



**DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DVRPA**

Date: 05 March 2010

From: Ann T. Schwartz, M.D.
Medical Officer, Clinical Review Branch 1

Through: Douglas Pratt, M.D, MPH
Chief, Clinical Review Branch 1

Subject: Clinical Review of Biologics License Application for *Coccidioidin SD* Skin test antigen

To: BLA STN# 125354/0

BLA review committee:

Sheldon Morris	Chairperson / Product
Karen Campbell	Product
Ann Schwartz	Clinical
Siobhan Cowley	CMC / Product
Juan Arciniega	Pertussis lot release and Diphtheria Toxoid ELISA
Jingyee Kou	Biostatistics
Catherine Miller	Promotional labeling and Proprietary name review
Dennis Cato	BioResearch Monitoring
Anthony Hawkins	BioResearch Monitoring
Deborah Trout	Facilities
Alexis Mosquera	Epidemiology
Jon Daugherty	Regulatory coordinator/DVRPA
Holly Weiland	Regulatory coordinator/DVRPA

1 Title and General Information

1.1 Medical Officer's (M.O.) Review Identifiers and Dates

1.1.1 BLA/NDA #: 125354 / 0

1.1.2 Related IND #(s):

IND -(b)(4)-: (Submission 07 Dec 2001) *Coccidioides immitis* Spherule-derived Skin Test Antigen (-(b)(4)---) – Allermed

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

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

1.1.3 Reviewer Name, Division and Mail Code (HFM number):

Ann T. Schwartz, M.D.
Division of Vaccines and Related Products Applications
HFM-485

1.1.4 Submission Received by FDA: 27 May 2009

1.1.5 Complete Response Review Completed: 05 March 2010

1.2 Product

1.2.1 Proper Name or Established Name: *Coccidioides immitis* Spherule-Derived Skin Test Antigen

1.2.2 Proposed Trade Name: Original proposal (14 May 2009) *Coccidioidin SD*. This proprietary name was found to be unacceptable by the Advertising and Promotional Labeling Branch (APLB), Division of Case Management (memo 27 October 2009). Subsequently the Applicant submitted a revised proposal (10 February 2010) for use of the proprietary name, Spherusol™(application for trademark submitted to the US Patent Office 02 Feb 2010). This proposal is currently under review by APLB. Until the current proposal is approved *Coccidioidin SD* will be used throughout this document to indicate the study product.

1.2.3 Product Formulation(s) Including Adjuvants, Preservatives, etc.:

Coccidioidin	1.27 µg -(b)(4)---/0.1 ml.
NaCl	0.9%
Phenol	0.4%
Thimerosal	1:1,000,000 (residual)
Sodium borate	0.014%

1.2.4 Chemical Name, Structure (optional): N/A

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

1.4 Pharmacologic Class or Category: Skin Test Antigen

1.5 Proposed Indication(s): *Coccidioidin SD* is a skin test antigen indicated for use in the detection of delayed hypersensitivity to *Coccidioides immitis*.

1.6 Proposed Populations(s): Not indicated

1.7 Dosage Form(s) and Route(s) of Administration: 1.27 mcg/0.1 mL, intradermal

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3 Draft Executive Summary

To be completed upon receipt of response to CR letter. This submission contains four studies evaluating the skin test antigen *Coccidioidin SD*. No information has been provided by the Applicant on how the product will be utilized in a clinical setting. Clinical studies were completed in subjects with a past history of pulmonary coccidioidomycosis, in subjects without prior exposure to *C. immitis* and in subjects who have a past history of Histoplasmosis to provide data on the sensitivity and specificity of the skin test antigen, *Coccidioidin SD*. The safety of the product can not be evaluated as incomplete safety data has been submitted to the BLA. Thus, the risks and benefits for the use of the product in a clinical setting are unknown.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)

Please see the reviews completed by the product reviewers.

4.2 Animal Pharmacology/Toxicology

Please see other discipline reviews.

5 Clinical and Regulatory Background

5.1 Disease or Health-Related Condition(s) Studied and Available Interventions

Coccidioides immitis is a dimorphic fungus endemic to the soil in the southwestern United States, northern Mexico and parts of Latin and South America. Hyperendemic areas located in the US include Kern county, California and Pima, Pinal and Maricopa counties in Arizona. Infections are acquired from the environment following the inhalation of arthroconidia (spores). Clinical manifestations of infection include non-specific complaints in immunocompetent individuals including fever, pleuritic substernal chest pain, cough, malaise, anorexia or chills. In greater than 60 % of infected individuals the disease is asymptomatic. Pulmonary disease can present as pneumonia, hilar adenopathy associated with infiltrates, or pleural effusions. Extrapulmonary dissemination of disease can occur, often within a few months of the primary infection. Populations at higher risk for disseminated disease include pregnant women (particularly during the third trimester), Hispanics, African Americans, Filipinos and those with depressed cellular immunity (acquired or iatrogenic). Extrapulmonary disease can manifest as granulomas in the skin, coccidioidal meningitis (with or without abscess formation) or bone infection.

Serodiagnosis is the primary method of indirect diagnosis with both qualitative and quantitative serologic tests being used in the diagnosis of coccidioidomycosis. Enzyme immunoassay, latex particle agglutination, and immunodiffusion are used as qualitative techniques, which yield positive results early in the course of the infection. Enzyme immunoassay provides rapid qualitative assessment of both IgM and IgG coccidioidal antibodies. Acute primary coccidioidomycosis is associated with positive IgM primary tube precipitin (IDTP) tests. IgG is measured by complement fixation and converts to positive later in disease than IDTP tests (2-3 weeks after primary infection). These highly specific titers usually correlate with the severity of disease with rising titers associated with progressive disease. False negative serologies do occur, primarily in those with HIV infection and immunosuppressed individuals. (Pappagianis & Zimmer. Clinical Microbiology Reviews, July 1990, p. 247-268; Yeo & Wong. Clinical Microbiology Reviews, July 2002, P. 465-484. Saubolle. Annals of the New York Academy of Science. 1111: 2007, p.301-304). The most specific method for diagnosis of disease is culture or

histopathologic evaluation of affected tissue. Growth of the mycelial form will occur on most culture mediums within 7-10 days after inoculation. *C. immitis* is designated as a “select agent” for bioterrorism because of its ease of growth (www.cdc.gov/od/sap).

Treatment of clinical disease involves the use of antifungal drugs. Clinical responses can be slow, incomplete or non-existent. Relapse may occur in approximately 30% of patients who achieve a disease free interval. No preventive vaccine, or other preventive measure other than avoidance of exposure, is available.

Historically there have been two skin test antigens used as epidemiologic tools to detect prior infection with *C. immitis*. Coccidioidin, an extract of the mycelial form of the fungus and Spherulin was developed from the spherule form of the fungus. Both products were previously licensed by the FDA. Results from previously conducted research have disagreed on which skin test antigen is more sensitive (Am J Public Health 1985; 75: 863-865). Skin testing has been used primarily in population studies to evaluate the overall trend in the incidence of coccidioidomycosis. It has been of limited usefulness in the diagnosis of acute infection as anergy may develop during active infection. The time from acute infection to development of a delayed type hypersensitivity reaction is thought to be several weeks. A positive skin test is thought to show waning reactivity after approximately 12-15 years. A positive skin test will not differentiate a current infection from prior infection.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

Previously licensed, but no longer licensed products (Coccidioidin and Spherulin™), were made from extracts of either the mycelial phase or spherule phase of *Coccidioides immitis*, and have been used previously to detect delayed type hypersensitivity to *C. immitis*, the causal agent of coccidioidomycosis. A positive skin test with induration ≥ 5mm has been accepted by clinicians and researchers as indicative of prior exposure to the fungus. These products have been used as an epidemiological tool to assess for prior exposure to the fungus in various populations and demographic regions.

