CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202860Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202860

COMPLETE RESPONSE

Vero Biotech, LLC
Attention: Alfred W. Schweikert, PhD, RAC
Vice President of Regulatory Affairs
387 Technology Circle NW
Suite 125
Atlanta, GA 30313

Dear Dr. Schweikert:

Please refer to your New Drug Application (NDA) dated and received July 23, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for GeNOsyl® (b) (4) Delivery System (b) (4) (Nitric Oxide).

We also acknowledge receipt of your amendment dated December 18, 2018, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection of the Vero Biotech manufacturing facility (FEI: 3014617112) for this NDA, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be considered for approval.

CDRH (DEVICE)

1. In prior communication, we noted your device incorporates sensory feedback for adjustment of Nitric Oxide delivery and flow rate. These sensors and the controlled outputs (b) (4) However, due to the closed-loop technology utilized in the design of the proposed device, FDA believes conformance to certain clauses of this standard will provide evidence of safety and adequate performance. This standard may be particularly relevant to (b) (4)

closed-loop systems whose failure may introduce the same risk to the patient as (b) (4) devices (e.g., over- and under-delivery of medication).

In order for FDA to be assured of the safety of your device, we previously requested that the following be provided in your submission.

a. evidence of conformity to the following clauses/sub-clauses:

(b) (4)

b. performance testing to demonstrate that under various disturbances or variabilities the device meets the following:

   i. The transient specifications will continue to be met. Please quantify the relevant transients such as overshoot, undershoot to show that the device meets its specifications as per (b) (4).

   ii. The control system continues to be stable. You may provide this evidence either analytically or experimentally.

      1. Analytic stability: In case you have developed a mathematical model and designed the control system based on pole/zero analysis, relative and absolute stability of the system may be conducted analytically. This would provide powerful evidence of stability.

      2. Experimental stability: If the control system design was not through a model-based technique, stability will need to be demonstrated experimentally. This will need to be demonstrated for an extended and sufficiently long period of time which will require the waveforms to be reproduced for long enough duration to provide reasonable evidence of output stability. The duration of this testing should be clinically relevant.

In the Performance Testing Summary provided in Section 2.3.R, you state that analysis (b) (4) is not applicable to the device. This information is not sufficient or complete. As stated above, we acknowledge that the controlled outputs are not (b) (4) standard. However, we believe that conformance to certain clauses of the standard will provide

evidence of safety and adequate performance of the device. Please provide the information requested above or provide itemized responses with rationale as to why the requested information is not applicable.

2. The device appears to be tested by software only to demonstrate delivery shutdown at NO_2 levels exceeding 3 ppm. Please provide testing of the physical device to demonstrate delivery shutdown.

3. The GeNOsyl (b) (4) DS was able to pass electrostatic discharge (ESD) immunity testing (b) (4) This information is needed so that we can assess the safety of the GeNOsyl (b) (4) in the electromagnetic environments of intended use.

4. The use of passive radio-frequency identification (RFID) tags that are interrogated by active readers (interrogators) for tracking material and personnel in hospitals is increasing. Because the GeNOsyl (b) (4) is a critical medical device, in addition to the EMC testing that was performed, we recommend that you test the GeNOsyl (b) (4) for immunity to RFID readers according to FDA-recognized AIM standard "Medical Electrical Equipment and System Electromagnetic Immunity Test for Exposure to Radio Frequency Identification Readers" (AIM catalog number 7351731) or equivalent. (AIM = Association for Automatic Identification and Mobility, www.aimglobal.org.) Please include information in the Operator's Manual specific to the risks and test results.

   An acceptable alternative to AIM 7351731 testing is ad hoc testing using RFID emitters at all the following frequencies emitting at the maximum RF output power, based on the environment of use.

   (b) (4)

   This information is needed so that we can assess the safety of the GeNOsyl (b) (4) in the healthcare electromagnetic environment.

5. Your device relies on an internal (b) (4) battery for backup if main power is lost. We could not locate any information in your submission related to this battery other than it complies with (b) (4) as supplied by the manufacturer. Additional information is needed to demonstrate the combination of the battery and system are safe. Please provide

the following information (or point to where it is in the submission) to demonstrate your battery safety when it is integrated with your device:

a. Device's surface temperature in the event of a battery short circuit,
Note: The surface temperature test should be conducted when the battery supplies the maximum current possible. The maximum current is the current amount that is just below the thermal or current protective circuit threshold at which these protective circuits disconnect the battery from the system.

b. Information to demonstrate that the battery manufacturer safety requirements such as environment, electrical, load, venting, air flow, charging speed, etc. are met after the battery is integrated in the system.

