CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-153

COMPLETE RESPONSE

INC Research LLC
U.S. Agent for
Draximage, a division of Draxis Specialty Pharmaceuticals Inc.
Attention: Greg Hockel, Ph.D.
7361 Calhoun Place, Suite 500
Rockville, MD 20855-2765

Dear Dr. Hockel:

Please refer to your New Drug Application (NDA) dated June 18, 2010, received June 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).

We acknowledge receipt of your amendments dated May 18, 20, August 29, December 6, 20, 2011, October 25 2012, January 17, February 14, May 21, August 3, September 19, 23, 2013, March 11, 25, and May 12, 2014.

We have completed our review of this application, as amended, and as stated in our December 12, and December 17, 2014 teleconference with your firm, 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.

CLINICAL

1. The reports of the human factor studies titled: "Ruby Rubidium Elution System Summative Usability Validation Report" and "Ruby Rb-82 Elution System Usability Risk Analysis" are materially incomplete. We request that you provide the following:

    a. study protocols;
    b. data (in the same format as the Hartford site) from subjects at the Brigham and Women's and Cardiac Imaging Associates sites participating in the study;
    c. training or user manual that was the basis of training for the validation report;
    d. mitigation strategies (such as responses to computer input errors) that have been instituted and thereport of any additional study performed to confirm the effect of these strategies.

2. A training/re-training program and training packages need to be finalized prior to marketing. We request that you provide:

a. an initial and on-going training program and a methodology to evaluate its effectiveness;

b. a final version of an Instructions for Use (IFU) document which is structured with a table of contents, index, page numbering and a section on responding to serious patient emergencies involving Ruby-Fill administration. Clarify whether this IFU is intended to also serve as a training manual or if a separate training manual will be provided.

PRODUCT QUALITY

3. The post-approval (b) (4) testing protocol proposed is not sufficient (b) (4) We request that you revise the testing protocol as follows:

   a. (b) (4)

   b. (b) (4)

   c. (b) (4)

4. Regarding the Ruby Elution SystemInstructions for Use (IFU) document:

   a. Clarify the description and sources of the listed supplies, and whether they are supplied by Jubilant DraxImage with the Elution System;

   b. specify the recommended (b) (4) (see page 10, supplies);

   c. describe and label (b) (4) as they are essential to the operation of the Elution System (page A|1– system consumables).

System Description and Requirements Specifications

5. The design implementation is not described technically in the submission. Some of the documents provide insight into the system requirements, such as the user manual, package insert and pharmaceutical development documentation (eCTD Module III – 3.2.P.2). However, it is not clear how these requirements have been implemented into

system specifications and it is not clear that the complete set of requirements has been documented. Please provide the following additional information:

a. Documentation describing system requirements and demonstrating the implementation of the requirements into the design.
b. A process model and a functional diagram depicting the functions of the system.
    i. The process model should describe automated controls, the controlled processes, and human interaction.

    ii. The functional diagram should identify functional components of the system and describe their interactions to achieve the intended use.

c. Identify and describe (b) (4) other disposable components

Hazards Analysis and Safety Requirements

6. We have completed our review of the documentation submitted in support of the Ruby Elution System. During our review we evaluated the documentation to determine if hazards associated with the use of this device are adequately addressed. A document titled "Draximage Rb-82 Version 3 Hazard Analysis", dated May 2011, was provided for review. This document does not provide the detailed analysis of hazards, hazard causes, and safety requirements implemented to assure the safety the Ruby Elution System. To assure the safety of the delivery system, we need to review documentation demonstrating that potential hazards to the patient and user have been reasonably mitigated. We have identified some of the system hazards that need to be addressed, which include:

    a. Unintended radiation exposure (patient and healthcare provider)
    b. Rubidium delivery error (overdose or underdose)
    c. Volume overload
    d. Embolus (air or particulate)
    e. Biological safety (biocompatibility, sterility, infectious agent cross-contamination between patients). It is noted that the final specifications for the delivery system (b) (4) and accessory components have not been submitted and there is no information in the submission to demonstrate that biocompatibility, sterility, shelf life of disposables, and infectious agent cross-contaminations of patients have been adequately addressed.