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

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

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

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

The product for licensure is produced by -----(b)(4)----- containing 0.4% phenol as preservative such that -----(b)(4)----- of *C. immitis* antigen contain 12.7 mcg/mL in the final product. Lots used in the clinical studies were made in 2001-2003.

5.3 Previous Human Experience with the Product Including Foreign Experience

See above. No previous history of the safety and use of this product is provided by the Applicant.

5.4 Regulatory Background Information

- Pre-BLA meeting: 27 August 2007

6 Clinical Data Sources (both IND and non-IND), Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 BLA/NDA Volume Numbers Which Serve as a Basis for the Clinical Review

IND -(b)(4)-, amendments 0 through
BLA STN 125354/0 (electronic submission in a modified eCTD)
Sections reviewed:
Section 2 - Labeling
Section 3 - Summary
Section 8 - Clinical
Section 11 – Case report tabulations
Section 12 – Case report forms

6.1.2 Literature

- Dodge et al. AJPB August 1985, Vol. 75, No. 8 (page 863-865)
- DiCaudo, D. J Am Acad Dermatol, December 2006, Volume 55, Number 6.
- Larwood, T. CID, March 2000; 30.
- Galgiani et al. CID April 2000; 30: 658-61.
- others as cited in review

6.1.3 Post-Marketing Experience

No data submitted for review.

6.2 Table(s) of Clinical Studies

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

TABLE 1: 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 <i>Coccidioidin SD</i> in persons with a history of pulmonary coccidioidomycosis confirmed by laboratory findings	54 (18-65 years)
S104-2 (Spokane)	Skin Test Specificity of 1.27mcg per 0.1 mL Spherule-Derived Coccidioidin in Adult Volunteers without A History of Pulmonary Coccidioidomycosis	To evaluate the DTH response to <i>Coccidioidin SD</i> 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 Spherule-Derived Coccidioidin in Adult Volunteers With a History of Pulmonary Histoplasmosis	To evaluate the DTH skin test response to <i>Coccidioidin SD</i> in persons with a history of pulmonary Histoplasmosis.	12 (> 18 years)

* Studies S104-1, S104- 2 and S104-3 are listed as one study NCT00690092 at <http://clinicaltrials.gov>.

** In Study S101A, the product *Coccidioidin SD* is referred to as ---(b)(4)---

6.3 Financial Disclosures

The applicant provided a statement which certifies that the physicians listed below and their sub-investigators and research associates who participated in the *Coccidioidin SD* studies submitted to the BLA had no financial interest in the outcome of these studies. Specifically, (a) the compensation paid to the investigator was not affected by the outcome of the clinical trial; (b) the investigator did not have an equity interest in *Coccidioidin SD*; (c) no significant monetary payments, goods or services were made to the investigator exclusive of the costs associated with conducting the trial.

Two subjects had accelerated (occurring within the first 24 hours after test placement) responses to the highest dose, 2.4 µg/0.1 mL “---(b)(4)--” within the first day of testing. The study was paused, and the decision was made to discontinue further testing at the 2.4 µg dose.

Initial study start: 04 June 2002
Study stopped: 04 June 2002
Study recommenced: 16 July 2002 (using doses of 0.4 µg, 0.8 µg, 1.6 µg and placebo)
Study completed: 14 January 2003

Test materials were coded and double-blinded. Each subject was to be observed for thirty minutes after administration to assess for immediate adverse events.

Procedures

Visit 1

1. Subjects were asked to complete a study related questionnaire and consent form.
2. Subjects were skin tested with the diluent control and three concentrations of ---(b)(4)--*. The test materials will be coded and double-blinded. The dose will be 0.1 mL intradermally of each test material.
3. Subjects were required to wait in the physician's office for 30 minutes after the last skin test has been administered.

Visit 2 (48 hrs. later)

1. Subjects will be asked to report any adverse reactions during the past 48 hours.
 2. Skin test sites will be examined for induration. If present, it will be measured in two diameters (longest and orthogonal) and outlined with a black ballpoint pen. The tracing will be recorded on the skin test record using transparent tape. This will be done by pressing the tape firmly over the tracing, removing it, and placing the tape on the skin test record.
- * Initially four doses of ---(b)(4)-- were to be used in the dose response study, with the highest dose being 2.4 µg / 0.1 mL. The first two subjects to receive this dose had induration reactions > 70 mm. The study was halted and the decision was made not to continue with the highest dose product. Therefore, the remaining 14 subjects received three strengths of the study product.

Performing the skin test

The Applicant did not submit information on the placement and performance of the skin testing to the license application.

8.1.1.3 Population

The study enrolled twenty subjects greater than 17 years of age with a history of pulmonary coccidioidomycosis diagnosed by laboratory and radiographic testing and confirmed by chart review.

Inclusion Criteria

- History of infection with *C. immitis* or positive delayed-type hypersensitivity response to Coccidioidin
- Male or non-pregnant female; women of child-bearing potential must have a negative urine or serum pregnancy test 48 hours prior to enrolment, or have evidence of surgical sterilization
- Greater than 17 years of age

Exclusion Criteria

- History of histoplasmosis
- History of an adverse reaction to antigens of *Coccidioides immitis*, i.e., strong local reaction to skin test with Spherulin or Coccidioidin ≥ 70 mm and/or systemic response
- HIV positive
- Presence of erythema nodosum
- Presence of eczema
- Presence of psoriasis
- Presence of cellulitis
- Treatment with immunosuppressive drugs
- History of immunodeficiency disease
- Breastfeeding

8.1.1.4 Products mandated by the protocol

1. Placebo Control*
 2. --(b)(4)--- 0.4 $\mu\text{g}/0.1$ mL with 0.4% phenol
 3. --(b)(4)--- 0.8 $\mu\text{g}/0.1$ mL with 0.4% phenol
 4. --(b)(4)--- 1.6 $\mu\text{g}/0.1$ mL with 0.4% phenol
 5. --(b)(4)--- 2.4 $\mu\text{g}/0.1$ mL with 0.4% phenol
- * Diluent used to prepare --(b)(4)--- contains 0.4% phenol and thimerosal at the same concentration as the residual thimerosal in 2.4 $\mu\text{g}/0.1$ mL --(b)(4)---.

The products were monitored for stability during the course of the study.

8.1.1.5 Endpoints

The endpoint of the dose-response study was to assess the size of induration 48 hours after receiving 0.1 mL of the four doses of study product and 0.1 mL of the placebo control. At 48 hours each area of induration was measured along two axes (not defined) and the mean was reported as the final measurement.

The mean response data were then plotted against the dose concentration and analyzed by linear regression using the following equation:

$$E(\text{induration/concentration}) = \text{---(b)(4)--- concentration}$$

Where "E"- Expectation is the mean of the conditional distribution of induration at any given concentration.

The Applicant also provided another equation for verification of the --(b)(4)--- Dose-Response Study results as:

$$E(\text{induration/concentration}) = \text{-----(b)(4)-----}$$

Discrepancy to be addressed in the Statistical Reviewer's comments.

Please see section 8.1.1.7 below.

Please statistical reviewer's comments for full review.

