

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS

Date: February 11, 2011

Coccidioides immitis Spherule-Derived Skin Test Antigen, Spherusol

CBER Reference Tracking #: CRMTS#7778; IND -(b)(4)-; BLA STN 125354

Sponsor Contact: H.S. Nielsen, Jr., Ph.D.

Company Name: Allermed laboratories, Inc.

Address: 7203 Convoy Court
San Diego, CA 92111

Telephone: 858-292-1060

Fax: 858-292-5934

From: Yolanda Stewart
Woodmont Office Center I
1401 Rockville Pike
HFM-475 Suite 370 North
Rockville, MD 20852-1448
1-301-827-3070 voice
1-301-827-3075 fax

Subject: FDA/Applicant Final Meeting Summary

Dear Dr. Nielsen:

Attached is a copy of the memorandum summarizing your January 12, 2011, teleconference meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the outcome differs from those expressed in this meeting summary, it is your responsibility to bring these discrepancies to CBER's attention for resolution. If you have any questions, please contact Dr. Jon Daugherty at (301) 827-3070.

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Coccidioides immitis Spherule-Derived Skin Test Antigen,
Spherusol

Sponsor:

Allermed Laboratories, Inc.
7203 Convoy Court
San Diego, CA 92111

Meeting Type: Type B

FDA Attendees: Dennis Cato, Siobhan Cowley, Jon Daugherty, Marion Gruber, Anthony Hawkins, Dana Jones, Jingyee Kou, Tammy Massie, Sheldon Morris, Alexis Mosquera, Douglas Pratt, Paul Richman, Ann Schwartz, Jay Slater, Wellington Sun, Holly Wieland, and Craig Zinderman.

Sponsor Attendees: Neil Ampel, Masoud Ansari, Robert Bottomy, Michael Durschlag, Royce Johnson, H.S Nielsen, Jr., Sonja Pasquariello and ----(b)(4)----.

Sponsor Meeting Objectives:

The purpose of the Type B meeting is to discuss outstanding issues of STN 125354/0 that must be resolved before Spherusol is approved as a U.S. licensed product.

The following comments were sent to the applicant on January 11, 2011 via facsimile. A meeting was held at 11:00 A.M. ET on January 12, 2011 via teleconference. Changes resulting from the discussion during that meeting consisted of CBER's interpretation of the applicant's responses to CBER's questions contained within item number 4, below, and are presented in bolded italics under the relevant question.

Sponsor Questions by Discipline:

CBER responses are in italics.

1. FDA has expressed concerns about the clinical use of Spherusol and the risks associated with the use of the product. Allermed believes that it will be useful for representatives of CBER to discuss these concerns with the physicians who will participate in the teleconference on behalf of Allermed (please see #9 below).

We acknowledge that you will include clinical experts on coccidioidomycosis as participants in the scheduled teleconference with you to discuss potential clinical use of your skin test product. We consider the issue of a clinical use of your skin test antigen to be the primary purpose of the scheduled meeting with you. In this regard, please see our response to item number 4, below.

2. A revised product circular for Spherusol was submitted with amendment 006. Please comment on the status of Allermed labeling for Spherusol.

We are currently reviewing your proposed product labeling and will provide comments on it after our review is complete.

3. A revised pharmacovigilance plan for Spherusol was submitted with amendment 006. Is this plan acceptable as submitted?

We are currently reviewing your proposed pharmacovigilance plan and will provide comments on it after our review is complete.

4. Allermed has replied to all of the issues and concerns of FDA regarding Spherusol. Does the FDA have any outstanding issues or concerns that must be addressed before Spherusol can be approved as a U.S. licensed biological product?

*We acknowledge receipt of the pre-read materials for the Type B meeting regarding the further clinical development and licensure of Spherusol. Although limited data have been provided on the specific local reactions following use of Spherusol, at this time we do not have major concerns regarding serious safety outcomes for the investigational product in the populations in which it was studied [healthy individuals with and without a known history of pulmonary coccidioidomycosis]. We do not currently have results from studies which show the use of the product to treat, mitigate, prevent or diagnosis the disease or condition associated with *C. immitis* infection. From the studies performed under IND and submitted in the BLA, a positive delayed type hypersensitivity reaction following placement of the skin test antigen is indicative of past pulmonary infection with *C. immitis*. It remains unclear to us how the skin test would be used to inform decisions about therapies. We agree with you (Clinical use of Spherusol, Page 6 of your meeting submission) that the investigational product has not*

been studied as a diagnostic or prognostic indicator.

In preparation for discussions during the meeting, we have the following questions for consideration by you and Drs. ---(b)(4)---, Royce Johnson and Neil Ampel regarding the use of the study product Spherusol in a clinical setting:

- In what population would the skin test be used?

