CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215700Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 137308

MEETING REQUEST-
WRITTEN RESPONSES

InfoRLife SA
Attention: Jeanne A Squeglia
VP, Technical Affair, Interchem Corporation
120 Route 17 North, Suite 115
Paramus, NJ 07652

Dear Ms. Squeglia:

Please refer to your Pre-Investigational New Drug Application (PIND) file for for Norepinephrine Bitartrate premixed Injection, USP 4 mg/ 250 mL (0.016 mg/mL), 8 mg/ 250 mL (0.032 mg/mL) and 16 mg/ 250 mL (0.064 mg/mL).

We also refer to your submission dated November 1, 2017, containing a meeting request. The purpose of the requested meeting was to discuss the acceptability of the identified Reference Listed Drug and the available published literature to support the approval of a 505(b)(2) NDA for Norepinephrine Bitartrate premixed Injection.

Further reference is made to our Meeting Granted letter dated November 6, 2017, 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 November 15, 2017 background package.

If you have any questions, call Maryam Changi at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
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:	137308
Product Name:	Norepinephrine Bitartrate premixed Injection, USP 4 mg/ 250 mL (0.016 mg/mL), 8 mg/ 250 mL (0.032 mg/mL) and 16 mg/ 250 mL (0.064 mg/mL).
Indication:	[Insert indication]
Sponsor Name:	InfoRLife SA
Regulatory Pathway:	505(b)(2)

1.0 BACKGROUND

Norepinephrine Bitartrate is an alpha-1 adrenergic receptor agonist indicated for [redacted] (b) (4)

InfoRLife plans to submit a 505(b)(2) NDA for premixed Norepinephrine Bitartrate Injection, USP, [redacted] (b) (4) packaged in [redacted] (b) (4) 250 mL flexible Nexcel bag. The sponsor is refrencing Levophed NDA 007513 as a Reference Listed Drug. Norepinephrine Bitartrate Injection, USP, [redacted] (b) (4) has the same route of administration, dosage form and strength when administered of Reference Listed Drug.

InfoRLife requested this meeting for the following purposes:

- Discuss the proposal to reference the efficacy and safety information from Levophed which will form the basis for approval of the 505(b) (2) application;
- Discuss the proposed presentation and strength for InfoRLife Norepinephrine Bitartrate Injection, USP ready to use product.
- Discuss any other concerns that the Division may have about the other filing issues specific to the reference product.

2.0 QUESTIONS AND RESPONSES

2.1. Regulatory/Procedural

<u>Question 1a:</u> *InfoRLife intends to utilize the 505(b)(2) NDA pathway of the Act for the proposed product. InfoRLife will base its NDA for Norepinephrine Bitartrate Injection, USP* [redacted] (b) (4)

[redacted] (b) (4) on the safety and efficacy of NDA 007513 Levophed® and its subsequent safety and efficacy supplements as well as supporting relevant published literature. The InfoRLife NDA will contain CMC data in support of drug product [redacted] (b) (4).
Does FDA agree? If not, why?

FDA Response to Question 1a:
A 505(b)(2) application appears acceptable, at this time, based on the available information. Information for sponsors considering the submission of an application through the 505(b)(2) pathway can be found under the 505(b)(2) REGULATORY PATHWAY heading in section 3.0 of this document.

Question 1b: *InfoRLife proposes to refer to the package insert for the reference drug product Levophed® NDA 007513 as the basis for the labeling of its product, with the appropriate changes based on the fact that the product is ready to use. Does the Division agree with this proposal? If not, why?*

FDA Response to Question 1b:
If approved, your prescribing information (PI) must contain a summary of the essential scientific information needed for the safe and effective use of your product and must be informative and accurate and neither promotional in tone nor false or misleading. Your proposed label will be primarily based on the label for the listed drug upon which your proposed application relies. However, the PI for your product should incorporate any information required to avoid being inaccurate, false, or misleading [see 21 CFR 201.56(a)]. You should include in your submission a summary review of published literature regarding the use of this product. You should consider whether revisions to the PI of the listed drug are required based on your summary review of the literature. Any clinical or nonclinical information that is relevant and new should be incorporated into your proposed label.

In particular please address the following:
- Review contraindications and evaluate the support for their continued inclusion.
- Evaluate the indication for [redacted] (b) (4), because it appears that use would be included in the first indication.
- Conduct a review of literature to confirm appropriate dosing.
- "Regitine" is no longer available (phentolamine is available generically) and references to it should be removed from labeling.