8.1.1.6 Surveillance

Subjects to be monitored for 30 minutes after skin test were administered.

Follow-up at 48 hours after skin test administered. Skin test sites would be measured at that time and adverse events recorded.

The subject was to record all adverse events on a diary card. Adverse events were to be graded for time, nature, severity and outcome of the event using the grading scale below :

1+ (mild) Noticeable systemic response, transient, symptoms subside within 20 minutes and/or induration or swelling at test site 30 to 40 mm in diameter.

2+ (moderate) Systemic response which persists for more than 20 minutes but self-limiting and/or induration or swelling at test site > 40 mm in diameter.

3+ (severe) Strong response which persists for more than 20 minutes and which requires intervention with emergency procedures/medication for treatment and/or necrosis at test site.

Adverse events listed by the sponsor in the text of the protocol included: swollen, painful arm, difficulty breathing, faintness, flushing, dizziness, weakness, tachycardia, abdominal cramps, marked hypertension or hypotension or other systemic reactions. However, it is not clear what events were solicited for on the subject diary card.

Adverse events were to be reported to the IRB, IND and MedWatch.

No adverse event data were submitted to the file except for the brief narrative on subjects (b)(6) and (b)(6) in section V of the study results.

8.1.1.7 Statistical considerations

The data was to be plotted on a dose response curve with the mean dose response plotted against the dose concentration. The dose response curve was to be analyzed by linear regression using the following linear equation:

$E(\text{induration} | \text{concentration}) = \text{-----}(b)(4)\text{----- concentration}$ (Dose-Response Study Protocol section VII, page 4/26, submitted to BLA, no pagination)

*NB: This equation appears to be incorrect (see “Verification of ---(b)(4)-- Dose Response Study Results”, pagination not provided). In this statement the consultant indicates that the equation presented in the protocol is incorrect. The Sponsor used the correct to calculate the linear regression, but may have included data points which should have been excluded, this is addressed by the Statistical Reviewer in their review and comments.

8.1.2 Results

8.1.2.1 Populations enrolled/analyzed

Twenty adults ages 22 to 54 years age (M/F = 8/12), with previous medical diagnosis of coccidioidomycosis using radiography, serology and culture. Mean age was 36 years.

8.1.2.2 Dose-Response endpoints/outcomes

Please see the Statistical reviewer’s comments for issues regarding the statistical evaluation of the data.

8.1.2.3 Safety outcomes

No summary of safety data was submitted to the file to include immediate, solicited, unsolicited or serious adverse events.

Two subjects had accelerated responses to the highest dose, 2.4 µg/0.1 mL --(b)(4)--- within the first day of testing. The study was paused, and after discussion with the FDA, the decision was made to discontinue further testing at the 2.4 µg dose of --(b)(4)---.

The Applicant did not provide coding to unblind the skin test measurements submitted to the BLA (table not numbered, pagination not provided). Review of the unblinded skin test measurements submitted to the BLA for Subject (b)(6), who had the skin test antigen (2.4 µg/0.01mL) placed on 04 June 2002 with the result read on 06 June 2002, showed a reaction of 62 x 90 mm was recorded for R1, 72 x 90 mm for R2 and the reaction for R3 could not be read. No reading is present for L2 and L1 which is recorded as negative. (where R= the right arm and L= the left arm). Data for Subject (b)(6) is presented as a single measurement of 55 mm across for R1 and 44 mm across for R2. It is not clear which test products were placed at those sites.

8.1.3 Comments & Conclusions

The study results submitted to the BLA do not include any safety data except for a brief narrative of the “accelerated” response that was seen in two subjects (Subject (b)(6) and Subject (b)(6)) at the 2.4 µg dose of -(b)(4)-. After review by the IRB, the IND committee and discussion with the FDA it was decided that the 2.4 µg dose would be discontinued. It appears from Table 3 in the BLA submission (no pagination provided) that six subjects received the 2.4 µg dose of the skin test antigen. The data from Subject (b)(6), who had only one axes measured for induration at what appears to be the 1.6 µg and the 2.4 µg doses, was used in the linear regression model. This may affect the final outcome of the linear regression. Please see Statistical Reviewer’s analysis of the data.

No assessment of the safety of the product at any dose can be made due to the lack of safety data submitted to the file.

The following comments regarding questions and deficiencies are provided to the Applicant for Study S101A:

- Please provide a summary table of the products used in the study S101A to include the lot of product, active and inactive ingredients, excipients and presentation.
- Subjects who were found to have a positive skin test to the placebo should to be omitted from the study as uninterpretable since the reactions may be due to the thimerosal in the placebo. According to the study protocol, under the preliminary analysis of skin test data,” Subjects that have non-linear data will be omitted from further analysis.” (page 4/5 S101A Study Protocol). It appears from Table 3 (Study S101A) that four subjects either reacted to the placebo (thimerosal) [subjects --(b)(6)--], the results could not be determined [subject (b)(6)] or non-linear data were obtained [subject (b)(6)]. This would mean that 4 of the 20 subject’s results would be omitted from the calculation of the dose response curve. However, we note in Figure 1, that the results from 19 subjects were used to calculate the dose response curve. Please recalculate the dose response curve omitting those subjects who had positive reactions to the placebo, had non-linear response or were otherwise uninterpretable.
- 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 provide in the BLA document for this study).

- 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.
- Please provide a summary table of demographic information of the enrolled population to include age, race/ethnicity and gender.
- Please provide summary tables for subjects enrolled, withdrawn and analyzed in the clinical study.
- 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 DTH reaction.
- 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.
- In future submission please provide pagination for all documents to facilitate reference and review.

8.2 Skin Test Sensitivity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers with a History of Pulmonary Coccidioidomycosis

8.2.1 Applicant's Protocol # and Protocol Title

Protocol S104-1 (Bakersfield, CA) (Tucson, AZ)

“Skin Test Sensitivity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers with a History of Pulmonary Coccidioidomycosis”

8.2.2 Objective/Rationale

From the Study Synopsis: To determine if *Coccidioidin SD* elicits a positive DTH skin test in persons with a history of pulmonary coccidioidomycosis

From Study Report: To evaluate the delayed-type hypersensitivity skin test response to *Coccidioidin SD* in persons with a history of pulmonary coccidioidomycosis confirmed by laboratory findings.

8.2.3 Design Overview

Subjects were screened prior to enrollment with a 1) a participant questionnaire, 2) signed informed consent, 3) pregnancy test (female), and 4) review of medical records to confirm previous pulmonary coccidioidomycosis.

Enrolled subjects were skin tested with five blinded, randomized reagents on Visit #1 of the study and asked to complete a diary for the next 48 hours.

The results of skin tests were read after 48 hours (\pm 4 hours) on Visit #2 of the study.

Subjects were asked to continue to keep their Daily Diary to monitor possible adverse events until they return to the physician's office for Visit #3 on the 7th day after Visit #2 (Day 10 of the study). During this visit the Diary was to be reviewed and a Post Procedure Evaluation Record and Study Completion Record completed by the study physician.

Vital signs were to be measured during each visit (#1, 2, and 3). Adverse events monitored and, if necessary, treated until resolution. The Sponsor states that subjects with invalid skin tests will be replaced with alternate participants until the desired number of volunteers was achieved, however, an invalid test is not defined in the protocol.