The applicant stated that the skin test could be used in a variety of populations, including primary care, individuals presenting with respiratory illness and pregnant women. It could be used for screening for the presence or absence of disease, and to make a tentative diagnosis. It could also be used as a prognostic indicator and thus guide the treatment of the patient.

- What clinical decisions would be based on the results of the skin test?

The applicant's clinical experts stated that any clinical decision would require evaluation beyond the test itself. A clinician would probably not base a clinical decision on only the skin test results, but could use the results to make a tentative diagnosis and start treatment early if indicated. The clinician would consider the presenting symptoms, residence of the patient, travel history, past history of skin test or cocci disease, serologies, and chest radiography, in addition to clinical judgment.

- What data would be useful to know before using the skin test to make diagnostic decisions?

Please see the previous response. The applicant's clinical experts added that in an acute illness, knowing the previous skin test status would be helpful in making a diagnosis, but other diagnostic measures would also be required.

- What confirmatory testing or data will be used to support the clinical use and findings from the skin test?

The applicant's clinical experts stated that the following confirmatory testing or data could be used: complement fixation; serologies, including

serial serologies; histological testing of cutaneous lesions; DNA testing (using probes and/or sequencing); bronchoscopy and chest radiography; patient's residential or travel history; presence of symptoms consistent with disease.

- Would this product be used as the definitive diagnostic test in the absence of serologies?

The applicant's clinical experts stated that the skin test could be used as the definitive diagnostic test in acute illness where the previous history of the skin test was known, i.e., in converting from negative to positive. One can derive unique information from the skin test because cellular immunity appears to be protective, while the role of humoral immunity is not as clear. Other diagnostic measures would also be used. In addition, in cases where a person presents as skin test positive, and is without symptoms, a clinician would understand that the person has been previously exposed to *C. immitis*.

- If serologies were used in conjunction with the skin test, how would discrepancies in results (e.g., positive skin test with negative serologies) be addressed?

The applicant's clinical experts stated that if the patient either has or has had *C. immitis*, and is skin test positive with negative serologies, then further evaluation is needed. A differential diagnosis approach would be needed and may include a bronchoscopy or an open lung biopsy. It was stated by the applicant's expert clinicians that the serologies for this disease may stay positive for one year or more.

- In the setting of currently immune competent individuals about to be pharmacologically immunocompromised, would a positive skin test be taken as evidence of latent cocci or simply prior exposure?

The applicant's clinical experts commented that a positive skin test would be indicative of latent *C. immitis* and that once an individual has *C. immitis*, he/she will have it for the rest of his/her life: infection is a form of immunization. In immune

surveillance, a positive skin test may be indicative of live C. immitis in the body. There is no current way to cure latent infection with C. immitis.

5. Allarmed has submitted data on a pilot lot (---(b)(4)---) of Spherusol that was intended to serve as a release lot following approval of Spherusol. The expiration data of Lot ---(b)(4)--- has elapsed. Can FDA provide guidance concerning the manufacture of a replacement lot that can be submitted for lot release pending approval of Spherusol?

The dating period for Spherusol Lot --(b)(4)--- has expired. Therefore, we recommend that a new lot of Spherusol be manufactured for product distribution. However, we would consider extending the expiration dating period for Lot ---(b)(4)--- if adequate stability data were generated and submitted to CBER for review.

Summary and action items:

After the presentation provided by the clinical practitioners, and others in attendance with the applicant, in response to the questions in Item 4, CBER had several comments.

CBER noted that the presentation was very helpful to identify potential medical uses for this product. Additionally, CBER pointed out that part of the review process was to discuss possible indications and examine the data used to support these uses. CBER acknowledged that the applicant presented potential uses for the product; however, the applicant has not provided the data to support these uses. The applicant asked CBER about the feasibility of using historical data to support the proposed indication. CBER replied that this was a difficult issue, but that CBER is bound by the regulations and therefore it has to examine the data to see if they support the proposed indication and usage.

CBER and the applicant discussed the possibility of using a very narrow indication, such as:

"Spherusol is indicated for use as a skin test antigen to detect delayed type hypersensitivity to C.immitis in people who have had a previous exposure to pulmonary Coccidioides immitis."

CBER and the applicant agreed to consider a post-marketing report requirement if the product is approved.

CBER and the applicant agreed that information in the labeling would be very limited and it may be necessary to add a caveat to say that the data is limited. CBER and the applicant also agreed that the applicant could not refer to historical data in the label.

The applicant agreed to provide in writing the answers to the questions in Item 4, and to submit them to CBER as soon as possible.

CBER advised the applicant that the submission was still under review, and acknowledged that the development process for this product has been long. CBER reiterated that it found the meeting to be useful and that the discussions were fruitful. CBER advised the applicant not to presume any outcome at this point. CBER also advised the applicant that a copy of the official meeting summary will be sent to it within 30 calendar days.