CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214652Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 141630

**MEETING REQUEST-
WRITTEN RESPONSES**

Accord Healthcare Inc.
Attention: Sabita Nair, RAC, ASQ-CPGP
Sr. 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 Atropine Sulfate Injection USP, 1 mg/mL and 0.4 mg/mL.

We also refer to your submission dated November 28, 2018, containing a Pre-NDA meeting request (Written Responses Only). The purpose of the requested meeting is to discuss your product development plan for a 505(b)(2) application for Atropine Sulfate Injection USP, 1 mg/mL and 0.4 mg/mL.

Further reference is made to our Meeting Granted letter dated December 7, 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 17, 2018 background package.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-NDA
Application Number:	PIND 141630
Product Name:	Atropine Sulfate Injection USP, 1 mg/mL and 0.4 mg/mL
Indication:	For temporary blockade of severe or life threatening muscarinic effects, e.g., as an antisialagogue, an antivagal agent, an antidote for organophosphorus or muscarinic mushroom poisoning, and to treat bradyasystolic cardiac arrest.
Sponsor/Applicant Name:	Accord Healthcare Inc.
Regulatory Pathway:	505(b)(2)

1.0 BACKGROUND

Accord Healthcare Inc. requested this Pre-NDA meeting (Written Responses Only) to discuss their product development plan for a 505(b)(2) new drug application (NDA) for Atropine Sulfate Injection USP, 1 mg/mL, 1 mL and 0.4 mg/mL, 1 mL in glass vials.

The proposed listed drug (LD) is Hospira, Inc.'s Atropine Sulfate Injection (Ansyr™ Plastic Syringe), 0.1 mg/mL, 5 mL and 10 mL, which was approved under NDA 021146.

Accord's proposed Atropine Sulfate Injection, USP is formulated with a strength of 1 mg/mL and 0.4 mg/mL compared to the proposed listed drug's strength of 0.1 mg/mL. Therefore, Accord intends to submit a 505(b)(2) NDA application under the clause of a change in strength. Accord's proposed formulation is identical to that of Hospira's approved product in terms of route of administration, dosage form and therapeutic indication.

For this Pre-NDA meeting, Accord wishes to obtain guidance specifically:

1) To determine whether the proposed product is eligible for submission as a 505(b)(2) NDA.
2) To determine the nature of any non-clinical, clinical, or pharmacokinetic studies that may be required to support the submission and approval of the NDA, pursuant to 21 CFR 314.54.
3) To determine whether the proposed product may be eligible for an "A" rating (therapeutically equivalent) against the Reference Listed Drug (RLD). [Same TE code will be assigned for proposed drug product and RLD].

2.0 QUESTIONS AND RESPONSES

2.1 General

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

FDA Response to Question 1:
A 505(b)(2) application appears acceptable, at this time, based on the available information. For information on the 505(b)(2) regulatory pathway, please see section 3.0 of this document.

2.2 Quality

Question 2:
The applicant proposes to submit Chemistry, Manufacturing and Controls (CMC) information on **three pilot scale 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 to Question 2:
We agree with your proposal to include at least twelve months of long-term stability data and six months of accelerated stability data at the time of NDA submission. For detailed recommendations regarding the batch selection, testing conditions, etc., refer to *ICH Q1A (R2) Guidance "Stability Testing of New Drug Substances and Products."*

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

FDA Response to Question 3:
Refer to our response to Questions 6 and 7.

Question 4:
Accord intends to perform pharmaceutical equivalency study of proposed product with RLD for test parameters assay, related substances, description, osmolality and specific gravity. Is this approach acceptable?

FDA Response to Question 4:
Refer to our response to Question 6.

Question 5:
(b) (4) is one of the impurities in finished product. Applicant wants to keep limit of NMT (b) (4) % beyond ICH threshold being a metabolite impurity. Is this approach acceptable?

FDA Response to Question 5:
(b) (4) please provide in your submission a justification for the proposed acceptance limits for the (b) (4) impurity in view of your batch analysis and stability data.

Question 6:
Accord intends to perform pharmaceutical equivalency study of diluted product of two formulations (Test product and RLD) of Atropine Sulfate Injection. Dilution study will be performed covering below particulars:

- Diluent: Water for injection and 0.9% sodium chloride injection
- Study temperature: 20°C - 25°C (normal room Light)
- Final concentration of drug: (b) (4) mg/mL and (b) (4) mg/mL
- Study time points: Initial and 24 hours
- Test parameters: description, pH, assay and related substances

Is this approach acceptable?

FDA Response to Question 6:
To support bridging of the proposed solution drug product to the Listed Drug Product, in addition to assay, related substances, description, osmolality and specific gravity, we recommend providing also comparative physicochemical properties such as pH and viscosity of the test and reference solution drug products when evaluated at concentrations achieved at the point of patient contact.

Additional Comments:
1. We recommend that minimum fill volume be included in the finished product QC specifications of the proposed drug product.
2. In the NDA, provide data to demonstrate compatibility of the two strengths of the proposed drug product with the primary packaging (container-closure system).
3. Pharmaceutical equivalents are drug products that have the same drug concentration or strength, in addition to the same active ingredients, dosage form, and route of administration. Therefore, FDA will likely consider the proposed drug product as a pharmaceutical alternative of ANSYR (the Listed Drug product).

