



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:

This letter is in regard to your biologics license application (BLA) for *Coccidioides immitis* Spherule –Derived skin Test Antigen, Spherusol, manufactured at Allermed at your San Diego, CA, location and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

CLINICAL

We have the following general comments:

1. In letters for IND -(b)(4)-, dated June 21, and November 18, 2004, we requested that you specify the proposed clinical indication that would be supported by the studies which you have now completed. You have proposed that the product, Spherusol, should be used for "the detection of delayed type hypersensitivity following exposure to *C. immitis*", but you have not provided any description of how this information will be used in a clinical setting. Without this description, we are unable to assess the risks and/or benefits of the use of this product. If this information is not available or is not sufficient to support a labeled indication for this product, further discussion and clinical studies may be necessary. Please provide in your response the proposed clinical use of the candidate product and data to support this clinical use. Of particular interest will be your explanation of how the "detection of delayed type hypersensitivity to *C. immitis*" will inform the clinical management of patients tested using your product.
2. In each of the studies presented in the application, please indicate the dose administered of each of the skin test antigens, Candin, Trichophyton, and the negative controls (-(b)(4)-- saline and thimerosal diluent).
3. Please indicate the time period during which the adverse events occurred and were reported for each study. In the summary tables of adverse events, please describe the time point at which assessments of events were made.

4. For the safety data collected from each study in support of your application, please provide the timing of the adverse events, which skin antigen elicited the local adverse reaction(s), when the adverse event occurred in relationship to the placement of the skin test antigen, when the adverse event resolved and any interventions (e.g., medication) given as a treatment of the adverse event.

Some of the comments under specific studies may pertain to more than one study.

The following comments pertain to the study entitled “A Dose-Response Study of --(b)(4)--- Skin Test Antigen” (Protocol S101A, Bakersfield, CA):

5. Please provide a summary of adverse events and safety outcomes for the subjects enrolled in the clinical study. We request that safety data that was obtained prior to vaccination (e.g. vital signs), immediately following intra-dermal placement and 48 hours after placement be submitted to the file. Please present the data as solicited local and systemic adverse events and unsolicited adverse events. Please provide summaries of all adverse events which were followed after the 48 hour visit. Please provide a copy of the subject diary card that was used by subjects to record adverse events.
6. Please provide a summary table of demographic information of the enrolled population to include age, race/ethnicity and gender.
7. Please provide summary tables for subjects enrolled, withdrawn and analyzed in the clinical study.
8. Please indicate if any of the enrolled subjects had previously received a coccidioidin-containing skin test, the timing in relationship to the study testing and results from previous tests. If available, for subjects with a previous positive skin test, please provide the measurement of the delayed-type hypersensitivity (DTH) reaction.
9. No key is provided for un-blinding the data presented in the study report. Please provide a key to allow for the assessment of skin test results for each subject as documented in the “Manual Skin Test Measurements.” (No pagination was provided in the document for this study.)
10. Please provide a summary table of the products used in the study S101A to include the lot number of product, active and inactive ingredients and excipients.
11. The placebo control appears to be the diluent used to prepare the 2.4 mcg/0.1 mL dose of --(b)(4)--- (section III, Study Drug). Please provide the concentration of thimerosal that was used in the diluent to prepare the other doses of --(b)(4)--- and the total concentration of thimerosal in each dose of --(b)(4)--- given to study participants.

The following comments pertain to the study entitled “Skin Test Sensitivity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers with a History of Pulmonary Coccidioidomycosis” (Protocol S104-1, Bakersfield, CA and Tucson, AZ):

