Summary Basis for Regulatory Action

Date: June 28, 2011

From: Sheldon Morris, Ph D, Chair of the Review Committee

BLA/ STN#: 125354/0

Applicant Name: Allermed Laboratories, Inc.

Date of Submission: May 27, 2009

PDUFA Goal Date: July 29, 2011

Proprietary Name: Spherusol

Established Name: *Coccidioides immitis* spherule-derived skin test antigen

Indication and Usage:
Spherusol is a skin test antigen indicated for the detection of delayed type hypersensitivity to *Coccidioides immitis* in individuals with a history of pulmonary coccidioidomycosis. Spherusol is approved for use in individuals 18-64 years of age.

- The use of Spherusol to detect delayed type hypersensitivity response in individuals with unknown exposure to *C. immitis* has not been evaluated.

- Persons with acute or disseminated coccidioidomycosis may not develop a delayed type hypersensitivity response to Spherusol.

- Persons with immunodeficiency and a history of coccidioidomycosis may not develop a delayed type hypersensitivity response to Spherusol.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Norman W. Baylor, Ph.D., Director, Office of Vaccine Research and Review

□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Review documents used in compiling this SBRA:

Review Category	Reviewer--date of review
Clinical Review	Ann Schwartz, MD, 27 June 2011
Statistical Review	Jingyee Kou, Ph.D. 9 June 2011
Pharmacovigilance Review	Alexis Mosquera MPH, RN 20 June, 2011
CMC Review	Siobhan Cowley, Ph.D., 24 June 2011
Bioresearch Monitoring	Dennis Cato - 23 February 2010
Container and Labeling	Dana C. Jones – 22 April 2011
Facility Review	Deborah Trout – 16 February 2010, August 11 2010, June 9 2011

SUMMARY

Allermed Laboratories, Inc. submitted a Biologics License Application (BLA) for a *Coccidioides immitis* spherule-derived skin test antigen on 5/27/2009. ---(b)(4)--
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---. CBER issued a Complete Response (CR) to the applicant on 3/24/2010 citing multiple CMC, statistical, and clinical issues, including comments about the proposed clinical use of the product and the overall collection of safety data. The applicant responded to the CR on 6/8/2010 by primarily revising the indication for the product. However, CBER concluded that the applicant's responses to specific clinical comments were inadequate and issued an incomplete response letter on 8/26/2010 which focused on the clinical study information, the safety results, and the validity of the revised indication. After the applicant responded on 9/15/2010, CBER issued a second incomplete response letter on 10/26/2010 requesting clarification on how this product (Spherusol) will be used in a clinical setting. Largely to address concerns about the proposed indication, a type B meeting was scheduled with the applicant. On 1/11/2011, before the planned type B meeting, CBER issued additional questions to the applicant regarding the product's indication and anticipated uses. The type B meeting was held on 1/12/2011 via teleconference with the sponsor and two clinicians with substantial experience in managing patients with coccidioidomycosis who were consultants for Allermed. On 1/28/2011, the applicant submitted a written response to CBER's questions from this meeting. After the review committee determined the adequacy of the applicant's 1/28/11 response, discussed comments made during the type B meeting, and assessed the impact of the previous licensure of the bulk extract, review of the BLA for consideration of approval resumed.

This document contains background on coccidioidomycosis, a history of the product, and summaries of the major review disciplines associated with review of the BLA. It also highlights the most important issues identified during this review. These include:

1. The proposed indication for the product and its use in a clinical setting
2. The overall safety database
3. The impact of the previous licensure of the product on the current BLA

BACKGROUND

Coccidioides immitis is a dimorphic fungus endemic in the southwestern United States, northern Mexico, and in regions of Latin and South America. The clinical symptoms of *C. immitis* infection (usually acquired by inhalation of spores) can include fever, chest pain, cough, malaise, and chills. Although the disease is asymptomatic in greater than 60% of infected individuals, pulmonary disease can present as pneumonia and other manifestations include skin disease, osteomyelitis, peritonitis, arthritis, and meningitis. It is estimated that more than 100,000 new infections occur each year in the U. S. but only 10,000 confirmed cases are reported to the CDC annually.

