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Our STN: BL 125354

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

Dear Dr. Nielsen:

We have received your June 8, 2010, amendment to your biologics license application submitted under section 351 of the Public Health Service Act for *Coccidioides Immitis* Spherule-Derived Skin Test Antigen (Spherusol).

We have determined that your amendment does not completely respond to our March 26, 2010, Complete Response letter. We stopped the review clock when we issued our Complete Response letter. Because your responding amendment is incomplete, we will not restart the clock until you address all the following deficiencies:

CLINICAL

1. Your responses to our questions relating to the safety of the investigational product are not sufficient to communicate the risks associated with use of Spherusol. Since you have indicated that antigen specific safety data were not collected for local adverse events associated with the intradermal placement of Spherusol and the control antigens, we request that you provide data which will allow us to quantify the rates of systemic and local reactions following intradermal inoculations of the antigens.

For each study please provide the following information:

- a. A summary table that provides identification of the solicited local and systemic adverse events by study;
- b. A summary table of the frequency of local adverse reactions within a study group (n, %);
- c. A summary table of the frequency of systemic reactions within a study group (n, %);

- d. A summary table comparing the rate of local adverse reactions for Spherusol relative to reactions seen following administration of the control antigens for each study group and,
- e. A summary of the range of values for induration following administration of Spherusol (maximum, minimum, and mean) indicating what proportion of subjects demonstrated induration which was ≥ 5 mm but less than 10 mm, ≥ 10 mm but less than 20 mm and reactions ≥ 20 mm.

Also, please revise the package insert to include a clear and concise presentation of these data.

- 2. With this submission, you have modified the clinical indication for Spherusol to read as follows:

“Spherusol is indicated for use as a skin test antigen to detect cellular hypersensitivity to *C.immitis*. A positive delayed-type skin test to Spherusol can be indicative of past or present infection with *C.immitis*.”

We note that detection of delayed type hypersensitivity during a “present” or active/current infection was not previously evaluated in studies conducted under the IND, and you did not address detection during active/current infection in the original BLA submission. You have provided Case Report Forms for seven subjects that are described as having a current infection with *C. immitis* to support the use of Spherusol as an agent to detect cellular hypersensitivity to *C. immitis* in active disease. However, the diagnostic criteria for active coccidioidal disease were not pre-specified in the IND studies. It appears that diagnostic criteria for active disease were set in a post hoc determination by study investigators. According to these criteria, subjects receiving anti-fungal therapy would be classified as having active disease regardless of symptoms. The post-hoc definitions for remission and active disease are reproduced from the submission below:

- a. For subjects on antifungal therapy, remission was considered to have occurred at the time therapy was stopped.
- b. For subjects not on antifungal therapy, remission was considered to have occurred when significant clinical improvement was observed, or when the subject was referred back to his/her primary care physician, or when follow-up was no longer required by the specialist.

No information was submitted to indicate the pre-specified parameters for the initiation or duration of antifungal therapy for subjects. The criteria provided above are not based on objective findings which were pre-determined prior to the conduct of the studies.

Additionally, treatment with anti-fungals as a marker of active disease may be misleading since drug treatment may be prolonged (usually for 3-6 months) and patients are often followed for resolution of radiographic findings and decrease in titers for up to a year.

We also note that the inclusion criteria for subjects in study S104-1 required a history of pulmonary coccidioidomycosis of at least 45 days duration confirmed by serologic, histologic or mycologic findings. Subjects with active medical disease, such as cavitary pulmonary disease or disseminated disease, were to be excluded from study participation.

We do not concur with the revised indication for Spherusol (page 9/66) as it is dependent upon a post hoc evaluation of the data. The submitted clinical studies do not support the use of Spherusol for diagnosis of active disease. An additional study or studies with a pre-specified case definition of disease would be necessary to allow consideration for the use of the product as a diagnostic in the evaluation of active disease.