8.2.4 Population

Up to 38 volunteers to be enrolled, age 18-65, with a history of non-disseminated, non-cavitary pulmonary coccidioidomycosis confirmed by radiography and serologic or mycological findings. If volunteers are currently taking anti-fungal medications they must be in overt good health with evidence of convalescence (e.g. declining serologic titer). The first thirty-five subjects will be used for the analysis of data.

8.2.4.1 Inclusion Criteria

- 18 – 65 years of age
- Overt good health (absence of Active Medical Disease*)
- History of pulmonary coccidioidomycosis of at least 45 days duration confirmed by serologic, histologic or mycologic findings

8.2.4.2 Exclusion Criteria

- Active Medical Disease*
- Alcohol abuse or illicit drug use
- History of histoplasmosis or blastomycosis

- Influenza-like illness within the past 4 weeks
- Immunizations within the last 4 weeks
- Current atopic or contact dermatitis, psoriasis, erythema nodosum, urticaria
- Current treatment with corticosteroids, cytotoxic or immunosuppressive drugs
- Immunodeficiency disease
- HIV infection
- Previous skin test with coccidioidin
- Pregnant or lactating **
- Adverse reaction to thimerosal
- Adverse reaction to Candida or Trichophyton skin test antigen
- Current cavitory or disseminated coccidioidomycosis

* **Active Medical Disease:** Any active physical or psychiatric condition that may increase the risks associated with participation in the study or interferes with the interpretation of study results. Included chronic medical illnesses are cardiovascular disease, renal insufficiency, chronic respiratory illness, cirrhosis, chronic hepatitis, chronic pancreatitis, chronic diarrhea, malnutrition, malignancy, autoimmune disease, and asthma.

** **Pregnancy Prevention:** Females were instructed to abstain from sexual relations or practice a medically acceptable form of birth control during the study. They were also instructed that, except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or a cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy.

Subjects may have been treated with anti-fungal drugs prior to enrollment or were receiving anti-fungal drugs during the study treatments.

Diagnosis of Pulmonary Coccidioidomycosis

The diagnosis of previous pulmonary coccidioidomycosis must include radiographic and serologic or mycological findings from medical record review (Documentation of diagnostic criteria used to was not included in the BLA submission).

Radiographic findings to include:

1. soft, furry hilar-thickenings
2. pneumonic-like infiltrate
3. parenchymatous well-circumscribed nodular lesions
4. mediastinal and hilar adenopathy
5. small pleural effusions

Positive Serology to *C. immitis* demonstrated by at least one of the following assays: (no other information provided on laboratory assays and validation) :

1. precipitation
2. complement-fixation
3. ELISA competition

Mycological diagnosis supported by :

1. Presence of spherules in sputum/biopsied tissue
2. Presence of mycelium with arthrospores on laboratory media, such as Sabouraud's Agar at 25-30°C.

Withdrawal and Removal Criteria

Participant Initiated: Volunteers will be allowed to withdraw from the study at any time without prejudice or loss of benefits to which they are entitled.

Investigator Initiated: Volunteers may be removed from the study at any time by the Principal Investigator or Sponsor should their continued participation be injurious to their health and well being. The IRB was to be notified whenever a subject is removed from the study for health related issues. Volunteers removed from the study subsequent to receiving the skin test, were to have a follow up visit at 1-2 weeks.

Alternate Participants: Based on the data reported to the sponsor, subjects with invalid tests (not defined) will be removed from the study (in terms of data analysis) and replaced with alternate participants.

8.2.5 Products mandated by the protocol

A dose of product was to have contained 1.27 micrograms of -----(b)(4)----- . The product is diluted in 0.9% sodium chloride, 0.4% phenol, and 0.014% sodium borate. The product contains 1:1,000,000 residual thimerosal preservative (NB: -----(b)(4)-----).
-----).

Table 2. Study S-104-1: Identification of products used in study

Reagent	Study Color Code	Code	Description
Coccidioidin SD (1.27µg/0.1mL) Lot # XSN04220301	Green	4101	Water extractables of <i>C.immitis</i> spherules in --(b)(4)-- saline containing 0.4% phenol as a preservative and 1:1,000,000 residual thimerosal preservative. Contains 1.27 mcg/0.1mL of dry spherule material as the active ingredient.
Thimerosal Control Lot # ----- (b)(4) -----	Red	6849	--(b)(4)-- saline without the active ingredient. The solution contains thimerosal 1:1,000,000. 0.4% Phenol added as a preservative.
Placebo(Saline) Control Lot # XDf06020301	Black	3546	--(b)(4)-- saline without the active ingredient and without thimerosal. 0.4% Phenol is added as a preservative.
Candin Lot # CA033	Blue	1287	Extract of <i>Candida albicans</i> preserved with 0.4% phenol
Trichophyton Extract Lot # XMm11080401	Yellow	5461	Extract of <i>T.rubrum</i> and <i>T.mentagrophytes</i> preserved with 0.4% phenol

Source: Study S-104-1, IND -(b)(4)-, Table: "Skin Reagents", section 8.4.2, page 13 of 37.

The five skin test reagents that were used in the study were color coded. Each reagent was assigned a clinical code to ensure the identity of the article. This code was different from the lot number. Candin and Trichophyton extracts are licensed for use and distribution by the FDA, but it is not clear if the extracts used in this study (or subsequent studies) are the licensed product(s).

8.2.6 Endpoints

Endpoints assessed were:

- Induration response at 48 hours for each antigen at the skin test site with an induration ≥ 5 mm at that time point demonstrating sensitivity. (The use of 5 mm induration indicating a positive response at 48 hours was used for the previously licensed product(s) SpherulinTM and Coccidioidin)

- Safety was assessed by collection of information on local and systemic adverse events occurring from time of placement until 48 hours after placement and then at one week following 48 hour evaluation.

8.2.7 Surveillance

Immediate Reactions

Subjects to be monitored for 60 minutes following the last injection

Local Reactions

- Reactions considered mild include (Category 1)
 - Itching
 - Tenderness not compromising limb function
 - Erythema and/or edema 50-80mm in any dimension
- Reactions considered moderate (Category 2)
 - Tenderness compromising limb function
 - Induration 80mm in any dimension
- Reactions considered severe (Category 3)
 - Skin breakdown with ulceration

Generalized/Systemic Reactions

- Reactions considered mild (Category 1)
 - Weakness, faintness, dizziness, nausea, cough, rhinorrhea lasting less than 1 hour, not requiring intervention
- Reactions considered moderate (Category 2)
 - Category 1 symptoms that persist for more than 1 hour, not requiring intervention
 - Flu-like symptoms
- Reaction considered severe – requiring intervention (Category 3)
 - Category 1 and 2 events requiring intervention
 - Progressive signs of an anaphylactic reaction
 - Hypertension or hypotension
 - Feeling of intense anxiety or panic
 - Flushing and sweating
 - Onset of vomiting, cramps or diarrhea
 - Onset of generalized pruritus in skin or mucous membranes
 - Onset of urticaria or angioedema
 - Acute onset of wheezing or dyspnea

8.2.8 Statistical considerations

The skin tests were read at 48 hours +/- 4 hours post-placement by measuring the area of induration (independent of erythema). Readings were confirmed by a second independent reader. Subjects who react to the saline control or the placebo control with an induration of ≤ 5 mm were to be excluded from analysis.

Induration response of ≥ 5 mm at 48 hours for *Coccidioidin SD* demonstrated sensitivity. Sensitivity was defined as the proportion of subjects with a history of pulmonary coccidioidomycosis who would demonstrate a delayed-type hypersensitivity reaction of ≥ 5 mm induration at 48 hours.