The most specific method for diagnosis of disease is culture or histopathologic evaluation of infected tissue. However, because of difficulties associated with these methods (e.g., length of time to make a histopathologic diagnosis, availability of tissue), serodiagnosis is often used as an indirect diagnostic assay. Historically, two skin reagents were used as epidemiologic tools to detect prior infection with *C. immitis.* Coccidioidin, an extract of the mycelial form of *C. immitis*, and Spherulin, developed from the spherule form of the fungus, were previously licensed by the FDA to detect cellular hypersensitivity to *C. immitis* but neither product is currently approved for use.

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CHEMISTRY, MANUFACTURING, AND CONTROLS

Spherusol Master Lot

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----------. The drug product (Spherusol) is made by diluting -(b)(4)-
---------- saline solution to a final concentration of 12.7 μg/ml; 0.4% phenol is added as a preservative. ----------(b)(4)----------
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----------, trace amounts of thimerosal (~0.00001%) will be present in the final product. ----------(b)(4)----------
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Manufacturing
Spherusol is manufactured according to the following formulation:

Table 1. The composition of Spherusol

Component		Supplier(s)
Sodium chloride, (b)(4)	(b)(4)	----------(b)(4)----------
Sodium borate, ------(b)(4)-----	(b)(4)	----------(b)(4)----------
--(b)(4)--- phenol, (b)(4)	(b)(4)	------(b)(4)--------
(b)(4)----------	(b)(4)	
Water for Injection, (b)(4)	------(b)(4)------	Allermed Laboratories, Inc.

*Spherule-derived coccidioidin bulk concentrate

----------(b)(4)----------

Lot Release Testing
The tests done on the final product are shown in Table 2.

Table 2. Lot Release Tests for Spherusol

Parameter	Specification	SOP#
Sterility	sterile	918-003
General Safety	pass	908-000
Phenol	--(b)(4)-----	930-000
(b)(4)	--(b)(4)-	405-000
Sodium chloride	--(b)(4)-----	969-000
Sodium borate	--(b)(4)----------	972-000
Identity	pass	944-101
Potency	pass	910-102
Colorless/particulate	pass	651-000

Relative Potency Assay
The relative potency of the Spherusol is determined by comparing the skin test reactivity of final product (in sensitized guinea pigs) to the activity of an internal reference standard. To begin the assay, guinea pigs ----------(b)(4)----------
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To estimate the relative potency of a lot of Spherusol, the Spherusol lot is tested in parallel with the internal reference standard using sensitized guinea pigs. The nominal potency of the internal reference is ----------(b)(4)----------
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----------. The final potency of the test lot is obtained by ----------(b)(4)----------. The relative potency must be between ----------(b)(4)---------- to be valid.

Stability testing
Stability of the final product
The stability of the final product was evaluated during a (b)(4) period. Vials were tested at 0, 3, 6, 9, 12, 18, 24, 36, -----(b)(4)-----. The parameters that were assessed were visual clarity, (b)(4), sterility, and potency as well as sodium chloride, sodium borate, and phenol concentrations. Final containers were stored in upright and inverted positions at -(b)(4)---- and 2 – 8 ºC. The results of the studies showed that the product was stable since the composition and potency did not change during storage at ----(b)(4)----- months

and during storage for 36 months at 2 – 8 ºC. Given the stability of this product, assignment of a 36 month expiration dating period is appropriate.

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Lot release testing by CBER
Since Spherusol is manufactured by a straightforward procedure involving --(b)(4)--
----------, CBER will not require the submission of samples from each production lot for FDA testing.

Manufacturing facility review
The initial review of facility data identified concerns about the validation protocol for the manufacturing process, the media fill procedures, validation of container closure integrity test method, and whether the formulated bulk was ----------(b)(4)----------.
These issues were noted in CBER CR letters. The applicant has responded adequately to each of CBER's comments.

