CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211226Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108407

MEETING MINUTES

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, R.A.C.
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

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

We also refer to your April 12, 2017, correspondence, received April 12, 2017, requesting meeting to discuss Spectrum's proposed plans to submit a 505(b)(2) application for Levoleucovorin for injection relying on the agency's previous finding for NDA 20140 for FUSILEV.

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 me at (240) 402-4392.

Sincerely,

{See appended electronic signature page}

Brendan Baggot
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	Wednesday, June 28, 2017, 12:00 PM to 1:00 PM (ET)
Meeting Location:	White Oak Building 21, Conference Room: 2560
Application Number:	IND 108407
Product Name:	(b) (4) levoleucovorin for injection
Indication:	1) As rescue after high-dose methotrexate therapy in osteosarcoma; 2) To diminish the toxicity and (b) (4) effects of impaired methotrexate elimination and of (b) (4) overdosage of folic acid antagonists; and 3) For use in combination chemotherapy with 5-fluorouracil (5-FU) in the (b) (4) treatment of patients with (b) (4) metastatic colorectal cancer (b) (4)
Sponsor/Applicant Name:	Spectrum Pharmaceuticals, Inc. (Spectrum)
Meeting Chair:	Martha Donoghue, M.D.
Meeting Recorder:	Brendan Baggot

FDA ATTENDEES:

Joe Gootenberg, M.D.	Deputy Director, DOP2
Martha Donoghue, M.D.	Clinical Team Leader, DOP2
Shan Pradhan, M. D.	Medical Reviewer, DOP2
Brendan Baggot, M.S.	Regulatory Health Project Manager, DOP2
Jessica Boehmer, M.B.A.	Regulatory Scientist, DOP2
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2
Whitney Helms, Ph.D.	Nonclinical Team Leader, DHOT
Emily Wearne, Ph.D.	Nonclinical Reviewer, DHOT
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, OCP
Saeho Chong, Ph.D.	Clinical Pharmacology Reviewer, OCP
Lisa Rodriguez, Ph.D.	Biometrics Team Leader, OBV
Janet Jiang, Ph.D.	Biometrics Reviewer, OBV

Joyce Crich, Ph.D.	Quality Assurance Lead, DNP 1
Okpo Eradiri, Ph.D.	Biopharmaceutics Lead, DB
Anand Om, Ph.D.	Biopharmaceutics Reviewer, DB

SPONSOR ATTENDEES:

Zane Yang, M.D.	Senior Vice President, Clinical Development
Guru Reddy, Ph.D.	Vice President, Pre-Clinical Research & Development
Pramod K. Gupta, Ph.D.	Senior Vice President, Pharmaceutical Operations
Ramsharan Singh, Ph.D., R.A.C.	Executive Director, Pharmaceutical Development
Anil K. Hiteshi, R.AC	Vice President, Global Regulatory Affairs
Joseph W. Turgeon	President and CEO

BACKGROUND:

On April 12, 2017, Spectrum Pharmaceuticals, Inc. (Spectrum) submitted a meeting request and meeting package to discuss Spectrum's plans to submit "a 505(b)(2) NDA for (b) (4) levoleucovorin for injection, 175 mg/vial and 300 mg/vial, as a bioequivalent alternative to FUSILEV." On May 3, 2017, FDA granted the request as a Type B face-to-face meeting.

The reference listed drug for the planned 505(b)(2) application is FUSILEV (levoleucovorin). FUSILEV is approved under NDA 20140 (*held by Spectrum*) for the following indications:

- Rescue after high-dose methotrexate therapy in osteosarcoma.
- Diminishing the toxicity and (b) (4) the effects of impaired methotrexate elimination and (b) (4) overdosage of folic acid antagonists.
- Use in combination chemotherapy with 5-fluorouracil in the (b) (4) treatment of patients with (b) (4) metastatic colorectal cancer.

According to Spectrum, FUSILEV is the calcium salt of levoleucovorin. FUSILEV is supplied as follows:

- FUSILEV for Injection: 50 mg single-use vial containing sterile lyophilized powder.
- FUSILEV Injection: 175 mg/17.5 mL and 250 mg/25 mL single use vials.

Spectrum plans to rely on FDA's findings of safety and effectiveness for FUSILEV and reference the nonclinical and clinical data from this new drug application (NDA). The planned 505(b)(2) will seek approval of (b) (4) levoleucovorin for injection for the same indications and dosage regimens currently approved for FUSILEV.

According to the meeting package, differences between (b) (4) levoleucovorin for injection and the reference product include a (b) (4) addition of a new 300 mg/vial strength.