    Your own analyses may have identified additional system hazards. Please provide a system level hazard analysis (e.g. fault tree analysis) identifying the causes of the system hazards we have identified from our review and any additional system hazards you may have identified. For each identified cause, provide the following:

    a. Describe the control method for each identified cause.

    b. For each cause, provide an explanation justifying the adequacy of the control to mitigate the respective system hazard.

c. Provide evidence verifying the control method adequately addresses the respective cause / hazard.

System Performance and Reliability

7. The system includes three delivery modes: [redacted] Provide the following information regarding these delivery modes:
   a. Identify the requirements and specifications for each delivery mode.
   b. Verify that the design of each delivery mode does not permit the system to exceed dose or volume limits.
   c. Provide evidence verifying and validating the software algorithms used to achieve each delivery mode are correctly implemented into the system.

8. The system contains several functional components necessary to achieve the system's intended use. These include [redacted] Provide data demonstrating that the implementation of these components achieve the specified performance and reliability specifications to assure the safe and effective use of the system.

9. [redacted] The submission does not provide information regarding possible degradation of system components over the 60 day use period. Possible causes of safety and effectiveness degradation include the following:

   a. Exposure to radiological activity.
   b. [redacted]
   c. [redacted]
   d. Microbiological growth.

   Provide data demonstrating that 60 day use of the components will not degrade the safety and effectiveness of the system to an unacceptable level.

10. [redacted] Describe the mechanism implemented [redacted] and present evidence demonstrating their effectiveness. As part of this assessment, consider scenarios [redacted]

11. The manual instructs users [redacted] Provide a risk assessment addressing this potential hazard.

12. The manual states that the system is [redacted] (b) (4) Please provide documentation to support this claim.

13. In addition to being a potential source of embolus, the submission notes that air in the infusion system can result in dose errors. The submission does not clearly address how you have assured that air will not be present within the infusion system, either as a dose error hazard or air embolus hazard. Please provide a risk assessment for these two hazards, identify appropriate controls and provide evidence to support the conclusions.

Software

14. The submission does not include documentation demonstrating that the software has been adequately verified and validated. Provide the following information:

    a. A software description providing a summary overview of the features and software operating environment.

    b. A device hazard analysis identifiying software hazards, including severity assessment and mitigations.

    c. The complete software requirements specification document.

    d. A detailed depiction of functional units and software modules.

    e. A traceability analysis demonstrating traceability among all requirements, specifications, identified hazards and mitigations, and verification and validation testing.

    f. A summary software life cycle development plan, which must include an annotated list of control documents generated during the development process, the configuration management plan and the maintenance plan.

    g. A description of verification and validation activities at the unit, integration, and system level. Unit, integration and system level test protocols must be provided and must include pass/fail criteria, test report, test summary and test results.

    h. The revision history log, including release version number and date.

    i. A list of unresolved anomalies. For each unresolved anomaly, provide the following information:

        i. A description of the anomaly from a symptom point of view and how it is manifested.
        ii. The location in the code where the anomaly occurs.
        iii. A description of how to fix the anomalous code.

iv. A search of the software source code for other possible instances of the anomaly. For example, if the problem was an off-by-one error in an array, provide evidence that all arrays were checked for off-by-one errors.
v. Provide evidence that a coupling analysis was performed to identify all parts of the software that accessed the anomalous code and that no problems would arise because of accessing this anomalous code.
vi. Provide evidence that the anomalies are corrected, or provide an explanation for why the anomaly is not likely to result in harm if it occurs.
vii. Provide a time-frame for resolving any unresolved anomalies determined to be low risk.

j. Provide a static analysis of all software in your system. The information provided should describe the static analysis tools used to evaluate your software, the criteria applied for correcting or not correcting coding errors/warnings, evaluation of the static analysis results, and conclusions.