8.2.9 Results

8.2.9.1 Populations enrolled/analyzed

Fifty-three subjects were enrolled [38 (72%) males, 15 (28%) females]. Age range 23-64 years of age. Racial and ethnic breakdown showed: thirty-seven (70%) subjects were Caucasian, six (11%) Hispanic, six (11%) African-American, one (2%) Asian, one (2%) Native American and two (4%) subjects did not specify ethnicity.

Fifty-two (98%) subjects completed the study. No subjects withdrew secondary to adverse events. One subject, enrolled to the Bakersfield site, had skin test reagents placed but did not return for skin test readings. The subject stated he had forgotten to return at 48 hours after placement of the study products.

8.2.9.2 Sensitivity endpoints/outcomes

The Sponsor presented the results of the study for the Intent-to-Treat population (ITT) which contained 53 subjects. Results were only available for 52 subjects (According to protocol-ATP population).

Table 3. Study S104-1: Induration \geq 5mm at 48 hours for all skin test antigens ITT population, Read at 48 hours (+/- 4 hours) N=53

Negative Controls		Positive Controls	Product	
Placebo Control	Thimerosal Control	Candin	Trichophyton	Coccidioidin SD
2 (4%)	1 (2%)	45 (85%)	46 (87%)	52 (98%)

Source: Study S104-1. Section 10.4.1, page 16 of 37.

Two subjects demonstrated a positive response to the negative controls, which were saline and the placebo [4% phenol and thimerosal (1:1,000,000)]. Subject (-b)(6)- at the Bakersfield site had an 8.0 mm response to the Placebo Control and a 10.5mm response to the Thimerosal Control. Subject (-b)(6)- at Tucson had a 7 mm induration response to the Placebo Control. These two subjects were excluded in the analysis of sensitivity to the study product.

The table provided above does not exclude subjects with invalid tests per the protocol. In the body of the study report there is no indication of the analyses performed. However, in the synopsis of the study we find the data is presented in a summary form as analyzed.

Table 4. Study S104-1: Induration response $>$ 5mm for Skin test Reagents at 48 hours Post-Placement N=53

Product	Bakersfield	Tucson	Combined Results
Coccidioidin SD	11/11*	41/42	52/53
Positive Controls:			
Candin	10/11	31/42	41/53
Trichophyton	11/11	31/42	42/53
Negative Controls			
Thimerosal	1/11^	0/42	1/42
Saline placebo	1/11^	1/42	2/42

Source: Table page 7/37 unlabeled- Synopsis

*numerator = number of subjects with positive DTH skin tests; denominator = number of subjects tested

^same subject

Excluding the two invalid tests mentioned above (one at each site) a total of 50 of 53 subjects demonstrated an induration of ≥ 5 mm. Using only evaluable results, 50/51 subjects demonstrated a induration of ≥ 5 mm, for a sensitivity of 98% (CI 0.896, 1.00).

Positive skin tests for Candin and Trichophyton were observed in approximately 85% of subjects.

A comparison is shown below of the size of the DTH responses to the positive controls and to the study product. The Applicant did not provide the number of subjects who were used to provide the values in Table 5.

Table 5. Study S104-1: DTH Response to Positive Controls and *Coccidioidin SD* *

	Candin	Trichophyton	<i>Coccidioidin SD</i>
Range	5 – 30mm	5 – 71mm	5 – 39.5mm
Mean	13.5mm	18.2mm	17.0mm

Source: Study S104-1, section 10.4.1, page 17 of 37.

*The number of subjects evaluated to give ranges and means is unknown.

Four subjects exhibited means of > 40 mm (42.0, 51.0, 55.0, 71.0 mm) induration response for Trichophyton.

The mean induration response for *Coccidioidin SD* was 17 mm, however it is unclear how many subjects were evaluated to give the means and ranges for each skin test.

The protocol was amended to allow enrollment of subjects who had received or were receiving antifungal drug treatment for coccidioidomycosis. Of the forty-two subjects who had not been treated with antifungal medications, 100% demonstrated a mean sum of induration of ≥ 5 mm, indicative of a positive response to *Coccidioidin SD*.

8.2.9.3 Safety outcomes

Data as presented by the applicant are unevaluable because the skin test antigen associated with the local adverse event is not identified. The timing of the adverse events is not presented.

A summary of adverse events is presented in section 11.2.1, however, this table corresponds to the cumulative adverse reactions seen in subjects who received *Coccidioidin SD*, Candin and Trichophyton. It is unclear which adverse events were associated with *Coccidioidin SD*. Severe local reactions were seen in three subjects and included itching, swelling and ulceration. No further information is provided on the treatment, and resolution of the severe adverse events. Although the Applicant does not implicitly state the timing of the adverse events, it is assumed that since the induration response were read at 48 hours +/- 4 hours, these adverse events may have occurred at this time point. Further clarification will be requested from the Applicant.

Table 6. Study S1104-1: Summary of Adverse Events occurring after administration of Coccidioidin SD, Candin and Trichophyton. #

Adverse Event	Mild (barely noticeable, not bothersome)	Moderate (definitely noticeable, discomfort)	Severe (needs medical attention)
<u>Local</u>			
Itching	19	25	1*
Swelling	19	22	1**
Pain	7	2	Ø
Necrosis (ulceration)	1	Ø	1**
<u>Systemic</u>			
Increased heart rate	1	1	Ø
Weakness	1	2	Ø
Faintness	Ø	Ø	Ø
Dizziness	1	Ø	Ø
Nausea/ cramps	1	Ø	Ø
Flu-like symptoms	1	3	Ø
Difficulty breathing/ shortness of breath	Ø	Ø	Ø

Source: "Summary of Adverse Events", section 11.2.1, page 20/37.

* Subject -(b)(6)-

** Subject -(b)(6)-

#The number of subjects reporting adverse events is not provided in the submission.

8.2.10 Comments & Conclusions for Study S104-1

A total of 53 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 (Coccidioidin SD, Trichophyton, Candin, saline placebo and thimerosal negative control). Two subjects were excluded prior to skin testing for not meeting inclusion/exclusion criteria and one subject was lost to follow-up. A total of fifty-four subjects had skin test antigens placed for evaluation at 48 hours. Fifty-one subjects had valid skin test results. Two subjects, one from each site, reacted to one or both of the negative controls. These subjects were to be excluded from the sensitivity analysis; however, it is unclear if this occurred. From the unnumbered table in section 10.4.1, the analysis of efficacy appears to include all subjects who were skin tested (N=53) that were enrolled and completed the study. Since valid reactions are available for only 51 subjects it is unclear how 52 subjects could return a positive result.

The results submitted for subjects who received anti-fungals drugs during the course of treatment for the coccidioidomycosis appears to be incomplete. Data is provided on 51 of the 53 subjects. The treatment status of the two subjects with positive reactions to the negative controls is not provided. It does appear that subjects who received anti-fungal treatment prior to the year 2006, demonstrated a smaller mean induration response. The clinical significance of this finding is unknown.

The safety data are unevaluable as presented for this study.

The following comments are for communication to the Applicant:

- 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.

- In the table labeled “DTH Response to Positive Controls and to *Coccidioidin SD* (page 18/37) please indicate how many subjects were evaluated to give the ranges and means of the reactions presented.
- 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.
- Please provide a summary table of the solicited local and systemic reactions following administration of “*Coccidioidin SD*”, 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.
- 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.
- 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 provide information on treatment with anti-fungal drugs for these subjects.
- 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.