Spectrum states that "upon reconstitution, [redacted] levoleucovorin for injection contains the biologically active l-isomer of folic acid [redacted] and that [redacted]

In the meeting package, Spectrum provided summary level data from a single-center, single-dose bioequivalence (BE) study conducted in 24 healthy volunteers. The bioequivalence (BE) study investigated the pharmacokinetic (PK) characteristics of [redacted] levofolinate (50 mg/mL, administered as a single 100 mg/m^2 IV dose) as compared to two products approved outside of the U.S., Isovorin (calcium levofolinate 10 mg/mL, administered as a single 100 mg/m^2 IV dose), and Sodiofolin (disodium l,d-folinate 50 mg/mL, administered as a single 200 mg/m^2 IV dose). The primary objective was to measure AUC_{0-t} for levo 5 formyl tetrahydrofolic acid (l-CHO-THF) and for the main metabolite 5-methyl tetrahydrofolic acid (CH3-THF). Secondary objectives included the measurement of $AUC_{0-\infty}$, C_{max}, $T_{1/2}$, MRT and T_{max} for l-CHO-THF and the main metabolite (CH3-THF); assessment of concentration-time profiles for both analytes; and safety assessment. According to Spectrum, this BE study generated data showing that [redacted] levofolinate was "bioequivalent to both reference products (disodium folinate and calcium levofolinate) for the primary PK parameter AUC for l-CHO-THF and for CH3-THF and for secondary PK parameters."

In addition to data from the BE study described above, the planned 505(b)(2) NDA will include a literature survey and risk:benefit assessment for [redacted] levofolinate based on recently published studies with *l*-FA preparations, case reports of serious adverse events, and a Periodic Safety Update Report (PSUR) prepared by [redacted]

DISCUSSION:

SPONSOR QUESTIONS AND FDA RESPONSES:

Regulatory – 505(b)(2) Submission Route:

1. *Spectrum wishes to submit a 505(b)(2) NDA for [redacted] levoleucovorin for injection, 175 mg/vial and 300 mg/vial, with reference to FUSILEV approved under NDA 020-140.*

   Does the Agency agree with the proposed 505(b)(2) NDA submission route with reference made to NDA 20-140 for the nonclinical and clinical data?

   FDA Response: FDA agrees that the proposed NDA for [redacted] levoleucovorin for injection may cross-reference relevant studies and data in FUSILEV NDA 20140; however, there is insufficient information for FDA to determine whether the proposed NDA should be submitted as a 505(b)(2) application because it is unclear which information that Spectrum does not have a right of reference to Spectrum intends to rely upon in the proposed NDA. If Spectrum owns or has a right of reference to all the data that is necessary for approval, then the proposed NDA would not be a 505(b)(2) application.

If cross-referenced portions of Spectrum's previously approved 505(b)(2) application (NDA 20140) that rely on FDA's finding of safety and/or effectiveness for a listed drug(s) or published literature (as distinguished from any cross-referenced investigations that were conducted by or for you or for which you have obtained a right of reference or use) are necessary to support approval of the new NDA, then the new NDA should be submitted pursuant to section 505(b)(2) of the FD&C Act. Spectrum's new 505(b)(2) application should identify this/these listed drug(s) as relied upon for the new 505(b)(2) application in accordance with the Agency's regulations at 21 CFR §314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification/statement and notification), apply to each listed drug upon which an applicant relies.

Spectrum's emailed response of June 27, 2017: As a further clarification to our previous information, the Sponsor will rely on the Hospira, Inc. NDA 08107, which was not withdrawn due to safety, and additional information as well as literature search submitted in the Spectrum NDA 20140.

Does the Agency agree that a 505(b)(2) application is acceptable with reference being made primarily to the Hospira NDA 08107 along with supportive information referenced in the Spectrum NDA 20140?

Discussion during the meeting of June 28, 2017: Spectrum acknowledged FDA's comments electronically mailed to Spectrum on June 27, 2017. FDA stated that if Spectrum plans to rely upon data, for approval, from an application for which you do not have right of reference, their proposed NDA would fall under the 505(b)(2) pathway. FDA cannot advise Spectrum on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, 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, Spectrum 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 Spectrum identifies a listed drug solely to comply with this regulatory requirement, Spectrum must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but Spectrum is 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.

For a proposed 505(b)(2) NDA, FDA recommends that Spectrum rely on the most recently approved label for a non-ANDA calcium levoleucovorin product. Information regarding recent approvals can be found at Drugs@FDA.gov, accessible at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

Spectrum agreed to submit to the IND a detailed discussion regarding which aspects of the referenced NDA(s) Spectrum feels would be necessary and sufficient for a 505(b)(2) submission. Spectrum also agreed to submit to the IND a detailed discussion regarding

any other information for which Spectrum, despite not having the right of reference to, nevertheless feels would be necessary and sufficient for a 505(b)(2) submission.