Waiver for pre-license inspection
Allermed Laboratories, Inc. FEI 300050721134
7203 Convoy Court San Diego CA 82111
A pre-license inspection of the Allermed facility was not performed prior to licensure. After consulting CBER SOPP 8410 "Determining when Pre-Licensing Pre-Approval Inspections are Necessary", the committee decided that a pre-license inspection was not required because of the following:

- Allermed is already approved to manufacture and fill licensed biological products
- The facility was inspected within the past two years
- The previous inspections were classified as voluntary action indicated
- There are no novel manufacturing issues associated with this product
- The manufacturing process begins with the final formulation and does not involve sufficiently different and unique production methods

CLINICAL/STATISTICAL REVIEW

This submission contains four studies evaluating the effectiveness of Spherusol for detecting delayed type hypersensitivity to *Coccidioides immitis* in individuals with a history of pulmonary coccidioidomycosis. The four completed clinical studies enrolled subjects with a history of pulmonary coccidioidomycosis in an endemic area (S101A, S104-1), subjects without prior exposure to *C. immitis* in a non-endemic area (S104-2) and subjects who have a history of histoplasmosis (S104-3) in a non-endemic area for C. *immitis*, to provide data on the sensitivity and specificity of Spherusol in each defined population.

Four clinical studies that were performed under the IND and were submitted for review in support of licensure are summarized in Table 3.

TABLE 3: Clinical Studies Submitted to BLA 125354

Study number (site)	Title	Primary Objective	Number of subjects enrolled (age)
S101A (Bakersfield, CA)	A Dose-Response Study of --(b)(4)--- Skin Test Antigen	To compare the dose-response of the current product at varying concentrations	20 (>17 years)
S104-1 (Bakersfield, CA & Tucson, AZ)	Skin Test Sensitivity of 1.27µg per 0.1mL Spherule-Derived Coccidioidin in Adult Volunteers With a History of Pulmonary Coccidioidomycosis	To evaluate the DTH skin test response to Spherusol in persons with a history of pulmonary coccidioidomycosis confirmed by laboratory findings	54 (18-65 years)
S104-2 (Spokane, WA)	Skin Test Specificity of 1.27µg per 0.1 mL Spherusol in Adult Volunteers without A History of Pulmonary Coccidioidomycosis	To evaluate the DTH response to Spherusol in persons without a history of coccidioidomycosis or exposure to the fungus.	60 (18-60 years)
S104-3 (Blair, NE)	Skin Test Specificity of 1.27µg per 0.1mL Spherusol in Adult Volunteers With a History of Pulmonary Histoplasmosis	To evaluate the DTH skin test response to Spherusol in persons with a history of pulmonary Histoplasmosis.	12 (> 18 years)

Study S101A – "A Dose-Response Study of --(b)(4)--- Derived Skin Test Antigen"
The initial study, S101A, was a dose response study to evaluate the dose to be used in the later clinical studies following the -----(b)(4)----- of the product. As described above, ----------(b)(4)---------- product. In ----------(b)(4)---------- ----------. For these studies, twenty subjects with a history of pulmonary coccidioidomycosis, diagnosed by serologies, culture and/or radiographs, received three to four different doses ranging from 0.4 – 2.4 μg/0.1 ml on the volar surface of the forearms. Induration responses were read at 48 hours following placement. A linear regression using the induration responses for the test doses supported the use of the 1.27 μg/0.1 ml dose in the subsequent studies.

The results for study S101A contain minimal safety data. From the available data, the most commonly reported AE was itching (70%). Although the absolute intensity of the adverse events were not reported, large injection site reactions were detected in two of six subjects given the 2.4 μg dose of Spherusol. After discussing these accelerated responses with the IRB and the FDA, the applicant decided to discontinue use of the 2.4 μg dose. Importantly, no serious adverse events occurred during this study.