8.3 Skin Test Specificity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers Without a History of Pulmonary Coccidioidomycosis

8.3.1 Applicant's Protocol # and Protocol Title

S104-2 (Spokane, WA) “Skin Test Specificity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers Without a History of Pulmonary Coccidioidomycosis”

8.3.2 Objective/Rationale

To evaluate the DTH skin test response to *Coccidioidin SD* in persons without a history of pulmonary coccidioidomycosis or known exposure to the fungus by prior residence or travel in endemic areas for *C.immitis*.

8.3.3 Design Overview

Subjects were screened prior to enrollment with a 1) a medical history questionnaire, 2) signed informed consent, 3) pregnancy test (female), 4) serological evaluation for *C. immitis* (ELISA, immunodiffusion and complement fixation* and 5) a residential and travel history to rule out exposure to *C. immitis* or history of coccidioidomycosis.

Enrolled subjects were skin tested with five blinded, randomized reagents on Visit #1 of the study and asked to complete a diary for the next 48 hours.

The results of skin tests were read after 48 hours (\pm 4 hours) on Visit #2 of the study.

Subjects were asked to continue to keep their Daily Diary to monitor possible adverse events until they return to the physician's office for Visit #3 on the 7th day after Visit #2 (Day 10 of the study). Vital signs were to be measured during each visit (#1, 2, and 3).

If subjects were found to be negative to all positive controls a lymphocytic profile was to be done to assess for immunosuppression.

8.3.4 Population

8.3.4.1 Inclusion Criteria

- 18 - 60 years of age
- Overt good health (absence of Active Medical Disease*)
- Lifetime residence in the states of WA, OR, ID, or MT
- Never employed as an agricultural worker
- Serology negative for *C.immitis* antibodies

8.3.4.2 Exclusion Criteria

- Active Medical Disease*
- Alcohol abuse or illicit drug use
- History of coccidioidomycosis, histoplasmosis, blastomycosis
- Influenza-like illness within the past 4 weeks
- Immunizations within the last 4 weeks
- Current atopic or contact dermatitis, psoriasis, erythema nodosum, urticaria
- Current treatment with corticosteroids, cytotoxic or immunosuppressive drugs, systemic antifungal medications
- Immunodeficiency disease
- HIV infection
- Previous skin test with coccidioidin or *Spherulin*
- Pregnant or lactating **
- Adverse reaction to thimerosal
- Adverse reaction to Candida or Trichophyton skin test antigen
- Travel for more than 30 days in designated areas of CA, AZ, NV, UT, NM, TX and Mexico, Central and South America. Travel for more than 7 days in restricted areas of CA, AZ, and TX

* **Active Medical Disease:** Any active physical or psychiatric condition that may increase the risks associated with participation in the study or interferes with the interpretation of study results. Included chronic medical illnesses are cardiovascular disease, renal insufficiency, chronic respiratory illness, cirrhosis, chronic hepatitis, chronic pancreatitis, chronic diarrhea, malnutrition, malignancy, autoimmune disease, and asthma.

** **Pregnancy Prevention:** Females were instructed to abstain from sexual relations or practice a medically acceptable form of birth control during the study. They were also instructed that, except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or a cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy.

Table 7. Study S104-2: *Coccidioides immitis* Serologic Tests and Interpretation

EIA (IgM) ¹	Immunodiffusion ²		Complement Fixation ³	Interpretation
	IgG	IgM		
-	-	-	-	negative
i	-	-	-	negative
i	Any other positive test			positive
+	+ or -	+ or -	+ or -	positive
+ or -	+	+ or -	+ or -	positive
+ or -	+ or -	+	+ or -	positive
+ or -	+ or -	+ or -	> 1:2	positive

Source: Laboratory reference values for serologic tests used to determine positive or negative antibodies to *C. immitis*. [Source Supplement C, IND -(b)(4)-, Protocol S104-2, pagination not provided]

- = negative test

+ = positive test

I = indeterminate (inconclusive)

+ or - = positive or negative

Reported Laboratory Results

1. EIA (IgM)
 - O.D. -(b)(4)- Negative
 - O.D. -(b)(4)- Indeterminate
 - OD -(b)(4)- Positive
2. Immunodiffusion (precipitin band)
 - Absent Negative
 - Present Positive
3. Complement Fixation (IgG) – serum dilution
 - (b)(4)----- Positive

*For EIA (IgM) and Immunodiffusion laboratory results are based on values established by -----(b)(4)----- with reagents and references supplied by serologic test manufacturer (------(b)(4)-----). For Complement fixation (igG) laboratory results, reference values were established by ---(b)(4)-- based on internal controls using reagents prepared by --(b)(4)--- and commercial vendors.[Source Supplement C, IND -(b)(4)-, Protocol S104-2, pagination not provided]

8.3.5 Products mandated by the protocol

Each subject was skin tested with an intradermal injection (0.1mL) of the study product, two positive controls, Candin and Trichophyton and two negative controls (Saline and thimerosal control).

Table 8. Study S104-2: Skin Test Reagents for use in Study S104-2

Reagent	Color	Code	Purpose
Coccidioidin SD (1.27µg/0.1mL) Lot # XSN04220301	Green	4101	Evaluate DTH response in subjects without a history of pulmonary coccidioidomycosis or known exposure to <i>C.immitis</i> from prior residence or travel in endemic areas
Thimerosal Control Lot # ----(b)(4)-----	Red	6849	Evaluate DTH response to residual thimerosal(1:1,000,000) in <i>Coccidioidin SD</i> -----(b)(4)----- with diluent containing 1: 1,000,000 concentration of thimerosal
Placebo Control Lot # XDf06020301	Black	3546	Evaluate DTH responses to ingredients in the --(b)(4)-- saline solution used to prepare <i>Coccidioidin SD</i>
Candin Lot #CA033	Blue	1287	Evaluate subject's ability to elicit a positive DTH response
Trichophyton Extract Lot # XMm11080401	Yellow	5461	Evaluate subject's ability to elicit a positive DTH response

Source: Table: Skin test Reagents, page 12/31, section 8.4.2.

8.3.6 Endpoints

Primary endpoint was induration response for each antigen at 48 hours.

Specificity of the *Coccidioidin SD* was measured by recording induration at the skin test site after 48 hours. The induration response was outlined with a black ballpoint pen and a permanent record was made by overlaying the tracing with transparent tape and placing the tape on the skin test record. The longest and orthogonal diameters of the tracing were measured in mm. Reactions ≥ 5 mm were considered to be a positive skin test. Induration less than 5mm at 48 hours demonstrated the absence of sensitivity and induration ≥ 5 mm at 48 hours demonstrated the presence of sensitivity in the population studied.

Safety was measured by reporting local and systemic reactions that occurred after skin tests were administered. A diary of adverse events was completed for the duration of the study.

Local reactions that were monitored included swelling, itching, pain, and necrosis. Systemic responses that were monitored included flu-like symptoms, increased heart rate, nausea/cramps, fatigue, weakness, faintness, difficulty breathing.

8.3.7 Surveillance

No information is provided in the final study report on the monitoring for adverse events, either solicited or unsolicited. Information provided is located in the synopsis on page 6/31. Local reactions that were monitored included swelling, itching, pain, and necrosis. Systemic responses that were monitored included flu-like symptoms, increased heart rate, nausea/cramps, fatigue, weakness, faintness, difficulty breathing. The Sponsor had stated that a diary card was to be used to capture adverse events, but no toxicity grading scale of events or diary card examples are provided.

