CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214628Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 135595

**MEETING REQUEST-
WRITTEN RESPONSES**

TechReg Services, Inc.
Attention: Steven Pikulin, Ph.D., RAC
President
17 McIntire Drive
Hillsborough, NJ 08844-2244

Dear Dr. Pikulin:

Please refer to your Pre-Investigational New Drug Application (PIND) file for NVK004 (Norepinephrine Bitartrate Ready-To-Use Injection).

We also refer to your submission dated May 26, 2017, received May 30, 2017, containing a Pre-IND meeting request. The purpose of the requested meeting was to discuss your plans to submit a 505(b)(2) NDA.

Further reference is made to our Meeting Granted Letter dated June 2, 2017, wherein we stated 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 June 28, 2017 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-IND
Application Number:	Pre-IND 135595
Product Name:	NVK004 (Norepinephrine Bitartrate Ready-To-Use Injection)
Indication:	For blood pressure control in certain acute hypotensive states [redacted (b) (4)].
Sponsor/Applicant Name:	Nevakar, LLC
Regulatory Pathway:	505(b)(2)

1.0 BACKGROUND

Nevakar is developing NVK004 (Norepinephrine Bitartrate Ready-To-Use Injection) for the proposed indications of blood pressure control in certain acute hypotensive states (e.g., pheochromocytomectomy, sympathectomy, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions) [redacted (b) (4)].

Norepinephrine Bitartrate Injection, USP was initially approved in the United States in 1950 and is currently marketed by Hospira as Levophed (NDA 007513). Levophed is currently supplied as a concentrate that must be diluted in 5% dextrose or 5% dextrose and sodium chloride for injection before administration.

Nevakar is developing NVK004 as a sterile ready-to-use injectable solution to avoid [redacted (b) (4)] and to reduce the potential for delays in administration, dosing errors and microbial contamination. The product will be available in three concentrations, containing Norepinephrine Bitartrate equivalent to16 µg/mL, 32 µg/mL and 64 µg/mL of norepinephrine base in a solution with Sodium Chloride [redacted (b) (4)] and Edetate Disodium [redacted (b) (4)].

The sponsor requested this Pre-IND meeting to confirm that:

- A 505(b)(2) NDA application is the appropriate regulatory pathway for NVK004 as an intravenous ready-to-use treatment.
- Use of FDA-approved Levophed as the RLD is appropriate.
- The composition and container closure system design are acceptable.
- No additional nonclinical studies are needed.
- No clinical studies are required.

In the Meeting Granted Letter dated June 2, 2017, the Division had stated that written responses to the sponsor's questions would be provided in lieu of a meeting. The sponsor's questions are listed below followed by the Division's responses.

2.0 QUESTIONS AND RESPONSES

2.1 Regulatory

Norepinephrine Bitartrate Injection, USP is approved in the US and is currently marketed as Levophed™ (RLD). Nevakar's proposed indications for Norepinephrine Bitartrate Ready-to-Use Injection (NVK004) are the same as the RLD, and the product will be available in three (3) concentrations filled in a 250mL [redacted] (b) (4) container.

Question 1:
Does the Agency agree that the 505(b)(2) NDA regulatory pathway is appropriate for the Nevakar Norepinephrine Bitartrate Ready-To-Use Injection IV product?

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

2.2 Chemistry, Manufacturing and Controls (CMC)

Nevakar has developed product formulations that are presented as Ready-To-Use intravenous solutions. In addition, the inactive ingredients used in the product are at amounts that do not exceed other approved FDA intravenous products based on information found in the FDA Inactive Ingredient Database. The proposed formulations are presented in Table 1 (see Section 10.1.2.1, Components/Composition).

Question 2:
Does the Agency have any specific comments regarding the qualitative and quantitative compositions of the formulation?

FDA Response to Question 2:
The proposed formulation seems reasonable. However, in your proposed NDA, you need to provide a detailed justification why your formulation is stable when diluted in saline, unlike Levophed, which is not recommended for dilution in saline solution alone for administration [redacted] (b) (4).

Question 3:
Does the Agency have any specific comments regarding Edetate Disodium in the composition?

FDA Response to Question 3:
Use of edetate disodium in the formulation seems reasonable.

[redacted] (b) (4)

Question 4:
Does the Agency agree that the proposed [redacted] (b) (4) ***container closure system is acceptable for drug products manufactured by*** [redacted] (b) (4) ***processing?***

FDA Response to Question 4:
From a CMC perspective, the (b) (4) container closure system is acceptable in general. However, the acceptability of your specific container closure system would be determined after a complete review of the information submitted in the NDA and cross-referenced DMFs. Please note that subsequent advice may be provided via a general advice letter based on the evaluation of the container closure system by the quality microbiology team, if necessary.

Question 5:
Does the Agency have any specific comments regarding the proposed container closure system?

