CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214408Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 142070

**MEETING REQUEST-
WRITTEN RESPONSES**

Accord Healthcare
Attention: Sabita Nair, RAC, ADQ-CPGP
Senior Director, Regulatory Affairs
1009 Slater Road Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

Please refer to your Pre-Investigational New Drug Application (PIND) file for pemetrexed injection.

We also refer to your submission dated December 6, 2018, containing a meeting request. The purpose of the requested meeting was to obtain definitive guidance on the development plan for a 505(b)(2) application.

Further reference is made to our Meeting Granted letter dated December 21, 2018, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your December 31, 2018, background package.

If you have any questions, call me at (301) 796-7910.

Sincerely,

{See appended electronic signature page}

Shubhangi (Gina) Mehta, PharmD
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: pre-IND/pre-NDA

Application Number: 142070

Product Name: Pemetrexed Injection
Indication: Treatment of patients with non-squamous non-small cell lung cancer and mesothelioma
Sponsor/Applicant Name: Accord Healthcare
Regulatory Pathway: 505(b)(2)

Proposed Indications:

Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Pemetrexed Injection is indicated:

- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC).
- (b) (4)
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.as a single agent for the treatment of patients with recurrent, metastatic nonsquamous, NSCLC after prior chemotherapy.

Limitations of Use: Pemetrexed Injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer

Mesothelioma
Pemetrexed Injection is indicated, in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

BACKGROUND

Regulatory

On December 6, 2018, Accord Healthcare Inc. submitted a pre-IND Type B meeting request to seek advice from FDA regarding their proposed development plan of a proposed pemetrexed formulation. On December 21, 2018, a written response only (WRO) meeting was granted and the meeting packages were received on December 31, 2018.

Accord Healthcare Inc. is proposing to develop a new drug product formulation of Pemetrexed Injection for IV administration and plans to submit a 505(b)(2) application for the product relying on FDA's findings of safety and effectiveness for the Listed Drug (LD) ALIMTA (Lilly).

The LD, ALIMTA is approved as a lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg of pemetrexed. Accord Healthcare Inc. proposed formulation is ready-to-dilute (RTD), multi-dose aqueous formulation of Pemetrexed Injection in the following presentations:

- 4 mL vial [100 mg / 4 mL (25 mg/mL)]
- 20 mL vial [500 mg / 20 mL (25 mg/mL)]
- 34 mL vial [850 mg / 34 mL (25 mg/mL)]
- 40 mL vial [1000 mg / 40 mL (25 mg/mL)]

Accord Healthcare Inc. states they are proposing a liquid formulation of Pemetrexed Injection for the following reasons:

- Low manufacturing cost as compare to lyophilized formulation.
- First preference of physicians and health care professionals due to its ease of handling and it doesn't require any skill/expertise.
- Does not require any reconstitution procedure.
- Less chance of any aseptic manipulations.

Accord Healthcare Inc.'s proposed Pemetrexed Injection differs from the LD in the following respects:

- Dosage form (from Lyophilized powder to aqueous formulation)
- Proposal of Pemetrexed Injection 850 mg/34 mL and 1000 mg/40 mL presentations
- Three additional inactive ingredients: anhydrous citric acid, L-methionine, monothioglycerol
- Not containing mannitol, the (b) (4) in the listed drug.

Accord proposes to submit no clinical data.

Chemistry, Manufacturing and Controls
Accord is proposing to submit a 505(b)(2) application for ready-to-use pemetrexed injection based on the supporting LD information from Alimta (pemetrexed for injection). The proposed drug product is qualitatively and quantitatively different from that of the LD, Alimta. The LD is manufactured as a lyophilized powder. After reconstitution with 0.9% sodium chloride solution it reaches a concentration of 25 mg/mL for pemetrexed. The proposed drug product is being developed as a ready-to-dilute solution at 25 mg/mL strength in 4 ml, 20 mL, 30 mL and 40 mL vials to contain 100 mg, 500 mg, 850 mg, and 1000 mg pemetrexed respectively.

Nonclinical
To support the proposed 505(b)(2) application, Accord will rely on FDA's findings of non-clinical safety from the LD, Alimta. Accord states that all excipients in the proposed formulation are within levels of other FDA-approved drug products, as described in the Inactive Ingredient Database. Accord does not plan to conduct any non-clinical studies to support the safety of the proposed formulation.

SPONSOR QUESTIONS AND FDA RESPONSES

FDA General Comment: The answers to the following questions should be considered preliminary advice to assist Accord Healthcare Inc. with planning for a potential future 505(b)(2) NDA submission, and should not be considered formal agreements regarding the contents of a complete application.

General

1. Does the Agency agree that the proposed product is eligible for submission under a 505(b)(2) application**?**

   FDA Response: Based on the information provided, submission of a 505(b)(2) application for Accord Healthcare Inc.'s proposed pemetrexed injection appears appropriate at this time. Please refer to the FDA section below entitled, "**505(b)(2) REGULATORY PATHWAY**," specifically, the last paragraph directly under the table.