8.3.8 Statistical considerations

Specificity was defined as the proportion of persons in the population without previous exposure to *C.immitis* who demonstrated a negative DTH test after placement of *Coccidioidin SD*. The Fisher's Exact Test was used to calculate the 95% two-sided confidence limits for product specificity. Subjects were to be excluded if they reacted to the negative controls, the saline placebo and/or the thimerosal control.

8.3.9 Results

8.3.9.1 Populations enrolled/analyzed

Sixty-one (61) subjects signed informed consent documents. One subject failed to meet all inclusion criteria. Sixty (60) subjects were enrolled and completed the trial as outlined in the protocol. Fifty-nine (59) subjects had valid data.

Age range: 18 to 56

M/F: 22 / 38

Fifty-eight (58) subjects were Caucasian. One (1) subject was Hispanic and one (1) subject was Asian.

Study participants had never lived in endemic areas for *C.immitis* including CA, AZ, NV, UT, NM, TX or Mexico and South and Central America. Travel to endemic areas was limited to 7 days in highly endemic areas and 30 days in other endemic locales.

8.3.9.2 Specificity endpoints/outcomes

A total of 60 subjects had skin test antigens placed per the protocol. One subject (-b)(6)- demonstrated a 5 mm reaction to thimerosal diluent control, indicative of an invalid test and was excluded from the analysis.

Coccidioidin SD did not elicit a positive DTH skin test in 58 of 59 subjects with valid skin test results. One subject (-b)(6)- had a 5mm induration response to *Coccidioidin SD* which was reported as a positive skin test to the antigen. This subject (-b)(6)- had traveled on a limited basis in AZ and CA. A second subject (-b)(6)- showed an induration response of 4.5mm which was reported as negative. The Placebo Control (diluent) elicited induration responses of 2.0mm (-b)(6)- and 4.0mm (-b)(6)-. The Thimerosal Control elicited induration responses of 3.5mm (-b)(6)-, 4.0mm (-----b)(6)-----), and 5.0mm (-b)(6)-. The 5mm response was considered a positive response; therefore, this subject was excluded from the cohort of 59 remaining subjects with valid tests that were included in the analysis of specificity to *Coccidioidin SD*.

Five subjects had a <5 mm response to all antigens. Of those subjects, the individuals with no induration at 48 hours to any skin test antigen or control had blood drawn for lymphocyte analysis. Subjects who were skin test negative to all test articles, including the two DTH antigens, were tested for a normal lymphocyte profile by blood specimens. The assay was performed to ensure that skin test negative subjects were not immunocompromised and incapable of mounting a cellular immune response. Blood samples were taken from five subjects (-----b)(6)-----) for lymphocyte analysis. In all five cases, the lymphocyte profile was normal. The Applicant concluded that the negative skin test results were due to the absence of sensitivity to the test article(s), rather than a dysfunctional cellular immune system.

Thus 58/59 valid tests were negative for an induration response of ≥ 5 mm for *Coccidioidin SD*, giving a specificity of 98.3% (CI 90.0, 100).

8.3.9.3 Safety outcomes

Local adverse events included mild to moderate itching, swelling, and pain at the site of positive skin tests. Per the Sponsor these events were observed as reactions to the Candin and/or Trichophyton Extract and not to the study product, *Coccidioidin SD*.

Table 9. Study S104-2: Summary of Adverse Events (Spokane, WA)#

Adverse Event	<u>Mild</u> (barely noticeable, not bothersome)	<u>Moderate</u> (definitely noticeable, discomfort)	<u>Severe</u> (needs medical attention)
<u>Local</u>			
Itching	25	15	1
Swelling	29	14	1
Pain	11	5	Ø
Necrosis (ulceration)	2	1	Ø
<u>Systemic</u>			
Increased heart rate	2	Ø	Ø
Weakness	3	Ø	Ø
Faintness	2	Ø	Ø
Dizziness	1	Ø	Ø
Nausea/ cramps	3	2	Ø
Flu-like symptoms	2	2	Ø
Difficulty breathing shortness of breath	Ø	1	Ø

Source: Table entitled "Summary of Adverse events, page 17/31, section 11.2.

Subjects were assessed at 48 hours +/- 4 hours after skin test placement.

#The number of subjects reporting adverse events is not reported in the submission.

Three subjects (------(b)(6)-----) reported ulceration at a skin test site(s), but no documentation is provided on which skin test antigen was placed at the areas of induration. The induration response was measured at 7, 11, 13 mm respectively. Two subjects (------(b)(6)-----) were treated with topical steroid cream. Of note, two of the cases of reported ulceration were felt to be "dermatitis" when evaluated by the study physicians. The third case of ulceration is not described. These events were reported as resolved at the end of the study.

The systemic adverse events shown above were reported by five subjects in their daily diaries. Several events were reported by the same subjects (------(b)(6)-----). All of the events resolved without intervention.

Narratives for the AEs are provided from a letter from the investigator sent to the Sponsor.

No narrative information is provided on the two severe adverse reactions of itching and swelling.

No serious adverse events were reported.

8.3.10 Comments & Conclusions for Study S104-2

Although the Applicant has provided data to show the specificity of the *Coccidioidin SD* in a population of subjects who have not been diagnosed with pulmonary coccidioidomycosis, the safety of the study product can not be assessed based on the data submitted. The specificity of the *Coccidioidin SD* to elicit a positive induration response of > 5 mm at 48 hours is over 98% in subjects who have not been sensitized or exposed to *Coccidioides immitis*.

The following comments are for communication to the Applicant regarding Study S104-2:

- Please provide a summary table of the solicited local and systemic reactions following administration of “*Coccidioidin SD*”, 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.
- 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.
- 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.

8.4 Skin Test Specificity of 1.27 µg per 0.1 mL Spherule-derived Coccidioidin in Adult Volunteers With a History of Pulmonary Histoplasmosis

8.4.1 Applicant's Protocol # and Protocol Title

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” (Blair, NE)

8.4.2 Objective/Rationale

- To determine if *Coccidioidin SD* elicits a positive DTH skin test in persons with a history of pulmonary Histoplasmosis.

It was unknown if the Coccidioidin containing skin test antigen would cross-react with antibodies to *H. capsulatum*. To determine if there would be a cross reaction in individuals who were previously infected with *H. capsulatum*, a study was design to enroll subjects in a known *H. capsulatum* endemic area with a history of pulmonary Histoplasmosis who had not travelled to regions endemic for *C. immitis*.

Clinical definition of the disease included fever and at least one additional symptom (headache, cough, chest pains and/or shortness of breath). In the individuals with the above symptom complex, serology was performed with confirming evidence being a complement fixation (CF) titer $\geq 1:32$ and/or the presence of an “H” or “M” band by immunodiffusion. From a MMWR report [November 5, 2004 / 53(43); 1020-1022], of the 724 potentially exposed persons, 108 had symptoms that were consistent with the case definition. Twenty-five (25) of these individuals had a positive *Histoplasma* serology.

8.4.3 Design Overview

The study was a double blinded, non-randomized observational study.