FDA Response to Question 5:
Please include in the NDA a characterization of the extractables and leachables profile of the product when stored in the proposed packaging. Also include information demonstrating that the proposed packaging will maintain the physicochemical and microbiological quality of the product over the expected in-use period once removed from the protective secondary packaging.

2.3 Nonclinical

In vitro hemolysis tests and *in vivo* pharmacokinetic/toxicity studies have been conducted to compare the NVK004 formulations with the RLD Levophed. Results for these studies demonstrate that the NVK004 formulations show no relevant differences in hemolysis, pharmacokinetics, or toxicity effects when compared to the RLD, Levophed. Therefore, Nevakar proposes to utilize the presented non-GLP nonclinical studies conducted with NVK004 and the available published nonclinical data for Levophed RLD to support an NDA 505(b)(2) application.

Question 6:
Does the Agency agree that this approach is acceptable to support a 505(b)(2) application for NVK004 and no further nonclinical/pre-clinical studies are required?

FDA Response to Question 6:
Yes, we agree, provided no safety issues arise due to impurities or degradants in the drug product.

2.4 BE Waiver/Clinical

Levophed is reconstituted at 4 µg/mL for low dose therapy. As explained above, the Levophed package insert provides flexibility in making the final admixture at concentrations lower or higher than 4 µg/mL as doses up to (b) (4) mg may be administered for high dose therapy. Nevakar is proposing a ready-to-use formulation in three concentrations. The dose/min and flow rate of Levophed diluted as stated on the label is compared to the three concentrations proposed by Nevakar and described in Table 3.

Question 7:
Are the proposed presentations of 16, 32 and 64 µg/mL acceptable to the Agency?

FDA Response to Question 7:
You propose the concentrations 16 µg/mL, 32 µg/mL, and 64 µg/mL as a ready-to-use injection.

Currently approved norepinephrine bitartrate products are supplied in 4 mg/4 mL (1 mg/mL) vials and ampules with labeled instructions to dilute to a concentration of 4 µg/mL before administration. Because the proposed concentrations of 16 µg/mL, 32 µg/mL, and 64 µg/mL are higher than the currently labeled admixture concentration, we recommend that you consider the

potential risk for dosing errors with the proposed presentations, and address the risk of dosing errors via adequate labeling differentiation, or by other mitigations, to minimize such risks.

Additionally, clarify the container closure system (glass bottle or intravenous bag) for your proposed Norepinephrine bitartrate product. Please provide a picture of the container closure system.

Nevakar's product is a ready-to-use formulation of Norepinephrine Bitartrate with set concentrations. The clinical indications, route of administration, and dose per minute remain the same as the RLD, Levophed; however, the only difference is in the flow-rates.

Question 8:

Therefore, the bioequivalence of the two products (Nevakar 's Norepinephrine Bitartrate Ready-To-Use Injection product and the RLD, Levophed) is self-evident and should therefore qualify for a waiver of in vivo bioequivalence under 21 CFR §320.22(b)(1) or such a waiver is compatible with the protection of the public health under 21 CFR §320.22(e). Nevakar anticipates that no additional clinical studies will be required in support of the marketing application. Does the Agency agree?

FDA Response to Question 8:

Biopharmaceutics:

Your proposal for FDA to consider waiving the requirement for the submission of in vivo bioavailability (BA) and/or bioequivalence (BE) data appears reasonable. However, your proposed drug product does not fully satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR 320.22(b)(1). Under this regulation, a drug product's in vivo bioavailability or bioequivalence may be considered self-evident and a waiver of in vivo studies may be granted if the drug product meets the following criteria:

a. Is a parenteral solution intended solely for administration by injection; and

b. Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

Therefore, because of the difference in the excipients [Sodium metabisulfite and Edetate Disodium], FDA may have concerns regarding the potential changes to the disposition kinetics of Norepinephrine in the proposed drug product compared to the listed drug product.

However, based on the information provided, FDA agrees to consider your biowaiver request under 21 CFR 320.24(b)(6), given the following information is provided in the NDA:

a. Formulation (qualitative and quantitative composition) before and after reconstitution and dilution, dosage form, administered volume, etc., for the proposed drug product and the listed drug in a side-by-side comparison table.

b. Comparative physicochemical data for the proposed drug product and the listed drug product. The measurements should be done in triplicate for each lot tested. Include the justification for any differences in the formulation's composition, pH, osmolality, dosage, mode of administration, drug concentration, administered volume, etc., relative to the listed drug product.

c. As supporting evidence, provide data and/or published literature results regarding the effects of the difference in the excipients in the proposed drug product and the listed drug product, on the disposition kinetics of Norepinephrine in human subjects.

Clinical
We agree that that no additional clinical studies will be required in support of your marketing application.

3.0 505(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.

4.0 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 pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

5.0 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.

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

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

6.0 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 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

7.0 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.

8.0 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.

9.0 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).

10. 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.

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/s/

NORMAN L STOCKBRIDGE
07/28/2017