In addition, your proposed prescribing information (PI) must conform 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). 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.
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

__Question 1c:__ *InfoRlife recognizes that its proposed* [redacted] (b) (4) *formulation is a change to the previously approved Reference Listed Drug (RLD) product 007513 Levophed because the proposed formulation is a* [redacted] (b) (4) *while the RLD is an undiluted solution. This difference will also be reflected in the labeling for the proposed product. The InfoRLife application contains information to demonstrate that the proposed product is identical in active ingredients, dosage form, and route of administration, quality and performance characteristic. Consistent with the October 1999 FDA draft guidance, application covered under 515(b)(2), InfoRLife plans to submit an NDA under FDC section 505(b)(2). Does the agency concur with InfoRLife that submission of this NDA under section 505(b)(2) of the Act is appropriate?*

__FDA Response to Question 1c:__
See response to Question 1a.

__Question 1d:__ *InfoRLife intends to submit a new 505(b)(2) application for a* [redacted] (b) (4) *formulation of Norepinephrine Bitartrate Injection with packaging material that differs from the reference listed drug packaging material. Does the FDA concur that the difference in packaging material, which has been previously approved for other products, will not require additional nonclinical studies to support the filing and review for approvability of InfoRLife Norepinephrine Bitartrate Injection?*

__FDA Response to Question 1d:__
In addition to establishing compatibility of the drug product formulations with the packaging material by evaluating stability, physical properties and sterility, studies to determine

extractables/leachables and potential elemental impurities should be performed by the time of an NDA submission.

Question 1e: *Norepinephrine Bitartrate Injection will be supplied in single dose non-PVC bags, each overwrapped with aluminum secondary packaging containing an oxygen absorber, similar to* [redacted] (b) (4)*. Since the Norepinephrine Bitartrate is oxygen sensitive, this permits to improve the stability of drug product. Is it acceptable for FDA the use of oxygen absorber? If not, why?*

FDA Response to Question 1e:
The use of the oxygen absorber may be acceptable, but this will be a matter for review. The effectiveness of the oxygen absorber must be demonstrated using long-term and accelerated drug product stability studies. Additionally, the aluminum secondary packaging should be shown to provide a robust protective barrier to limit oxygen ingress sufficiently to ensure that the oxygen sensor remains effective through shelf life. For batch release and stability studies we recommend monitoring degradants/related substances and osmolality in addition to the listed specifications.

Question 1f: *InfoRLife has found during stability trials that color of the solution will turn brown if exposed to oxygen.* (b) (4) [redacted]

FDA Response to Question 1f:
We recommend that you include an oxygen indicator in the secondary packaging. (b) (4) [redacted] In addition to ensuring the effectiveness of the oxygen absorber, an oxygen indicator would provide an alert for damaged or ruptured secondary packaging.

Question 1g: *Market Research and FDA through its Safe Use Initiative awarded ASHP to develop and implement national standardized concentrations. As such, three concentrations were developed by InfoRLife: 4 mg / 250 ml (0.016 mg / mL), 8 mg / 250 mL (0.032 mg / mL) and 16 mg / 250 mL (0.064 mg / mL). Does the Agency agree with the proposed three strengths? If not, why?*

FDA Response to Question 1g:
The national standard concentrations for norepinephrine are 16, 32, and 128 mcg/mL. Your proposed dosing is aligned with the ASHP recommendation except for highest proposed strength of 64 mcg/mL Please provide a justification for this discrepancy.

2.2. Preclinical

Question 2: *InfoRLife does not intend to conduct any nonclinical pharmacology, toxicology, or PK (pharmacokinetics) studies for Norepinephrine Bitartrate Injection to support the 505(b)(2) NDA for approval of the proposed indication. InfoRLife intends to rely on: the safety of the product Levophed NDA 007513 as described in product labeling. Is this proposed preclinical approach adequate to filing and review the approvability of the NDA for Norepinephrine Bitartrate premixed Injection, USP 4 mg / 250 ml (0.016 mg / mL), 8 mg / 250 mL (0.032 mg /*

mL) and 16 mg / 250 mL (0.064 mg / mL). [redacted] (b) (4) *in 250 mL Nexcel infusion bags, for the proposed indication?*

<u>FDA Response to Question 2:</u>
Yes, we agree.

2.3. Clinical

<u>Question 3a:</u> *InfoRLife plans to provide evidence of clinical safety based on FDA's previous determination of safety and efficacy as demonstrated by approval of Levophed NDA 007513. Is this proposed clinical approach adequate to filing and review the approvability of the NDA for Norepinephrine Bitartrate premixed Injection, USP 4 mg / 250 ml (0.016 mg / mL), 8 mg / 250 mL (0.032 mg / mL) and 16 mg / 250 mL (0.064 mg / mL). for the proposed indication? Does the agency agree that no additional clinical studies will be required to support approval of InfoRLife's 505(b)(2) application?*

<u>FDA Response to Question 3a:</u>
Levophed NDA 007513 should provide a sufficient basis for establishing safety and efectivness; you should not require clinical studies.