2.3 Non-clinical

Question 7:
The proposed product is an injection that contains the same active ingredient as RLD. The inactive ingredient that will used for the product is sodium chloride which is qualitative and quantitative same as reference product. Sodium hydroxide and sulfuric acid will be used as pH adjusting agent in the formulation like RLD. Since Accord intends to rely on the Agency's finding of safety for the Reference Listed Drug [Atropine Sulfate Injection 0.1 mg/mL, 5 mL and 10 mL (NDA # 021146), a product of Hospira, Inc., USA.], Accord believes that no additional toxicological studies would be required for the intended NDA. Does the Agency agree?

FDA Response to Question 7:
In general, we agree. However, we have the following comments related to the higher strengths (0.4 and 1 mg/mL) you proposed than the RLD strength (0.1 mg/mL) for multiple routes of administration.

- Please conduct an in vitro hemolysis assay with human blood at the highest proposed strength for I.V. administration.
- Please provide information (perhaps from published data) on local tolerability with the proposed higher strength products.

In addition, please be reminded:

- Any novel excipients, metabolites or excipients exceeding levels in currently approved products will require qualification for safety to support the proposed clinical use.
- Any impurities/degradants in drug substance/product exceeding the qualification threshold should be qualified per ICH Q3A (R2) and ICH Q3B(R2).
- Impurities/degradants that are identified as structural alerts should not exceed acceptable qualification thresholds as described in ICH guidance M7(R1).

2.4 Clinical

Question 8:
The active ingredient, route of administration, proposed indications and dosing regimen remain the same as for the Reference Listed Drug [Atropine Sulfate Injection 0.1 mg/mL, 5 mL and 10 mL (NDA # 021146)] and in light of Accord's intention to rely on the Agency's findings of safety and efficacy for Atropine Sulfate Injection 0.1 mg/mL, 5 mL and 10 mL (NDA # 021146), 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 the Agency doesn't agree, please advise [what] type of study which applicant needs to perform.

FDA Response to Question 8:
It is reasonable not to perform an in vivo BE study between the proposed solution drug product and the Listed Drug Product (ANSYR), as long as impurities and degradants are no higher than with the RLD.

Question 9:
Is there any other specific study [which] will be required for submission and approval of the NDA?

FDA Response to Question 9:
No.

2.5 Interchangeability

Since the obtainment of an "A" rating (comprising pharmaceutical equivalence and therapeutic equivalence) is critical to Accord's business plan for this product, we wish to review and obtain the Agency's consensus on the criteria for obtaining an "A" rating. The table on the following page illustrates our understanding of the criteria for an "A" rating, and the status of the proposed product in relationship to these criteria: (Note: Several questions are posed after the table.)

Criterion	Yes/No or to be Confirmed
1) Product is approved as safe and effective	To be confirmed at time of NDA approval
2) Product contains the identical amount of same active ingredient in the same dosage form and route of administration as the RLD	Yes [Total concentration of active ingredient in applicant's product is 1mg and 0.4 mg for 1 mg/mL (1 mL) and 0.4 mg/mL (1 mL) respectively. This is within range of RLD total concentration of active ingredient (i.e., 1 mg and 0.5 mg for 0.1 mg/mL (10 mL and 0.1 mg/mL (5 mL), respectively)]. The dosage form and route of administration of applicant's product is same as RLD.
3) Product meets compendial or other applicable standards of strength, quality purity and identity	To be confirmed during NDA review
4) Product is bioequivalent to the RLD in that it does not present a known or potential bioequivalence problem and meets an acceptable in vitro standard or if it does present a known or potential problem, it has been shown to meet a bioequivalence standard	To be confirmed during NDA review
5)Product is adequately labeled	To be confirmed during NDA review
6) Product is manufactured in compliance with cGMPs	To be confirmed during NDA review

Question 10:
Does the Agency agree with the criteria for an "A" rating listing in the table above?

FDA Response to Question 10:
See our response to Question 6.

Therapeutic Equivalence (TE) codes are reviewed and determined by the Orange Book staff only after approval of a drug product. Please consult the Orange Book staff (OrangeBook@fda.hhs.gov) on matters pertaining to TE determinations.

Question 11:
Does the Agency agree that the proposed product would be eligible for an "A" rating based on the criteria defined in the table above? If not, then what types of studies would be required to satisfy this criterion for purposes of enabling an "A" rating?

FDA Response to Question 11:
See our response to Question 10.

2.7 Other Information - *PREA Requirements*

Question 12:
The active ingredient, indications, dosage forms, dosing regimens and route of administration for the Proposed product Atropine Sulfate Injection USP 1 mg/mL, 1 mL and 0.4 mg/mL, 1 mL will remain same as that of the Reference Listed Drug [Atropine Sulfate Injection (Ansyr™ Plastic Syringe) 0.1 mg/mL, 5 mL and 10 mL (NDA# 021146) of Hospira, Inc., USA]. The marketing application for Accord's proposed product does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration for which an applicant is required to submit an iPSP. Hence, Accord believes that requirement of assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients is **inapplicable**. Does the Agency agree?

FDA Response to Question 12:
Exemption from PREA statutory requirements can be granted if the following conditions are met: 1) not a new active ingredient; 2) not a new indication; 3) not a new dosage form; 4) not a new dosage regimen; and 5) not a new route of administration. If you believe that PREA does not apply to your product, please include a side-by-side comparison of the PREA criteria for your proposed product and Hospira's product. This would facilitate our assessment of whether you would be exempt.

2.8 Additional FDA Comments

Please follow the 1994 *"Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."*

3.0 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.

4.0 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.

5.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

6.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

7.0 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.

8.0 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).

9.0 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.				

10.0 505(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/

NORMAN L STOCKBRIDGE
01/23/2019 09:45:48 AM