Study S104-1 – "Skin Test Sensitivity of 1.27 μg per 0.1 ml Spherule-derived Coccidioidin in Adult Volunteers with a History of Pulmonary Coccidioidomycosis"
The objective of study S104-1 was to determine whether the 1.27 mg/0.1 ml dose (Study S101A) was appropriate. A total of 56 subjects with a previous history of pulmonary coccidioidomycosis were enrolled at two sites (Bakersfield, CA and Tucson, AZ) to receive skin testing with five skin test antigens (Spherusol, Trichophyton, Candin, a saline placebo and a thimerosal negative control). Two subjects were excluded prior to skin testing for not meeting inclusion/exclusion criteria and one subject was later lost to follow-up. A total of 54 subjects had skin test antigens placed for evaluation at 48 hours and 53 subjects completed the study. Fifty-one subjects had valid skin test results. Two subjects, one from each site, reacted to one or both of the negative controls and were excluded from further analyses.

Table 4. Summary of the skin test response rates in subjects with a history of coccidioidomycosis.

Sites	Total Tests Read	Invalid Tests	Total Valid Subjects	Valid Tests	
				Spherusol Positive	Spherusol Negative
Bakersfield, CA	11	1	10	10	0
Tucson, AZ	42	1	41	40	1
Total	53	2	51	50	1

Of the 51 subjects with evaluable skin test results, 50 subjects had a positive reaction to Spherusol. Thus, 98% [95% confidence interval (CI) 89.6%, 100%] of subjects with a

previous history of pulmonary coccidioidomycosis reacted at 48 hours with induration responses measuring 5 millimeters or greater. Therefore, the positive response rate in this population is 98%. However, it should be emphasized that no predictive value can be assessed for the use of Spherusol outside this specific population of subjects with a previous history of pulmonary coccidioidomycosis.

The Applicant did not collect skin test specific reactogenicity data for reactions occurring at each skin test individually. Reported local reactogenicity is therefore presumed to be associated with the study product. Of the 53 subjects evaluated following administration of the five skin test antigens, 48 (91%) reported solicited adverse events during the 7 days following injection. The most commonly reported solicited local reactions were itching and swelling occurring in 85% and 79% of subjects respectively. Flu-like symptoms were the most commonly occurring systemic reaction, reported by 7% of subjects. Three severe adverse events (swelling and itching) occurred in two subjects. Importantly, no serious adverse events occurred during the study.

Study S104-2 "Skin Test Specificity of 1.27 μg per 0.1 ml Spherule-derived Coccidioidin in Adult Volunteers Without a History of Pulmonary Coccidioidomycosis"

The objective of study S104-2 was to evaluate skin test responses to Spherusol in persons without a history of pulmonary coccidioidomycosis or known exposure to the fungus by prior residence in or travel to the southwestern U.S. which is endemic for *C. immitis*. Since the absence of disease is strongly suggested for this patient population prior to initiating the study, the results from this study provide an estimate of the negative response rate for people without a history of pulmonary coccidioidomycosis, but do not provide an estimate of the specificity of the skin test.

In Study S-104-2, each subject was skin tested with an intradermal injections of Spherusol (1.27 μg/0.1 ml), two positive controls (Candin and Trichophyton) and two negative controls (saline and thimerosal). Table 5 shows the results for the skin tests performed on subjects with no history of coccidioidomycosis.

Table 5. Summary of the skin test response rates in subjects with no history of coccidioidmycosis.

				Valid Tests	
Site	Total Tested	Invalid Tests	Total Valid Subjects	Spherusol Positive	Spherusol Negative
Spokane, Washington	60	1	59	1	58

As seen in Table 5, 59 of 60 volunteers had valid skin tests. One skin test result was considered invalid because a positive response was detected to the thimerosal negative

control. Since 58 out of 59 valid tests showed negative response, the estimated negative response rate is 0.98 (95% CI; 0.91, 1.00)