12. Please submit documentation which confirms by serologic, radiographic, histologic or mycologic findings that enrolled subjects have a history of pulmonary coccidioidomycosis of at least 45 days duration. Please include the date of initial diagnosis, results of testing used to make the diagnosis, treatment(s) received and date of remission of disease
13. In the table labeled “DTH Response to Positive Controls and to Coccidioides immitis Spherule-Derived Skin Test Antigen” (page 18/37) please indicate how many subjects were evaluated to give the ranges and means of the reactions presented.
14. Please define the “combination of test outcomes” section 4.15, page 13/20 S104-1, which would make a skin test invalid and excluded from analysis.
15. Please provide a summary table of the solicited local and systemic reactions following administration of Spherusol, Candin and/or Trichophyton. The data as currently presented in the “Summary of Adverse Events” page 20/37 and in Table 12.1.2 does not provide identification of the product producing the local reactions and is therefore unevaluable. Please include the total number of subjects evaluated and the percentage of subjects with each local adverse event in the revised tables.
16. Please provide a narrative for all “severe” reactions, defined as needing medical attention, to include identification of test agent producing the severe reaction, any medical intervention which occurred and the duration of the adverse event.
17. We note that two subjects who demonstrated invalid responses to the negative controls, Subject -(b)(6)- with a positive reaction to both the saline placebo and thimerosal and subject -(b)(6)- with a positive reaction to saline placebo, were excluded from Tables 12.3.1, 12.3.2, and 12.3.3. Please revise the referenced tables to include information for these subjects.
18. We note that Table 12.3.1, states that data for 27 subjects (N=27) are included in the table. We find that data are presented on only 25 subjects. Please clarify this apparent discrepancy.

The following comments pertain to the study entitled “Skin Test Specificity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers Without a History of Pulmonary Coccidioidomycosis” (Protocol S104-2, Spokane, WA):

19. Please provide a summary table of the solicited local and systemic reactions following administration of Spherusol, Candin and/or Trichophyton and the time point at which the adverse events occurred. The data as currently presented in the “Summary of Adverse Events” page 17/31 does not provide identification of the product producing the local reactions, or the timing of the adverse events and as such is unevaluable. Please include the total number of subjects evaluated and the percentage of subjects with each local adverse event in the revised tables.
20. Please provide a narrative for the two severe local adverse reactions that were noted during the study. Please indicate what antigen site(s) were responsible for these reactions, what treatment was given and the time to resolution of the event with any subsequent sequelae.
21. We note that the study protocol included safety monitoring for one week after the 48 hour visit. We find no safety data in the submission for this time period. Please submit to the file a summary of the safety data collected after the 48 hour visit.

LABELING

22. Please revise the submitted package insert (PI) [section I] to provide the proposed dosing regimen for the product, the age group indicated to receive the product, information on drug-drug interactions, and information of use in special populations in the appropriate sections. We reserve further comment on the proposed labeling until the application is otherwise acceptable. We may have additional comments when we see the proposed final labeling.

CHEMISTRY, MANUFACTURING AND CONTROL

23. Please describe the source of the killed *C. immitis* for the guinea pig sensitization procedure (SOP 910-101) and describe how the spherules are killed.
24. -----(b)(4)-----

25. In the validation of accuracy of the relative potency test method, please discuss why an acceptable result for percent recovery was -----(b)(4)-----.
26. Please discuss the actions that will be taken if a decline in the potency of the ---(b)(4)--- is detected.

27. SOP 910-104 (Coccidioidin Internal Reference Standard Relative Potency Test method) states that an investigation will be triggered -----(b)(4)-----

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28. As we discussed during our August 27, 2008, pre-BLA meeting with you, based upon the data provided at the time, an expiration dating period of at least three years when stored at 2-8°C is being considered. However, we note that the most recent clinical lot of Spherusol was manufactured in 2007. Since the current lot is already three years old, please discuss your plans for manufacturing a new lot of Spherusol for eventual distribution.
29. On page 2, you indicate that testing for bioburden and excipients is done -----(b)(4)-----
-----, while Figure 1, page 3, indicates that this in-process testing is done
----- (b)(4) ----- . Please clarify the stage of manufacture when these tests are performed.
30. SOP 969-000 (NaCl assay) states that the error percent for each sample is ----(b)(4)----
NaCl. Since the product specification is -----(b)(4)----, please comment on the ability of this assay to accurately determine NaCl concentrations in the product.
31. Please provide the concentrations of the negative fungal controls (----- (b)(4) -----
-----) used in the validation of identity testing for Spherusol.
32. Please provide data supporting the stability of the -----(b)(4)----- used in the identity test under the storage conditions chosen.
33. Please provide data using more than one lot of Spherusol for the validation of the specificity of the Identity Test.
34. It is unclear from your response dated October 15, 2009 whether a process validation protocol was executed for critical manufacturing steps. Please note the objective of process validation is to ensure that the manufacturing process will consistently yield product with specific quality attributes. Further, a process validation protocol is a prospectively written plan pre-approved by the quality unit that specifies critical steps, controls, and measurements. The process validation protocol states how validation will be conducted, identifying sampling, assays, specific acceptance criteria, production equipment, and operating ranges. Results obtained for each study described in the protocol should be evaluated in an associated process validation report. Please comment.
35. It appears from your response dated October 15, 2009 that the media fill procedure does not include the -----(b)(4)----- . Please provide validation data to support the -----(b)(4)-----
-----.