HUMAN FACTORS

The human factors (HF) validation study, submitted on July 23, 2018, does not provide sufficient evidence to demonstrate that your proposed product can be used safely and effectively by the intended users for its intended uses and use environments. We acknowledge your written responses, dated November 20, 2018 and November 30, 2018, submitted in response to the General Advice Letter dated November 16, 2018, however, the information provided does not adequately address our concerns.

1. Your study did not adequately evaluate participants' ability to detect, comprehend, and implement the appropriate actions in response to critical alarms. We acknowledge your written response including the trace matrix matching the critical high priority alarms to applicable use scenarios and user comprehension knowledge tasks. We also acknowledge that the HF study did evaluate participant performance of some tasks that would be applicable in an alarm scenario. However, none of the scenarios in the HF study evaluated critical audible and visual alarms within the context of an alarm status. Therefore, the participants in the study had no opportunity to detect the alarm during simulated use, then troubleshoot the alarm to determine and perform the appropriate response to address the alarm in the timeframe necessary to prevent patient harm. While we do not expect that all critical alarms are evaluated in a simulated use scenario, we remain concerned that the study methodology employed remains deficient to demonstrate that users will be able to identify an alarm and know how to respond to the alarm in a manner and timeframe necessary to avoid patient harm. Given the critical alarms are system features intended to alert the user to dose deviations and system failures, we believe that the HF study methodology was inadequate to provide sufficient evidence to demonstrate the effectiveness of these aspects of the user interface.

2. Confounding variables (incorrect system set-up for the testing scenarios, moderator error, and missing device components) occurred during the study, interrupting participant simulation of several critical tasks, which may have confounded the interpretation of your study results. It is not possible to discern whether these study interruptions may have impacted the participant performance of the critical tasks.

3. Numerous use errors and use difficulties with critical tasks occurred in the study that could result in delay of therapy, interruption of therapy, and overdose. We acknowledge the clinical evidence provided in your response that supports the safety of brief interruption (b) (4) of nitric oxide doses and short-term variation of nitric oxide doses over a range of (b) (4). However, the data provided in the HF study is inadequate to demonstrate that intended users can detect critical alarms and implement the appropriate response within the brief timeframe necessary to avoid patient harm (see number 1 above).

4. We acknowledge your revised Usability FMEA and modifications to the user interface (i.e., revisions to the Quick References Guide (QRG), Operator's Manual (OM), and Training Program) to address use errors and use difficulties observed in the study; however, none of these modifications were validated in a subsequent human factors study. You state that none of the changes made as part of the mitigation strategy altered the user interface or modes of use and thus no additional human factors testing is required. We disagree. Per the Applying Human Factors and Usability Engineering to Medical Devices guidance (2016), all sources of information transmitted by the device (including packaging, labeling), training and all physical controls and display elements (including alarms and the logic of operation of each device component and of the user interface system as a whole) comprise the user interface. Thus, the modifications and revisions to the, QRG, OM, and Training Program are considered alterations of the user interface. We expect user performance to be evaluated using all components of the final intend-to-market user interface, including the QRG, OM, and training program, for the final intend-to-market device to provide the data to demonstrate that the mitigation strategies are effective and do not introduce new use-related risks.

To address these concerns, we recommend you evaluate the use-related errors observed in the HF study, employ additional mitigation strategies as appropriate, update your use-related risk analysis, and conduct another HF validation study using appropriate study methodology, and the finalized intend-to-market user interface. We provide additional recommendations in the enclosed table for your consideration and recommend they are implemented prior to conducting your HF study. Ensure that your device, Training Program, QRG, and OM used in the new HF study are representative of the intend-to-market commercial product.

We strongly encourage to you to submit your HF study protocol for the Agency's review and feedback prior to commencing your HF validation study, although such review is not a requirement.

Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Please refer to our draft guidance titled "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications" for the content of a human factors validation study protocol submission. The guidance is available online at

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621902.pdf

Guidance on human factors procedures to follow can be found in "Applying Human Factors and Usability Engineering to Medical Devices," available online at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

See also the Guidance titled "Safety Considerations for Product Design to Minimize Medication Errors" available online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

"Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development," found online at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

"Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors," found online at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

REGULATORY

We refer to the Paragraph IV certifications under 21 CFR 314.50(i)(1)(i)(A)(4) that you submitted in your July 23, 2018, resubmission and remind you of the requirement to amend your application to include documentation of timely sending and receipt of notice of Paragraph IV certification as described under 21 CFR 314.52(e), by each person required to receive notice.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of

labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

The review of your proposed proprietary name has been suspended pending response to the deficiencies with the application as described in this letter. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

DETERMINATION OF PRODUCT EXPIRATION DATE

Regarding the stability studies, we note that a hold-time for the antioxidant cartridges used in the manufacture of the cassettes has not been adequately established. Based on your submitted stability data, the proposed expiration dating of 12 months for the GēNOsyl (b) (4)® drug product cassette is acceptable. However, the date of expiration needs to be marked based on the date of manufacture of the oldest cartridge used in the cassette assembly, as opposed to the manufacturing date of the cassette.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,” December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

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:
Labeling Comments

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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 11:20:55 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202860

COMPLETE RESPONSE

GeNO LLC
Attention: David Fine, Ph.D.
President
2941 Oxbow Circle
Cocoa, FL 32926

Dear Dr. Fine:

Please refer to your New Drug Application (NDA), originally submitted March 20, 2012, our refuse to file letter dated May 18, 2012, and your resubmission dated August 31, 2012, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for GeNOsyl™ [redacted] (b) (4) (nitric oxide for inhalation).

We acknowledge receipt of your amendments dated May 7, June 14, October 5, 12, 31, November 13, 2012, and January 29, 2013.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Provide data on the quantitative determination o [redacted] (b) (4) from at least three different batches. Use this data to propose a specification to be used for release and stability determination. Provide data to show the cartridge [redacted] (b) (4)

2. The Agency does not accept the quality control method used to determine batch release and used to set cartridge expiration dating based on the current method using [redacted] (b) (4) nitrogen dioxide at a flow rate of [redacted] (b) (4). We recommend providing data on the cartridges (randomly selected from at least three different batches) using the conversion of 800 ppm nitrogen dioxide tested at the flow rates of [redacted] (b) (4) output levels. Present these data in the application and use it to propose a specification for release and stability determination for cartridges. We recommend demonstrating that the specification limits be correlated to performance that ensures that the cartridges meeting release and stability specifications when used under conditions representing projected use at minimum convert the contents of one cylinder of 800 ppm nitrogen dioxide [redacted] (b) (4) to acceptable levels of output for nitric oxide and nitrogen dioxide.

3. Provide data from stability studies at long term and accelerated storage conditions to support the proposed cartridge expiration dating period. These data should be from at least three representative commercial scale batches and the cartridges are to be selected randomly. The stability data are to be based on the stability indicating criteria described above. Provide a proposed post approval commitment to a stability protocol to continue to monitor stability of new batches of cartridges on at least one new batch on an annual basis.

4. We find your proposed studies to demonstrate cartridge capacity (time to cartridge failure) under simulated real conditions (tandem cartridges on the MVG-2000 delivery system) adequate. Provide these data on cartridges representing at least three batches from production. In addition provide data showing this performance for at least one cartridge which is close to the minimum standards for an acceptable cartridge.

5. Provide adequate data demonstrating the effectiveness of the [(b) (4)] filters with the MVG-2000 to prevent microbiological contamination of the breathing air, and to prevent particulates from the cartridges and MVG-2000 system from entering the patient.

6. Include an Identity Parameter in the release specification for 800 ppm nitrogen dioxide [(b) (4)] for the acceptance specification ([(b) (4)]).

7. Remove all references to [(b) (4)] as the "drug substance" from the application. If necessary to refer to it by another designation, [(b) (4)] can be referred to in general as a drug substance intermediate.

8. DMF # [(b) (4)], referenced in this application was found to be deficient; a list of deficiencies was communicated to the holder of DMF# [(b) (4)]. These deficiencies impact the approvability of this application and must be corrected by the DMF holder in the form of an amendment to the DMF.