In this study, 5 subjects failed to respond to all test articles, including the two positive controls. According to the applicant, the blood tests show that the subjects were not immunocompromised but results were likely due to the absence of sensitivity to the test articles. Because these subjects failed to respond to all test articles, their true responses to the coccidioidin skin test are not attainable. The results should not be considered to imply that all subjects negatively responded as the applicant has assumed. Using a conservative evaluation approach, the non-responders can be considered as not valid negative responses to the coccidioidin skin test. Hence, only 54 subjects should be considered as valid and the estimated negative response rate should be 53/54 = 0.98 (95% CI; 0.90, 1.00). Alternatively, the worst case scenario would be that they had a positive response that was not manifested in the form of induration. In that case, the negative response rate would be 53/59 = 0.90 (95% CI; 0.79, 0.96).

For the sixty subjects enrolled in S104-2, adverse events were reported by 53 (83%) subjects following the administration of the five skin test reagents. The most frequently reported adverse events were itching, swelling and pain. Swelling was reported by 42 (70%) subjects, itching was reported by 40 (67%) subjects, and pain was reported by 15 (25%) subjects over the 7 day study period. Importantly, no serious adverse events occurred during the study.

Study S104-3 "Skin Test Specificity of 1.27 μg per 0.1 ml Spherule-derived Coccidioidin in Adult Volunteers with a History of Pulmonary Histoplasmosis"

The rationale for Study S104-3 was to determine if Spherusol administration elicited a positive skin test response in individuals with a history of pulmonary histoplasmosis. This disease is caused by *Histoplasma capsulatum*, a fungus with antigenic similarities to *C. immitis*. For this study, subjects with a previous history of pulmonary histoplasmosis and no travel or residence in areas endemic for *C. immitis* were skin tested with Spherusol, two positive controls (Candin and Trichophyton) and two negative controls (saline and thimerosal). Table 6 shows the results of these skin tests.

Table 6. Summary of reactions to reagents in subjects with a history of pulmonary histoplasmosis.

Test Reagent	N	Subjects with Induration ≥ 5 mm	Proportion	95% Confidence Interval
Trichophyton Extract	12	6	0.50	(0.21, 0.79)
Spherusol	12	0	0.00	(0.00, 0.26)
Placebo	12	0	0.00	(0.00, 0.26)
Candin	12	11	0.92	(0.62, 1.00)
Thimerosal	12	0	0.00	(0.00, 0.26)

All twelve adults with a recent history of pulmonary histoplasmosis failed to react to Spherusol, but were positive to either Candin or Trichophyton Extract, which served as positive controls. This finding supports the conclusion that the Spherusol product did not induce cross-reactive skin test responses in persons with past exposure to *H. capsulatum*.

Regarding the safety outcomes from Study S104-3, the majority of local adverse reactions were itching and swelling at unidentified skin test sites. No severe reactions were seen. Two subjects reported systemic adverse events. One subject reported mild difficulty breathing, and required treatment with a prescription inhaled β agonist within 24 hours of antigen placements. Another subject reported mild flu-like symptoms which included nausea and vomiting within 24-48 hours after skin test placements. Again, no serious adverse events occurred during the study.

Overview of the Clinical Study Results

Overall, the four studies submitted for review included one dose finding study, one study to assess sensitivity in a specific population and two studies to assess specificity of Spherusol in different populationwith low risk of exposure to *C. immitis*. Three of the study populations [S101A, S104-1 and S104-2] were defined by past exposure and disease caused by *C. immitis*. The fourth study population [S104-3] represented individuals with previous diagnosis of exposure and disease caused by *H. capsulatum*.

A summary of these clinical study results is shown below.

1. A positive induration response (defined as ≥ 5mm of induration) to Spherusol was seen in 98% (95% CI; 89.6%, 100%) of subjects with a previous history of coccidioidomycosis at 48 hours following intra-dermal administration 0.1 µg of Spherusol in Study S104-1.