36. Please provide data demonstrating that you have achieved adequate -----(b)(4)-----
-----.
37. There is no description of the container closure system used in Validation 1036 “Validation Report for Holding Time of -(b)(4)- Allergenic Extract Bulks” dated June 21, 1999. Please describe how you determined that this study adequately represents the container closure system used for the Coccidioidin bulk drug substance.
38. Please provide method validation for the -----(b)(4)----- Test used to test container closure integrity.
39. The regulation cited under Section 4, Environmental Assessment for your Categorical Exclusion made in pursuant to 21 CFR 25.31(f), is not appropriate. Please submit a corrected citation.

STATISTICS

The following comments pertain to the study entitled “A Dose-Response Study of --(b)(4)--- Skin Test Antigen” (Protocol S101A, Bakersfield, CA):

40. In this study, you have collected induration response data from 20 subjects, each of whom received 5 different dose concentrations. After eliminating the placebo dose, the highest dose due to incomplete data, and one subject for no data, you plotted the mean induration response of 19 subjects for each of the 3 doses against the dose concentration. In section VII, Data Analysis, you state: “The dose-response curve was analyzed by linear regression and it was determined that a dose of 1.27 μg corresponded to a mean response of 22 mm.” We have the following comments:
 - a. Please provide a rationale for using the mean induration response as the dependent variable. Note that by taking the mean, you have arbitrarily reduced the variation within each dose.
 - b. Please provide a rationale or justification illustrating how you determined that the relationship between induration response and dose is linear.
41. In section VII, Data Analysis, you state: “Based on our experience with other skin test antigens, we believe that a 20% variance in the induration response associated with cellular hypersensitivity is indicative of equipotency.”

In the same section, you obtained an acceptable range of 17.6 to 26.4 mm by subtracting and adding 4.4 mm (20% of 22 mm) to 22 mm which was considered the corresponding mean response for the dose concentration 1.27 μg from the linear regression. Then using the same data and the SAS MIXED procedure, you fit a mixed linear model. In the same section, you state: “From the ... model, the estimated mean induration for a 1.27 concentration is 22.24mm and the associated 95% confidence interval computed through the MIXED procedure is between 19.383 and 25.091 mm.

The 95% confidence limits fall well within the acceptable range of 17.6 and 26.4.” We have the following comments:

- a. Please provide documentation to support your statement that 20% variance in induration response associated with cellular hypersensitivity is indicative of equipotency for this product.
 - b. You use the same data to determine an acceptable range and to fit the mixed linear model. Please provide data from independent sources to support your claim that the mean induration response corresponding to a dose concentration of 1.27 µg is about 22 mm. Please also provide independent sources to support your proposed acceptable range. For example, these independent sources may be either historical data or information in the published literature.
42. This study was conducted under IND -(b)(4)-. When you submitted the original submission to the IND (received by CBER on December 12, 2001), you included a document titled “Statistical Protocol for Skin-Test --(b)(4)--- Dose/Response Study” as part of the study protocol. In this document, a detailed analysis plan was provided. We have determined that you did not follow the steps outlined in that document and you did not submit the document to the current BLA. We request that you re-analyze your data following the steps outlined in the statistical protocol and submit the results as well as the statistical protocol to the BLA. Furthermore, we consider the following four subjects should not be included in the analysis:
- Subject ID -(b)(6)-: Due to results that could not be determined.
 - Subjects ID --(b)(6)--: These two subjects responded to the placebo, thimerosal, which makes other results uninterpretable since the reactions might be due to the thimerosal in the placebo.
 - Subject -(b)(6)-: Due to the subject having a non-linear response with increasing dose, which does not satisfy the criterion for inclusion in the analysis.
43. In the afore-mentioned statistical protocol, you state: “The mean induration response from the -----(b)(4)----- data was -(b)(4)-.” Please submit the --(b)(4)- ---- data to the BLA to enable our independent verification of this result.