Chemistry, Manufacturing and Controls

2. The applicant proposes to submit Chemistry, Manufacturing and Controls (CMC) information on batches of the proposed product with 6 months of accelerated and 12 months real time stability data.
   The applicant will propose a shelf life of 24 months at the time of submission and the application will be updated with additional stability data during the review cycle. Is this acceptable?

FDA Response: The proposed approach appears reasonable. FDA recommends that in the original NDA Accord submit stability data from 3 distinct batches of each strength using different drug substance lots under upright and inverted orientations. Matrixing and bracketing are allowed. For details of stability recommendation follow ICH Q1 A(R)2 and related ICH stability guidance. The shelf life will be determined based on the quality and quantity of the stability data provided in the NDA.

3. Are any in-vitro studies required to support the equivalency of the proposed product with the Reference Listed Drug?

FDA Response: Provide comparative physico-chemical properties of the proposed and listed drug products after dilution prior to administration. The monitored properties may include: pH, osmolality, viscosity, specific gravity, physico-chemical, and microbiological stability of the diluted solution. The physical stability may be determined by comparison of the assay values of un-filtered and filtered (through 0.22-micron filter) samples.

4. As per package insert of RLD, Alimta® is to be further diluted with 0.9% SodiumChloride Injection to achieve a total volume of 100 mL for intravenous infusion. While dilution (concentration 9 mg/mL) of applicant's proposed product Pemetrexed for Injection, applicant is getting osmolality results as 325-331 mosm/kg, which is near about iso-osmolar range. Is this approach acceptable?

FDA Response: FDA agrees that the range is above the normal iso-osmolar range for blood (280-295 mOsm/kg) but it appears reasonable. In addition, provide comparative pH and osmolality values of the diluted solution prior to administration for the proposed and listed drug products in the NDA. The final decision on acceptability of the proposed osmolality range will be made during the NDA review.

5. Accord intends to perform pharmaceutical equivalency study of proposed product Pemetrexed Injection 25 mg/mL with Reference listed drug. Is this approach acceptable?

FDA Response: Accord's approach appears reasonable. The final determination will be made during the NDA review.

6. (a) The concentration of proposed drug product after dilution will remain same as LD (As shown under table 02). Accord will carry out dilution study on Accord's proposed product (Pemetrexed Injection 25 mg/mL). If required, results of the same will be compared with RLD. Is this approach acceptable?

FDA Response: Accord's approach appears reasonable.

The package insert for the LD (ALIMTA) indicates that the post-diluted reconstituted LD is stored for no more than 24 hours under refrigerated conditions (2-8ºC) from the time of reconstitution. If the proposed drug product is stored

post-diluted under the same storage condition and time frame as that of the post-diluted LD (no more than 24 hours under refrigerated conditions), microbial challenge studies for the post-diluted drug product are not required.

However, if the post dilution storage time exceeds 4 hours at room temperature or 24 hours at refrigerated temperature, in the NDA submission provide microbial challenge studies demonstrating that the diluted drug product does not support microbial growth under the specified storage conditions. The LD may be tested in parallel to demonstrate equivalence.

Also, see FDA's response to question 3.

(b) The applicant's proposed product Pemetrexed Injection is having same concentration (25 mg/mL) for all the proposed fill volume (4 mL, 20 mL, 34 mL and 40 mL). Hence, dilution study (concentration 9 mg/mL) will be carried on any three batches from all proposed fill volumes packs. Is this approach acceptable?

FDA Response: Accord's approach appears reasonable. Also, see FDA's responses to question 3 and 6a. The microbial challenge study for the post-diluted solution, 9 mg/mL pemetrexed solution, may be performed by using any proposed fill volume pack(s).

7. Is there any specific study will be required for submission and approval of the NDA?

FDA Response: If an adequate bridge is established, FDA does not require any further clinical studies.

In the NDA, include data/information that would establish the bridge between the proposed drug product and the LD, based on Code of Federal Regulations 21 CFR §320.24(b)(5)/(6) available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=320.24**.**

In addition, include the assay of antioxidants as a quality attribute and the drug product must comply with applicable requirements of USP<1>. Submit the leachable and extractable information for the container/closure system and all product contact parts of manufacturing equipment including tubing, filter, and mixing vessel, etc. Additionally, submit the NDA with all the relevant information based on review of CMC guidance/requirements. For example, set the limits for related substances (degradation products) based on the recommendation of ICH Q3B(R)2 and set the elemental impurities limits based on ICH Q3D. The determination regarding approval of the NDA will be made after review of the NDA.

For detailed information on the data to be submitted in the NDA for product quality microbiology assessment, please refer to the following guidance documents: FDA *Guidance for Industry for the Submission Documentation for Sterilization Process*

Validation in Applications for Human and Veterinary Drug Products (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf), and FDA *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* (https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf).