The indication and limitations of use for Spherusol must reflect how the product was studied under IND. We suggest the following language might be considered for the indication of Spherusol:

“Spherusol is indicated for use as a skin test antigen for the detection of delayed type (IV) cell-mediated hypersensitivity following pulmonary infection with *C. immitis*.

“Spherusol should not be used to diagnose active disease or disseminated disease caused by *C. immitis* because it has not been studied for use in diagnosing those conditions”

In order for us to complete our review of your application, you will need to provide the information requested in this letter and a revised package insert reflecting the information requests as an amendment to the Biologics License Application. We refer you to 21 CFR 201 for the requirements on the format and content of biologics labeling.

CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

3. Regarding your response to item 35 of our Complete Response letter, you have not provided the requested information. Please note -----(b)(4)-----
----- Please supply validation data to support -----(b)(4)-----
----- If -----(b)(4)----- is
unavailable please explain how -----(b)(4)----- was validated to ensure its capacity
for excluding contamination for the longest hold period encountered during routine
production.
4. Regarding your response to item 36 of our Complete Response letter, the data provided did not address -----(b)(4)----- Please provide data demonstrating that you have
achieved -----(b)(4)-----.

STATISTICS

5. In your responses to items 40, 41 and 42 of our March 26, 2010, Complete Response letter to you, you requested that the protocol entitled “Statistical Protocol for Skin-test
--(b)(4)--- Dose/Response Study” dated September 28, 2001, be withdrawn from

consideration during CBER review of your coccidioidan skin test BLA, STN 125354. Furthermore, you requested that a new study report prepared by -----(b)(4)-----, entitled “Statistical Evaluation of Dose-Response Study of Spherosol-Derived Coccidioidin Skin Test Antigen (Study Protocol S101A, amended on June 19, 2002)” be considered in place of the September 28, 2001, protocol. In your BLA submission, neither document was provided. The original statistical protocol dated September 28, 2001, was provided in the original submission of BB-IND -(b)(4)-. If there is a need to change the analysis plan, concurrence by CBER is required well before the study completion. Furthermore, revisions to the protocol after study inception typically should be minor or administrative in nature. Revisions in data collection or analysis may impact sample size requirements and type I error rates. Please provide a detailed timeline as to when ----(b)(4)---- started his employment and when the analysis protocol was revised. If ----(b)(4)---- was employed after the study was completed, his analysis would be considered to be post-hoc. Please note that usually this type of analysis for pivotal trials would not be permitted to support licensure.

Please submit a revised report for this study to include:

- a. Time line of the statistical protocol development and ---(b)(4)--- employment;
- b. Rationale for changing the method used in analyzing the data;
- c. ---(b)(4)--- analysis in detail; and
- d. References for supporting the new method.

CBER will review the revised report in order to determine whether the result from the new analysis is acceptable to replace the old report.

6. In your response to our item 43 of our March 26, 2010, Complete Response letter, you stated that the requested data are not available. However, the value -(b)(4)- was used as the standard for establishing the final dose. Please provide any information, such as reports, articles, or other reference material (in its entirety) that can substantiate this claim.

PHARMACOVIGILANCE PLAN (PVP)

7. In your response to item number 49 of our March 26, 2010, Complete Response letter, you note that you intend to select sites for the survey that are located within endemic areas for coccidioidomycosis, depending on the number of cases seen at the site annually. Please provide additional details; specifically, provide the number of sites that will be chosen and the number of annual cases at a site that would be required for a site to participate.
8. Regarding your response to item number 53 in our March 26, 2010, Complete Response letter, we asked that you describe in detail what criteria you will use to detect and confirm sensitivity to *Coccidioides immitis*.

However, your response was unclear and did not appear to answer our question. Please provide the requested information for review by CBER.

When submitting revised information e.g., labeling changes, to your BLA, we request that you provide a paginated copy containing tracked changes in order to facilitate CBER's review of the revised documents.

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

Sincerely yours,

Wellington Sun, M.D.
Director
Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research