9. In addition to the data requested in items 1 and 2 above, the following are required. The release specification for the [(b) (4)] cartridge is not adequate. The [(b) (4)] nitrogen dioxide conversion used as the standard method with bridging studies [(b) (4)] method is not acceptable. Release testing should provide a means for assuring the following quality parameters with adequate representative data:

   A. Amount of [(b) (4)] in cartridge; with assay for [(b) (4)] indicated by a stability indicating method

   B. Assurance that no significant amount of [(b) (4)] is lost from the cartridge during the assembly, [(b) (4)]; in other words, demonstrate that the matrix of cartridge is stable throughout variations in the assembly, [(b) (4)] processes of the cartridge

   C. [(b) (4)] of the cartridge

   D. Functional effectiveness of the cartridge in converting 800 ppm nitrogen dioxide [(b) (4)] with a stability indicating method

10. In addition to the data requested in item 3 above, the following are required. Provide a stability protocol and criteria for registration stability of the cartridges and postapproval stability commitments. Provide specifications that use the same method of functional effectiveness of the cartridge in converting 800 ppm nitrogen dioxide [(b) (4)] to nitric oxide. Cartridges should be tested at long term storage and accelerated conditions using storage in commercial packaging. Data from at least three commercial scale batches should be provided to justify the proposed expiration period for the cartridges. Specifications should also include how [(b) (4)] sealing is evaluated at stability timepoints.

The following comments are not requirements for the complete response to this application, but they are recommendations to assist in more efficient review of the application:

11. We encountered difficulty in re-locating pieces of information in your version of organization using the electronic common technical document format. On resubmission, we recommend a re-formatting. Since the drug substance, nitric oxide, (b) (4) we recommend presenting the information in the 3.2.S sections as separate components. (b) (4) The MVG-2000 Delivery system can be described in the 3.2.P section, normally reserved for the drug product. This MVG-2000 Delivery System (b) (4) delivered to the patient.

12. It is important that detailed manufacturing descriptions be provided in each unit. In the 3.2.S sections, the manufacturing description belongs in section 3.2.S.2.2. In the 3.2.P sections, the manufacturing description belongs in section 3.2.P.3.3.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

FACILITY INSPECTIONS

The Agency expects all facilities involved in the manufacture, processing, packing or holding, which includes packaging and labeling operations, testing and quality control, of the drug product to be ready for inspection at the time of application submission.

1. Inspections of the following manufacturing facilities included in this application were attempted. However, inspections could not be completed as these sites were not ready for inspection.

   - (b) (4)
   - GeNO LLC: FEI 3010143995

2. Because of deficiencies related to the manufacture and stability of the (b) (4) cartridges noted in our letter to you dated February 21, 2013, we have deferred the inspection of (b) (4) manufacturing facility during this review cycle.

Note that all new facilities and those that were inspected before and are relisted for the manufacture, processing, packing or holding of the product must be ready for inspection with your re-submission. Satisfactory inspections are required before this application may be approved.

PATENT CERTIFCATIONS

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 20845 for INOmax (nitric oxide) for inhalation, 100 and 800 ppm, but does not contain a patent

certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)). After you submitted your 505(b)(2) application, the NDA holder for INOmax (nitric oxide) for inhalation, 100 and 800 ppm, timely filed information on U.S. Patent No. 8,431,163 ('163 patent) for listing in the Orange Book. In accordance with section 505(b)(2) of the FDCA and 21 CFR 314.50(i), you must submit an appropriate patent certification or statement with respect to the '163 patent.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

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

cc: GeNO LLC
Attention: Ruth E. Stevens, Ph.D., MBA
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

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
06/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202860

REFUSAL TO FILE

GeNO LLC
Attention: Ruth E. Stevens, PhD, MBA
9825 Kenwood Road
Suite 203
Cincinnati, OH 45242

Dear Dr. Stevens:

Please refer to your March 20, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GeNOsyl™ MVG 2000 Delivery System (nitric oxide for inhalation).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

You have designated (b) (4) as the drug substance and formatted your application accordingly. We do not agree with this designation. (b) (4) oes not meet the definition of drug substance in 21 CFR 314.3(b). Moreover, nitric oxide is the established name in the labeling for INOmax, which you cite as the reference listed drug for your 505(b)(2) application.

We also do not agree with your designation of (b) (4) raw material/starting material. Any changes to the manufacturing and/or sourcing of (b) (4) have a high potential of affecting the quality of nitric oxide and eventually the final drug product delivered to the patient. You will need to provide the full chemistry, manufacturing and control information for the manufacture of (b) (4) along with the information about the manufacturing facility and certification that the facility is ready for GMP inspection.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

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

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
05/18/2012