Nonclinical

8. The proposed product is an injection concentrate that contains the same final concentration of the active ingredient as the reference listed drug, Alimta®. The inactive ingredients that will be used are listed in the Inactive Ingredient Database(IIG), and have been previously approved for use in the same route of administration, at levels above those reflected in the formulation for Accord's proposed product. Since Accord intends to rely on the agency's finding of safety for the Reference Listed Drug, Alimta®, and in light of the previously approved levels of the inactive ingredients contained in the proposed formulation, Accord believes that no additional toxicological studies would be required for the NDA. Does the agency agree? If not, what types of study will be required for submission and approval of the NDA?

   FDA Response: Accord's approach appears acceptable.

Clinical

9. The active ingredient, route of administration, proposed indications and dosing regimen remain are the same as for the Reference Listed Drug, Alimta®. In light of Accord's intention to rely on the Agency's findings of safety and efficacy for Alimta®, as a basis for this NDA submission, Accord believes that clinical studies should not be required for submission and approval of the NDA.
   Does the agency agree? If not, what types of study will be required for submission and approval of the NDA?

   FDA Response: See response to #7, if an adequate bridge is established, the FDA does not require any further clinical studies.

10. Is there any other specific study will be required for submission and approval of the NDA?

    FDA Response: See response to #7 and #9.

Clinical Pharmacology/Biopharmaceutics

11. Will the proposed product be eligible for a waiver of the requirement to provide evidence of in-vivo bioavailability or bioequivalence on the basis that it is a solution that is intended to be administered intravenously?
If not, what types of study will be required for submission and approval of the NDA?

FDA Response: If an adequate in vitro bridge is established between the proposed drug product and the LD, an in vivo bioavailability/bioequivalence study may not be needed. In the NDA, include data/information that would establish the bridge between the proposed drug product and the Listed Drug product, based on 21 CFR 320.24. Include justification that the differences in formulation composition (removal of mannitol; addition of the proposed levels of anhydrous citric acid, L-methionine, monothioglycerol), dosage form (lyophilized powder in single-use vial vs. multi-dose ready-to-dilute/RTD solution in vial), drug content/presentations (850 mg/34 mL and 1000 mg/40 mL), as well as any other observed differences (e.g., in impurities level of the RTD solution when stored at 25°C and under refrigeration, physicochemical properties such as pH, osmolality, viscosity, specific gravity, etc.) between the test and the reference drug products will not impact the PK/disposition (i.e., renal elimination) of the drug and the efficacy and tolerability/safety of the proposed drug product. If the proposed RTD solution is intended to be labeled for multi-dose use, include in the justification the rationale for not incorporating an antimicrobial preservative in the formulation. The adequacy of the data/information to establish the bridge between these two drug products will be determined at the time of NDA review.

FDA recommends that all comparative studies aimed to support the safety/tolerability of the proposed RTD solution drug product evaluate a range of test concentrations encompassing those of the test and reference solutions, i.e., prior to and after dilution according to the pre-administration instructions provided in the approved/proposed package inserts.

Interchangeability

12. After all criteria of Accord's NDA approval will be satisfied, the proposed drug product should be considered Pharmaceutically Equivalent to the RLD and interchangeability of the proposed product with the RLD will be allowed?

FDA Response: The Office of Generic Drugs (OGD) has conveyed that 505(b)(2) products are not normally assigned a Therapeutic Equivalence (TE) Code. However, some 505(b)(2) products may be assigned a TE Code (e.g., some injectable products that receive a biowaiver). If Accord would like the proposed product to be considered for a TE Code in the Orange Book, submit a general correspondence to the NDA following full approval. The correspondence should provide detail and justification. Also, email a

courtesy copy of that request to the Orange Book general inbox at drugproducts@cder.fda.gov.

For further information on how these evaluations are made, refer to the Preface of the Orange Book, Section 1.2.: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

Other Information (PREA Requirements)

13. As per 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.

It is evident that the formulation change will not lead to any specific influence to Pediatric population. Accord is seeking approval for Indications for which reference listed drug (Alimta) has been approved and seeking waiver to carry out pediatric studies. Accord requests FDA to waive us from the requirement for pediatric assessments for each of the approved indications of the referenced listed drug cancer for all pediatric age groups because available data indicates that conducting studies in pediatric population would be impossible or highly impractical because of the small number of pediatric patients. Accord will submit Initial Pediatric Study Plan (iPSP) through amendment in pIND (142070). Applicant will submit the iPSP no later than 210 calendar days before New Drug Application submission.

Does the agency agree?

FDA Response: Yes. The Initial Pediatric Study Plan Template can be found in Appendix 1 of 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

Please use the template for full waiver requests and note that only the title page and sections 1, 2, 4 and 12 are applicable, all other sections should be removed. Ensure that the indication statement is clear.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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 OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@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.

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.				

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please

note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.

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/

SHUBHANGI H MEHTA
01/28/2019 01:27:07 PM