The following comments pertain to the study entitled “Skin Test Sensitivity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers with a History of Pulmonary Coccidioidomycosis” (Protocol S104-1, Bakersfield, CA and Tucson, AZ):

44. In the section of Efficacy Results of the Synopsis (page 7 of 37), you state: “A total of 50 subjects out of 51 valid subjects were skin test positive to Spherusol.” However, in section 10.4.1, Analysis of Efficacy, you provided a table that indicates 52 out of 53 subjects responded to Spherusol. Please revise your report to make your results consistent or explain explicitly why the number of subjects varies.

45. In section 10.4.2 Statistical/Analytical Issues, you indicated that 25 subjects were treated with antifungal medication and 26 were not treated. However, in the dataset, untreated.xpt, only 22 subjects were found. Please submit the complete dataset for the untreated subjects to the BLA or provide a rationale for these missing data.

The following comment pertains to the protocol entitled “Skin Test Specificity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers Without a History of Pulmonary Coccidioidomycosis” (Protocol S104-2, Spokane, WA)

46. In section 10.4.1, Analysis of Efficacy, (page 15 of 31), you state: “Negative DTH skin tests to Spherusol in 58 of 59 study subjects ...” However, in this study report, no statistical testing results are included or reported. Please revise this section so that the statistical hypotheses, summary of the data, the results of the data analysis, and the conclusions obtained from the results are included.

The following comments pertain to the study entitled “Skin Test Specificity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers With a History of Pulmonary Histoplasmosis” (Protocol S104-3 Blair, NE):

47. In the section of Statistical Methods in the Synopsis (Page 6 of 21), you reported “Observed Specificity” as 100%. Then in section 10.4.1, Analysis of Efficacy, you reported “Observed Sensitivity” as 1.000. Since this study was exploratory in nature, the terminologies “sensitivity” or “specificity” are not applicable. Please revise your report to include your findings in the form of proportions and corresponding 95% confidence intervals of subjects who had induration response ≥ 5 mm for each of the 5 skin test reagents.

PHARMACOVIGILANCE PLAN

In our review of the proposed pharmacovigilance plan there was limited information regarding the proposed active surveillance activity. We have the following specific items:

48. Please state the objectives of the proposed active surveillance.
49. Please describe your methods for the selection of individuals and sites for the proposed surveillance activity.
50. Please describe how the participant size of 300 patients was chosen.
51. Please describe the method for collecting the surveillance data, and address how Allermed will quantify the number of skin tests administered at each participating site.

52. Please revise the reporting form to include:
 - a. the age of the participating individual,
 - b. the gender of the participating individual,
 - c. a place to enter adverse event (AE) data,
 - d. a place to enter information about the individual who may have active coccidioidomycosis, and
 - e. a place to enter a history of *Coccidioides immitis* or “Valley Fever,” and if so, how it was diagnosed. (See question 7 on the reporting form.)
53. Please describe in detail what criteria you will use to detect and confirm sensitivity to *Coccidioides immitis*. (See question 5 on the reporting form.)
54. Please describe how the product will be distributed to the participating sites.
55. Please estimate the extent of use of the product after approval.
56. Please submit a proposed schedule for conducting each study that includes all major milestones for the study such as:
 - a. submission of finalized protocol
 - b. completion of patient accrual,
 - c. completion of the study, and
 - d. submission of the final study report,
 - e. submission of the SAS datasets, and submission of the applicable revised labeling.

Please submit complete protocols for review and comment to your IND. You may cross-reference them in your response to this letter.

In future submissions, please provide continuous pagination for all documents to facilitate reference and review. Additionally, please title and number all data tables.

The proposed proprietary name, Spherosol, has been reviewed and found to be tentatively acceptable. Final acceptability of the name will be determined within 90 days of product approval, when the application is otherwise found acceptable.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Holly Wieland at (301) 827-3070.

Sincerely yours,

Wellington Sun, M.D.
Director
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