

Filing Review Letter - Spherusol

Our STN: BL 125354/0

Allermed Laboratories, Inc.
Attention: H.S. Nielsen, Jr., Ph.D.
7203 Convoy Court
San Diego, CA 92111

Dear Dr. Nielsen:

Please refer to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, and to our filing letter dated July 15, 2009. While conducting our filing review we identified the following potential review issues:

The following items pertain to the manufacture of *Coccidioidin immitis* SD skin test antigen:

1. Please provide a description of the overall process for the filling, capping and aseptic assembly of the drug product.
2. Please provide a description of the washing, sterilization and depyrogenation process and the associated validation data for containers, closures and equipment.
3. Please provide the procedures, specifications and data for aseptic processing and media fills, both sterile bulk and final fill.
4. Please provide a description of the method and results demonstrating container closure integrity.
5. Please provide a summary of process validation studies, including the protocol and test results of each critical process or factor that affects the drug product.
6. Please provide a description of container/closure compatibility with the drug product to include the results of compatibility studies.
7. Please provide a description of the cross contamination issues, to include the cleaning procedures and validation data for product contact equipment. Clarify whether the product contact equipment is shared or dedicated.
8. Please provide a description of the containment features, including a description of the segregation and containment procedures for each processing area, and a description of the manufacturing operations, personnel, equipment and waste materials designed to prevent contamination of the product.

You may refer to the following guidance documents pertaining to the above items: "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products," and "Guidance for Industry on the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test.

The following items pertain to the tests designed to characterize the *Coccidioidin SD* skin test antigen:

9. In the validation report for the Coccidioidin SD identity test, -(b)(4)- antigens were used as negative controls. However, in the SOP for the identity test, only -(b)(4)- antigens (------(b)(4)-----) are listed. Please comment on this difference and describe the source of the ------(b)(4)----- antigens.
10. In the inter-assay studies of the identity test, the -(b)(4)- readings, Coccidioidin SD Lot ------(b)(4)-----, reported for technicians 2 and 3, are significantly different on days 1, 2 and 3. Please comment on the impact this significant variability in -(b)(4)- readings may have on the performance of the identity test.
11. Please describe how the 95% confidence interval for the potency test was determined, and submit data to the BLA supporting this confidence interval calculation.
12. For the relative potency studies, please clarify why the acceptance criteria within a lot is defined as ------(b)(4)-----.
13. For the relative potency validation studies, please discuss why the acceptance criteria for the slope calculations on page 8, and linearity calculations on page 10, was selected to be between ----(b)(4)---.
14. Please identify the testing lab for the guinea pig potency and general safety tests and indicate whether this lab has earned AAALAC accreditation.

The following item pertains to statistical design:

15. In your study report for S104-1 titled "Skin Test Sensitivity of 1.27 µg per 0.1 mL Spherule-Derived Coccidioidin in Adult volunteers with a History of Pulmonary Coccidioidomycosis," on page 6 of 37 of the Synopsis, Statistical Methods section, you state: "The trial was designed to show that the population sensitivity to Coccidioidin SD is greater than 80%, i.e. the null and alternative hypotheses were: H0: Sensitivity ≥ 0.80 vs. HA: Sensitivity < 0.80." Similarly, in your study report for S104-2, you state: "The trial was designed to show that the population specificity to Coccidioidin SD is at least 85%, i.e. the null and alternative hypotheses were: H0: Specificity ≥ 0.85 vs. HA: Specificity < 0.85." Conventionally, a study goal is stated in the alternative hypothesis and the data collected are used to support the conclusion of rejecting the null hypothesis. Your statements seem to contradict your goals. Please clarify.

The following item pertains to post-marketing surveillance:

16. Please submit a detailed pharmacovigilance plan in accordance with the E2E Pharmacovigilance Planning (PVP) guidance available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm129411.htm>. Please note that when a new product is marketed, the exposed population may differ from the population studied in pre-approval trials. For example, the exposed subjects in pre-approval trials for Coccidioidin SD (Skin Test) are limited in number and may not include the variety of types of patients who will likely be exposed to the product after licensure. Pharmacovigilance plans are designed by a product's sponsor to identify and describe potential new serious safety risks and/or evaluate already

identified safety risks, to identify and describe important missing information or inadequately studied at-risk populations, and should include routine pharmacovigilance (i.e., compliance with applicable postmarket reporting requirements under FDA regulations) and possibly additional post-market safety monitoring activities. Please note that the ICH E2E PVP guidance indicates that for products with important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered as part of a pharmacovigilance plan.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Dr. Jon Daugherty, at (301) 827-3070.

Sincerely yours,

Wellington Sun, M.D.
Director
Division of Vaccines and
Related Products Applications
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