15. If the system includes off-the-shelf (OTS) software, you should provide the following information:

a. An analysis of hazards associated with the implementation of OTS software in the Ruby Elution System. The OTS software hazards analysis must include:

b. A list of all potential hazards identified.

c. The estimated severity of each identified hazard.

d. A list of all potential causes of each identified hazard.

e. The steps taken to mitigate each hazard.

f. Evidence that the product development methodologies used by the OTS Software developer are appropriate and sufficient for the intended use of the OTS Software within the Ruby Elution System. This should include an audit of the OTS Software developer's design and development methodologies used in the construction of the OTS Software. This audit should thoroughly assess the development and qualification documentation generated for the OTS Software.

g. Evidence that the procedures and results of the verification and validation activities performed for the OTS Software are appropriate and sufficient for the safety and effectiveness requirements of the Ruby Elution System. Verification and validation activities include not only those performed by the OTS Software developer, but also include those performed by the Jubilant Draximage when qualifying the OTS Software for its use in the Ruby Elution System.

h. Demonstrate the existence of appropriate mechanisms for assuring the continued maintenance and support of the OTS Software should the original OTS Software developer terminate their support.

Electrical Safety and Electromagnetic Compatibility

16. Provide information demonstrating compliance with relevant electrical safety and electromagnetic compatibility requirements of IEC 60601-1 (1988): Medical electrical equipment – Part 1: General requirements for safety, including Amendment 1 (1991) and Amendment 2 (1995) for Type B equipment and IEC 60601-1 Collateral Standard: Safety requirements for medical electrical systems and IEC 60601-1-2 (2001): Medical Electrical Equipment, Part 1: General Requirements for Safety, 2. Collateral Standard: Electromagnetic Compatibility - Requirements and Tests.

Biocompatibility and Infection Control

17. All drug path devices are required to be sterile. The submission does not contain any data demonstrating assurance and maintenance of sterility for the disposable components of the Ruby Elution System. Provide the following information:
    a. A copy of the package labeling for each disposable component indicating the contents are sterile.
    b. Description of the sterilization method.
    c. If using radiation sterilization methods, identify the dose.
    d. If using ethylene oxide gas sterilization, identify the acceptable limits for sterilant residuals remaining on the device.
    e. A description of the Validation Method for the sterilization cycle.
    f. Sterility assurance level (SAL).
    g. Provide pyrogen testing and acceptable endpoints.
    h. A description of the [redacted] (b) (4) packaging.
    i. Provide documentation supporting the shelf life of the disposable components.

18. Identify the finished products that comprise the drug pathway and provide data demonstrating the biocompatibility of these products. Included in this, you should provide a chemical and particulate characterization on the final, finished, fluid contacting drug pathway components demonstrating that risk of harm from device-related residues is reasonably low. All testing should be conducted on finished, sterile product. For the assessment, we recommend the following:

    a. For device-related chemical residual characterization, the Agency recommends performing a leachables and extractables (L&E) study.

    b. For device-related particulate evaluation, you should follow current USP <788> Particulate Matter in Injections. FDA considers USP <788> to be limited to evaluation of micron particles.

    c. Device-related residual characterization alone may not provide appropriate information for risk of harm from device-related residues. The Agency recommends a comprehensive risk assessment of the device-related residuals

based on route of exposure, toxicokinetics and toxicodynamics, and allowable limits in the intended population proposed for the new device.

19. We are concerned about the risk of disease transmission occurring from cross-contamination in devices (b) (4) such as yours. The information in your submission does not provide adequate assurance that the risk of cross-contamination has been adequately mitigated by the design of your system and that the risk outweighed by the benefit (b) (4) Provide the following information:

    a. Demonstrate that the risk of cross-contamination has been adequately mitigated, which should include suitable challenge testing to support your conclusions.

    b. Provide information supporting the conclusion that cross-contamination risks are outweighed by the benefit (b) (4)

PRESCRIBING INFORMATION

Complete labeling revisions will be provided at the time of an Approval action. However, at the time we have the following suggested revision:
Section 2.5 Elution testing protocol and Boxed Warning: Repeat testing for Strontium breakthrough after every 4 patients may lead to variability since elution volumes may differ with individual patients. Provide an elution volume in mL between which repeat testing for Strontium breakthrough should take place.

20. 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. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

    - The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
    - 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 42 important format items from labeling regulations and guidances.

    Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the 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.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

21. Please refer to correspondence dated, DATE which addresses the proposed proprietary name, PROPRIETARY NAME. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
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/

LIBERO L MARZELLA
12/18/2014