2. A negative induration response (defined as <5 mm of induration) to Spherusol was seen in 90% (95% CI; 79.5%, 96.2%) of subjects who had no history of disease caused by *C. immitis*, negative serologies for antibodies to *C. immitis* or travel to an area endemic for *C. immitis*. Five subjects enrolled in this study did not react to any skin test antigen or control. These subjects were analyzed as having a positive induration response to Spherusol to illustrate the worst case scenario for the study product. If these subjects were excluded from the analysis, the negative induration response to Spherusol in this population was 98% (53/54).

3. A negative induration response to Spherusol was seen in 100% of subjects (N=12) who had a previous history of disease caused by *H. capsulatum* and no history of travel to areas endemic for *C. immitis.* This supports the lack of cross-reaction between the cellular immune responses induced by the two fungal species.

Overview of Safety Data from the Clinical Trials
Four trials enrolling 146 subjects who received at least one dose of Spherusol were submitted in support of licensure. It should be emphasized that safety data was not collected in a manner which allowed for the assessment of local reactions caused by Spherusol alone. In studies S104-1, S104-2 and S104-3, three skin test antigens (Spherusol, Candin and Trichophyton) and two controls (Thimerosal control and Saline/phenol control) were administered on the volar surfaces of the arms of each enrolled subject. Local adverse reactions were documented at 48 hours and through seven days, but not for the administered site of each of the individual skin tests. Thus, all local adverse reactions have been ascribed to Spherusol. The most common solicited adverse events reported were swelling and itching occurring in a range of 67-85% for subjects who received all five skin tests. The majority of reactions were mild to moderate in nature, but severe itching and swelling did occur in 2% of subjects in studies S104-1 and S104-2. There were no severe solicited local reactions in study S104-3. Flu-like symptoms were the most common solicited systemic adverse event occurring in a range of 7-8%. One subject in S104-2 reported severe difficulty breathing requiring medical treatment in the 24 hours following administration of the test products. There were no serious adverse events or deaths in the clinical studies.

Discussions about the Proposed Indication with the Applicant
The review committee had several discussions about the clinical utility of the proposed indication for Spherusol – Detection of delayed-type hypersensitivity to *Coccidiodes immitis* in healthy individuals with a history of pulmonary coccidioimycosis. Given that the product was not studied as a diagnostic test to detect active infection with *C. immitis*, the applicant was asked to describe the clinical usefulness of the product. The applicant responded by stating that Spherusol skin test data could be useful in detecting past infection, indicating the clinical course of the disease, and suggesting the presence of latent infection resulting from previous exposure to *C. immitis*. The detection of latent *C. immitis* infections could be potentially clinically relevant in persons undergoing immunosuppressive therapy prior to solid organ transplantation or treatment for severe arthritis. However, the application did not contain any data that would allow for a definition of risk for developing coccidioidal disease.

Discussions about an Advisory Committee Review
The committee's review of the information submitted in the BLA, including the clinical study design and the trial results, did not raise major concerns or controversial issues which would have benefited from an advisory committee discussion.

Bioresearch Monitoring
----------Withheld due to Privacy Act----------

Pharmacovigilance

The pharmacovigilance review concluded that there were no serious safety risks identified as adverse events in the clinical trials of Spherusol. However, the safety database for this Application was limited to less than 150 subjects between the ages of only 18 and 64 years of age. To collect additional safety and skin test reactivity data post-licensure, Allermed plans to conduct a survey in four endemic areas for coccidioidomycosis of least 300 individuals that were tested with Spherusol. This post-licensure study was proposed by Allermed. It is not a post-marketing study solicited by CBER.

Conclusions

- Analysis of the clinical results for the Spherusol skin testing studies showed adequate positive response rates among people with a history of pulmonary coccidioidomycosis and negative response rates among people without a history of pulmonary coccidioidomycosis. Moreover, Spherusol did not induce cross-reactive cellular responses in persons with past exposure to *H. capsulatum*.

- While the clinical safety data were limited, the safety profile was acceptable for use as a skin test agent. These safety results are consistent with the known safety profile of the previously licensed product manufactured from the same spherule-based extract.

- The manufacturing process is well-defined and the product characterization assays are adequate. ----------(b)(4)----------
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