

FDA Response to Question 5:
Yes. However, you should provide dose-proportionality data comparing 95 mg vs 2x95 mg.

Meeting Discussion: Banner stated that the lower strength is used for titration and not efficacy and, therefore, there is no need to demonstrate dose proportionality. Banner also stated that they have information to show that MMF is a class I drug. FDA reiterated the need to show dose-proportionality data for adequate PK bridging to Tecfidera, because safety and tolerability data from PK studies is limited. FDA stated that they would evaluate a justification for not performing a dose-proportionality study in the NDA submission.

Question 6: The Division's criteria bulleted above have been met: BannerLS believes that a request a Biowaiver for the 95 mg dose can be included in the NDA. Does the Division concur?

FDA Response to Question 6:
We concur that a request for a Biowaiver for the proposed 95 mg strength is not needed.

Meeting Discussion: FDA explained that no biowaiver is needed because Banner has proposed only one strength (95 mg).

Question 7: Efficacy studies have not been conducted by BannerLS with the MMF formulation it developed; instead BannerLS will rely on, as agreed with the Division, previous findings of efficacy for Tecfidera. As such an ISE will not be submitted in this NDA.

Does the Division agree?

FDA Response to Question 7:
Yes.

Meeting Discussion: There was no discussion during the meeting.

Question 8: The Division is requested to comment on the adequacy of the ISS and the SAP as illustrated by the shell and its Appendices. Does the Division agree to do so?

FDA Response to Question 8:
Your plan for the ISS and the safety analysis appears to be adequate.

Meeting Discussion: There was no discussion during the meeting.

Question 9: Based on the iPSP feedback, BannerLS will not be submitting pediatric studies or studies conducted in juvenile animals in the initial NDA. Does the Division concur with this approach?

FDA Response to Question 9:
We concur that you do not need to include clinical pediatric studies or a juvenile animal toxicology study in the initial NDA.

Meeting Discussion: There was no discussion during the meeting.

2.4. Regulatory

Question 10: These briefing materials provide a status on the issues and items raised in the Division's feedback of 29 May 2015 (please see Appendix 2), as well as provide the expected Table of Contents for the NDA (Appendix 5).

The Division is asked to comment on Appendix 1 and Appendix 2 each of the items.

FDA Response to Question 10:
On face, your response to the Biopharmaceutics comments in Appendix 2 regarding the in vitro dissolution testing seems reasonable. In order for FDA to make a final decision on the acceptability of dissolution method and acceptance criteria, a thorough review of the proposed dissolution method (with complete dissolution method development report and data) is required in the NDA. The dissolution acceptance criteria will also be determined at the NDA stage.

From a technical standpoint (not content related) the proposed Table of Contents for the planned NDA in Appendix 5 is acceptable. However, see the additional comments below.

a) Providing a linked reviewer's aid/guide in module m1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application, is helpful to reviewers
b) List of investigators should reside in m5 (not m1.3.4.), under the study tagging file (STF) of the respective study and tagged as "list-description-investigator-site"
c) Do not create additional nodes in m2.4 - m2.7, m5.3.6. (e.g. 2.4.1 – 2.4.6, 2.5.1 – 2.5.7, m5.2.1-m5.2.2, m5.3.6.1 – m5.3.6.3.2, etc.,) in the eCTD structure beyond what is in the specifications. Please make sure your approach fits the DTD and the "Granularity Annex", located at:- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf
d) The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.
e) To submit PADER descriptive portion (only) in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section, m5.3.6. Since each report is for a specific time period, please ensure that the leaf title of the report includes the reporting period, and it also helps when the leaf

title follows a standard format, so reviewers can quickly differentiate one report from another.

f) Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Do not use 5.3.7 as a heading element in the index.xml

Sponsors' options of cross referencing information submitted to another application (if any), would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

a) To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (non- eCTD or paper) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document and if possible, hyperlinks to the referenced documents.

b) To use the second option (i.e. cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. xlink:href="../../**indXXXXXX**/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, it is recommended that the leaf title indicate the words "cross reference to" and the application number (e.g. Cross Ref to indXXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application and to ensure successful use of cross application links, it is recommended that sponsor submits an "eCTD cross application links" sample.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page.[1]

Meeting Discussion: There was no discussion during the meeting.

[1] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf

Question 11: As part of the CMC development, Banner LS included Quality-by-Design studies. Does the Division have a preference for the eCTD location for these studies?