FDA agreed to provide further written guidance upon receipt of Spectrum's proposed submission to the IND.

Clinical / Nonclinical – BE Study:

2. *Spectrum wishes to confirm that submission of a bioequivalence (BE) study that demonstrated equivalent activity of* (b) (4) *levofolinate to sodium folinate and to calcium levofolinate is the appropriate study for the Agency's review of the 505(b)(2) NDA for the proposed indications and usage.*

   Does the Agency agree that submission of a BE study comparing the activity of (b) (4) *levoleucovorin to disodium leucovorin and to calcium levoleucovorin is sufficient to support the Agency's review of the 505(b)(2) NDA for the proposed indications and usage of* (b) (4) *levoleucovorin for injection?*

   FDA Response: FDA agrees that data from a BE study comparing the systemic exposure of (b) (4) levoleucovorin to disodium leucovorin and to calcium levoleucovorin can potentially support filing of the proposed 505(b)(2) for (b) (4) levoleucovorin for injection. However, the adequacy of the data and analyses included in the planned NDA submission will be assessed during the review of the NDA.

   Alternatively, FDA can also consider waiving the requirement for the submission of in vivo bioavailability (BA) and/or BE data under 21 CFR 320.24(b)(6). In order to adequately bridge the proposed drug product with the U.S.-approved listed drug, provide the following in the future NDA:

   - Qualitative and quantitative composition before and after reconstitution and dilution, the dosage form, administration volume, etc., for the proposed drug product and the listed drug in a side-by-side comparison table.
   - Comparative physicochemical data for the proposed drug product and listed drug product. The measurements should be done after reconstitution and dilution in triplicate for each lot tested. Include justification for any differences in the formulation's composition, pH, osmolality, dosage, mode of administration, drug concentration, administered volume, etc., relative to the listed drug product.
   - As supporting evidence, provide data and/or published literature results which demonstrate that the differences in excipients between the proposed and listed drug products do not affect the disposition kinetics of Levoleucovorin in human subjects.

   Please refer to FDA's response to Question #1 regarding the appropriate pathway for submission of the proposed NDA.

Spectrum's emailed response of June 27, 2017: The sponsor acknowledges the Agency's comments and plans to request a waiver under 21 CFR 320.24(b)(6). Accordingly, the Sponsor plans to provide the bridging information listed above in the future NDA.

Does the Agency agree that a 505(b)(2) application as described in response #1 is acceptable with submission of a waiver under 21 CFR 320.24(b)(6)?

Discussion during the meeting of June 28, 2017: Refer to FDA's response and discussion during the meeting to Question #1.

Spectrum acknowledged FDA's comments electronically mailed to Spectrum on June 27, 2017. Spectrum agreed to submit to the IND a detailed discussion regarding a U.S. approved comparator along with the qualitative and quantitative chemical composition of the proposed product. Furthermore, Spectrum will provide justification regarding the differences in enantiomers, salt forms and pharmacologic activity with supporting scientific data, and information from the public literature for which Spectrum does not have the right of reference to. FDA agreed to provide further written guidance upon receipt of Spectrum's proposed submission to the IND.

Clinical / Nonclinical – Comparator Product:

3. *Spectrum wishes to confirm acceptability of the BE study in which* (b) (4) *levoleucovorin for injection was compared to Isovorin (marketed in the United Kingdom by Pfizer Limited) and Sodiofolin (marketed in the United Kingdom by medac GmbH).*

   Does the Agency confirm acceptability of the comparator product?

   FDA Response: Please refer to FDA's response to Question #2. FDA does not normally recommend specific comparators for use in clinical studies. However, if Spectrum decides to conduct a BE study, provide the following in the IND/NDA in order for FDA to consider accepting the use of the non-U.S. reference drug products in the BE study:

   a. A Certificate of Analysis (COA) for each batch used;
   b. Statement of composition;
   c. Site of manufacture;
   d. Statement of comparability to the U.S.-approved drug product, i.e., a head to head comparison table demonstrating that the qualitative and quantitative compositions of the formulations for the non-U.S. and U.S.-drug products; and
   e. Confirmation that the non-U.S.-approved drug product is approved for marketing in an ICH region.

Spectrum's emailed response of June 27, 2017: As stated in response to question 2, the Sponsor intends to submit a waiver under 21 CFR 320.24(b)(6).