<u>Question 3b:</u> *Average dosage of Levophed is defined from 8 mcg to 12 mcg per minute. Much larger or even enormous daily dose up to 68 mg are clearly contemplated in the package insert, clinical use and literature data. Does the agency agree that the proposed presentation 4 mg/250 mL, 8 mg/250 mL and 16 mg/250 mL are supported by the approved dosage recommendation of Norepinephrine Bitartrate?*

<u>FDA Response to question 3b:</u>
The proposed dosing presentation appears reasonable.

<u>Question 3c:</u> *The average dose of Levophed recommends a dilution at 0.04 mg/mL. When large volumes of fluid are clinically undesirable, a concentration greater than 4 mcg per mL may be necessary.[1] Norepinephrine Bitartrate premixed Injection USP is available as 0.016 mg/mL (4 mg/250 mL), 0.032 mg/mL (8 mg/250 mL) and 0.064 mg/mL (16 mg/250 mL) concentration. Does the agency agree that the proposed presentation 4 mg/250 mL, 8 mg/250 mL, 16 mg/250 mL are supported by the approved concentration recommendation of Norepinephrine Bitartrate?*

<u>FDA Response to Question 3c:</u>
Your proposal appears reasonable. We believe the first sentence in your question contains a typographical error (i.e. 0.04 mg/mL should be 0.004 mg/mL).

<u>Question 3d:</u> *Levophed® NDA007513 must be diluted in 0.5% dextrose or dextrose and sodium chloride. Administration in saline solution alone is not recommended. Literature data and stability studies suggest as well as demonstrate the stability of Norepinephrine Bitartrate Injection, USP in 0.9% sodium chloride alone. Does the agency agree in the usage of 0.9% alone in Norepinephrine Bitartrate injection, USP* [redacted] (b) (4)*?*

FDA Response to question 3d:
To support the usage of 0.9% sodium chloride alone in Norepinephrine Bitartrate injection, drug product at the proposed concentrations must meet specified acceptance criteria on release and throughout shelf life. Additionally, in-use stability and compatibility with the 0.9% sodium chloride in the proposed container closure system must be established. This will be a matter for review.

Question 3e: *InfoRLife intends to rely on the pharmacokinetic (PK) and pharmacodynamics (PD) studies described in NDA 007513 Levophed® as the sole source of PK/PD data to support its premix presentation of Norepinephrine Bitartrate Injection. The proposed Norepinephrine Bitartrate Injection,* (b) (4) *drug product will be administered as IV infusion, in the same manner as the RLD. The excipients used in the proposed Norepinephrine Bitartrate formulation, when reconstituted, are the same as the RLD formulation. The recommended dosage and administration regimen is the same as RLD. Therefore, it is expected that the proposed Norepinephrine Bitartrate Injection Injection,* (b) (4) *will have the same PK/PD profile as the RLD. Based upon this rationale, InfoRLife intends to request a waiver of evidence of in vivo bioavability or bioequivalence in accordance with the provisions of 21CFR320.22. Does the Agency agree that such waiver is appropriate?*

FDA Response to question 3e:
We agree that a biowaiver request is appropriate for your product.

Question 3f: *Under PREA, a pediatric assessment must be submitted for new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration . Please note our product does not differ from the RLD for any of those criteria. The Hospira product is a concentrate that must be diluted prior to administration (see Dosage and Administration Section of Product Insert: Norepinephrine bitartrate injection should be diluted in 5 percent dextrose injection or 5 percent dextrose and sodium chloride injections). The* (b) (4) *proposed product is a ready to use solution that does not require dilution like the RLD. Does the Agency agree that the above is sufficient for waiver of PREA requirements?*

FDA Response to question 3f:
This is not actually a waiver; PREA would not be "triggered" by submission of an NDA for your proposed norepinephrine product.

3.0 OTHER IMPORTANT MEETING LANGUAGE

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.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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 start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or 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 start 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.

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

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

COMPOUNDED DRUG PRODUCT REQUIREMENTS

As described at 21 CFR 210.2(c), a drug product, including a compounded product, intended for use in a clinical study must be prepared in accordance with the current good manufacturing practice requirements appropriate for the product. For questions or clarification, contact Compounding@fda.hhs.gov.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. 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.

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.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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

/s/

NORMAN L STOCKBRIDGE
12/22/2017