FDA Response to Question 11:
Studies performed to support formulation or manufacturing process development should be located in the appropriate section of Module 3.2.P.2 Pharmaceutical Development. If you intend to propose any "design space(s)" applicable to the manufacturing process, the design space(s) should be described in Module 3.2.P.3.3 Manufacturing Process and Process Controls and (if appropriate) Module 3.2.P.3.4. Refer to ICH Q8 (R2) Pharmaceutical Development for additional guidance.

Meeting Discussion: There was no discussion during the meeting.

Question 12: Will the Division agree to a submission including 9 months long term and intermediate and 6 months stability data to be amended when 12 month data become available in the 1st quarter of 2018.

FDA Response to Question 12:
See response to Question 2.

Meeting Discussion: There was no discussion during the meeting.

Question 13: At the time of submission all clinical study datasets will be available in Clinical Data Interchange Standards Consortium (CDISC) format; both Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) format datasets will be provided per the FDA Guidance for Industry.

The Division is asked to describe any other specific needs with respect to the data sets and/or data formats required.

FDA Response to Question 13:
SDTM and ADaM format datasets are adequate for the safety data.

You should assign the same subject identifier to each subject across all datasets in the application.

Meeting Discussion: There was no discussion during the meeting.

Question 14: The Division will be asked to confirm that BLS-11 is considered a New Chemical Entity.

FDA Response to Question 14:
NCE determination is made after approval. Please refer to The CDER Manual of Policies and Procedures 5018.2 titled, "Office of Pharmaceutical Quality NDA Classification Codes,"

dated November 4, 2015, for further information regarding chemical classification of drug products.

Meeting Discussion: There was no discussion during the meeting.

Question 15: Since the current legislative authority for PDUFA expires in September 2017 and our submission is anticipated for October 2017 (i.e., in Fiscal year 2018), how in the absence of new legislation reauthorizing PDUFA how should the user fee coversheet be addressed/submitted?

FDA Response to Question 15:
PDUFA has been reauthorized. The Agency anticipates that by October 1, 2017, firms will be able to submit an FY 2018 cover sheet. Please consider subscribing to the PDUFA email distribution list for further updates.[2]

Meeting Discussion: There was no discussion during the meeting.

Question 16: The content of the BannerLS application in many respects is similar to that for an abbreviated New Drug Application (ANDA) application and does not rely on clinical data (other than the aforementioned bioequivalence studies) with respect to safety or effectiveness or for any other aspect of clinical information (e.g. drug interaction studies). BannerLS therefore assumes that the fee scale will be that for generic (ANDA) application. Can the Division confirm this?

FDA Response to Question 16:
The proposed BannerLS application is a 505(b)(2) NDA and is subject to PDUFA fees. The user fee amount for an original application depends on whether clinical data with respect to safety and efficacy are required to form the primary basis for approval. At this time, the fees have not been finalized yet for applications to be submitted during FY18 (October 1, 2017 – September 30, 2018). The Agency anticipates that the fees will be set by October 1, 2017. Please consider subscribing to the PDUFA email distribution list for further updates.[2]

Meeting Discussion: There was no discussion during the meeting.

Additional Comments:

General Submission Contents:

1. Include a copy of each clinical study protocol. For amended protocols, include a summary of changes and both clean and tracked-changes versions of each amended protocol with the dates the Amendments were implemented.
2. Submit a table detailing all of the tables and figures featured in the safety section of the application. The table should contain the following:
    a. Title of the table or the figure in the application
    b. A hyperlink to the location of the table or figure with the page number

[2] https://www.fda.gov/AboutFDA/ContactFDA/StayInformed/GetEmailUpdates/default htm

c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used).

3. Include active hyperlinks from the list of references to the referenced article.
4. Include information regarding important regulatory actions in other countries and foreign labeling, if applicable (translated).

Adverse Events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection Points to Consider" document accessible at MedDRA.
2. For each study, the submitted datasets should contain both the verbatim term and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event the MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials, if they are different.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."

Additional Meeting Discussion: Banner asked how they should name the study drug in the clinical study section of the label they propose in the NDA application. FDA suggested that Banner refer to the labels for sumatriptan products approved under 505(b)(2) as an example of the approach to follow.

3.0 Additional Meeting Information

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 8, 2017 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 https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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.

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

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

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of

such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

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

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

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

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

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

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

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

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

there were no attachments or handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
10/05/2017