Discussion during the meeting of June 28, 2017: Spectrum acknowledged FDA's response. There was no further discussion during the meeting.

Clinical / Nonclinical – Clinical Data:

4. *The BE Clinical Study Report (CSR) will be prepared consistent with ICH E3 Structure and Content of Clinical Study Reports, and will include all the requisite data tables and figures. However, the data sets used to produce the data tables and figures are not available for inclusion in the 505(b)(2) submission.*

   Does the Agency confirm acceptability of submitting in the NDA the CSR without raw data files?

   FDA Response: Please refer to FDA's response to Question #2. In the absence of a biowaiver, raw datasets would be required in the NDA submission because raw data files from the pivotal BE study are needed in order for FDA to verify the outcome of this study.

   Spectrum's emailed response of June 27, 2017: As stated in response to question 2, the Sponsor intends to submit a waiver under 21 CFR 320.24(b)(6).

   Discussion during June 28, 2017 meeting: Spectrum acknowledged FDA's response. There was no further discussion during the meeting.

Clinical / Nonclinical – Risk-Benefit Assessment:

5. *Spectrum wishes to confirm the acceptability of our plan to submit a literature survey and risk-benefit ratio assessment of* (b) (4) *levoleucovorin for injection based on recently published studies with l-FA preparations, case reports of serious adverse events as well as the Periodic Safety Update Report (PSUR) from the company* (b) (4).

   Does the Agency agree with the plan to submit a literature survey and risk-benefit ratio assessment?

   FDA Response: FDA agrees with the proposed submission of this information, but requests clarification regarding whether Spectrum intends to include this as supportive information for the proposed NDA or whether Spectrum considers this information necessary to support the safety of (b) (4) levoleucovorin for injection. Please refer to FDA's response to Questions #1 and #2.

Spectrum's emailed response of June 27, 2017: Spectrum acknowledges the Agency comments and agrees that the Risk-Benefit Assessment will serve as supportive information.

Discussion during the meeting of June 28, 2017: Spectrum acknowledged FDA's response. There was no further discussion during the meeting.

CMC - Impurity Specification:

6. *Spectrum proposes to establish the impurity specification for* (b) (4) *levoleucovorin for injection based on the currently approved impurity specification for the FUSILEV liquid product.*

   Does the Agency agree with our approach to establishing the impurity specification?

   FDA Response: The proposed acceptance criteria for assay and the same impurities in the listed drug product, FUSILEV for injection appear to be reasonable. However, because the meeting package does not provide a complete profile of impurities and degradation products in the proposed drug product, and the related detailed CMC information for the proposed drug substance and the drug product, FDA cannot comment on this approach for other impurities/degradation products in the proposed drug product which are different from those in the listed drug. In general, FDA recommends that Spectrum follow ICH Q3A and related guidances to establish impurity specifications with appropriate acceptance criteria suitable for the proposed drug product.

   A side by side rodent qualification study may be warranted if new impurities are identified in (b) (4) levoleucovorin for injection.

   Spectrum's emailed response of June 27, 2017: The Sponsor acknowledges the Agency comments and will provide side-by-side data of the two formulations to demonstrate no new impurities are identified in (b) (4) Levoleucovorin for Injection.

   Discussion during the meeting of June 28, 2017: Spectrum acknowledged FDA's response. There was no further discussion during the meeting.

Regulatory – 505(b)(2) NDA Organization:

7. *A draft high level eCTD Table of Contents for the proposed 505(b)(2) NDA is provided in Appendix 2 of the Briefing Package.*

   Does the Agency agree with the proposed organization of the 505(b)(2) NDA?

   FDA Response: Please refer to FDA's response to Questions 1-5 above.

Spectrum's emailed response of June 27, 2017: The Sponsor acknowledges the Agency comments and has no additional questions at this time.

Discussion during the meeting of June 28, 2017: Spectrum acknowledged FDA's response. There was no further discussion during the meeting.

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.

Under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of this meeting, but no later than 210 calendar days before a marketing application or supplement is submitted. Failure to include an Agreed iPSP with a future marketing application could result in a refuse to file action. Please note that currently orphan designation has not been granted for (b) (4) levoleucovorin for injection for the proposed indications:

1. As rescue after high-dose methotrexate therapy in osteosarcoma;
2. To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists; and
3. For use in combination chemotherapy with 5-fluorouracil (5-FU) in the palliative treatment of patients with advanced metastatic colorectal cancer.

Therefore, you are subject PREA and an iPSP must be submitted for this development program as outlined below. The PSP 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 PSP 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 pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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 BA 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.

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/s/

BRENDAN O BAGGOT
07/20/2017