Volunteers were identified by -----(b)(4)----- (----- (b)(4)-----). Of the twenty-five identified individuals, 13 volunteers consented to participate in the study. All volunteers were screened prior to enrollment with a participant questionnaire, informed consent documents, pregnancy test (female), serologic evaluation for *C. immitis* and *H. capsulatum* and a residential and travel history. Eligible participants were skin tested on Visit # 1 and asked to complete a diary for the next 48 hours. The results of skin tests were read after 48 hours (\pm 4 hours) on Visit # 2. Subjects were asked to continue to keep a diary to monitor possible adverse events until they returned to the physician's office one week later. Vital signs were measured during each visit and subjects with a positive serology to *Histoplasma* were given a final physical exam to assess the status of their health.

No subjects received anti-fungal medications/treatments during the course of the study.

8.4.4 Population

Subjects with previous history of pulmonary histoplasmosis confirmed by laboratory testing with no travel or residence in areas endemic for *C. immitis*.

No age limits or gender specifications are noted in the study.

Inclusion Criteria

- 18 years of age or older
- Overt good health (absence of Active Medical Disease*)
- History of pulmonary histoplasmosis confirmed by serology

Exclusion Criteria

- Active Medical Disease*
- Alcohol abuse or illicit drug use
- History of coccidioidomycosis
- Influenza-like illness within the past 4 weeks
- Immunizations within the last 4 weeks
- Current atopic or contact dermatitis, psoriasis, erythema nodosum, urticaria
- Current treatment with corticosteroids, cytotoxic or immunosuppressive drugs
- Immunodeficiency disease
- HIV infection
- Previous skin test with coccidioidin
- Pregnant or lactating**
- Adverse reaction to thimerosal
- Adverse reaction to *Candida* or *Trichophyton* skin test antigen

***Active Medical Disease:** Any active physical or psychiatric condition that may increase the risks associated with participation in the study or interferes with the interpretation of study results. Included chronic medical illnesses are cardiovascular disease, renal insufficiency, chronic respiratory illness, cirrhosis, chronic hepatitis, chronic pancreatitis, chronic diarrhea, malnutrition, malignancy, autoimmune disease, and asthma.

** **Pregnancy Prevention:** Females were instructed to abstain from sexual relations or practice a medically acceptable form of birth control during the study. They were also instructed that, except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or a cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy.

Removal of Subjects from the Study

Participant Initiated: Volunteers were allowed to withdraw from the study at any time without prejudice or loss of benefits to which they were entitled.

Investigator Initiated: Volunteers could be removed from the study at any time by the principal investigator if they failed to meet all inclusion criteria or if their continued participation was judged to be injurious to their health and well being.

8.4.5 Products mandated by the protocol

Each subject received an intradermal injection of the study product, *Coccidioidin SD*, Trichophyton skin test antigen, Candin skin test antigen and the negative controls of placebo --(b)(4)-- saline) and 1:1,000,000 thimerosal.

Table 10. Study S104-3: Skin Test Reagents (Blair, NE)

Reagent	Color	Code	Purpose
Coccidioidin SD (1.27µg/0.1mL) Lot # XSN04220301	Green	4101	Evaluate DTH response in subjects with a history of pulmonary histoplasmosis
Thimerosal Control Lot # ----- (b)(4) -----	Red	6849	Evaluate DTH response to residual thimerosal(1:1,000,000) in Coccidioidin SD from Thimerosal Positive Control
Placebo Control Lot # XDf06020301	Black	3546	Evaluate DTH responses to ingredients in the --(b)(4)-- saline solution used to prepare Coccidioidin SD
Candin Lot # CA033	Blue	1287	Evaluate subject's ability to elicit a positive DTH response
Trichophyton Extract Lot # XMm11080401	Yellow	5461	Evaluate subject's ability to elicit a positive DTH response

Source: Study 104-3, section 8.4.2, page 11/21.

8.4.6 Endpoints (how measured, appropriateness)

The endpoints of the study are not clearly elucidated by the Sponsor as such. The outcome monitored was the induration response for each skin test agent at 48 hours following placement. Safety (local and systemic adverse events) were monitored by diary card. No information is provided on the length of monitoring, the parameters for assessment, or grading scale of events.

8.4.7 Surveillance

“Efficacy”: measured by recording induration at the skin test site after 48 hours. The induration response was outlined with a black ballpoint pen and a permanent record was made by overlaying the tracing with transparent tape and placing the tape on the skin test record. The longest and orthogonal diameters of the tracing were measured in mm. Reactions ≥ 5 mm were considered to be a positive skin test.

“Safety”: measured by reporting local and systemic reactions that occurred after skin tests were administered. A diary of adverse events was completed for the duration of the study.

8.4.8 Statistical considerations

The Fisher's Exact Test was used to calculate the 95% two-sided confidence limits for the specificity of *Coccidioidin SD*.

8.4.9 Results for Study S104-3

8.4.9.1 Populations enrolled/analyzed

Thirteen of the original 25 subjects in the group diagnosed with Histoplasmosis in 2004 consented to participate in the study. Twelve subjects qualified for enrollment.

Twelve subjects were enrolled, all Caucasian adults, 33 to 60 years of age. Five females and 7 males.

8.4.9.2 Efficacy endpoints/outcomes

Skin test responses were measured for induration at 48 hours after administration.

Table 11. Study S104-3: Induration \geq 5mm at 48 hours Following Administration for All Skin Test Reagents

Negatives Controls		Positive Controls		Study product
Placebo	Thimerosal	Candin	Trichophyton	<i>Coccidioidin SD</i>
0/12	0/12	11/12	6/12	0/12

Source: Table entitled "Induration \geq mm at 48 hours to Skin Test Reagents", section 10.4.1, page 14/21.

All subjects enrolled were negative to *Coccidioidin SD* skin test for past exposure to *C. immitis*.

The Applicant states that the "sensitivity" is 100% (CI 73.5, 100). This study was not designed to assess sensitivity or specificity. Please see statistical review for discussion.

There were no induration responses to the negative controls, thimerosal diluent and --(b)(4)-- saline, thus all results are valid.

8.4.9.3 Safety outcomes

Local adverse events included mild to moderate itching, swelling, and pain at the site of positive skin tests. The Applicant does not provide information on the which skin test elicited the local adverse reactions that were documented at 48 hours following placement of the study products. No reactions are documented for the negative test sites associated with administration of the study product. No local adverse events were documented for *Coccidioidin SD*. Subject -(b)(6)- experienced a single episode of chest tightness and wheezing lasting approximately 15 minutes on the day following skin testing. These symptoms were resolved with a single dose of Albuterol. This subject had a 30 x 30 mm DTH response to Candin; all other skin tests were negative. Subject -(b)(6)- experienced nausea without vomiting, diarrhea, fever or chills the evening following skin testing. This person had a positive DTH skin tests to Candin; all other skin tests were negative. A summary of the adverse events that were observed in this trial are shown below.

Table 12. Study S104-3: Summary of Adverse Events following administration of Skin Test Reagents #

Adverse Event	<u>Mild</u> (barely noticeable, not bothersome)	<u>Moderate</u> (definitely noticeable, discomfort)	<u>Severe</u> (needs medical attention)
<u>Local</u>			
Itching	6	2	Ø
Swelling	7	2	Ø
Pain	1	Ø	Ø
Necrosis (ulceration)	Ø	Ø	Ø
<u>Systemic</u>			
Increased heart rate	Ø	Ø	Ø
Weakness	Ø	Ø	Ø
Faintness	Ø	Ø	Ø
Dizziness	Ø	Ø	Ø
Nausea/ cramps	1	Ø	Ø
Flu-like symptoms	Ø	1	Ø
Difficulty breathing shortness of breath	1	Ø	Ø

Source: Study S104-3, section 11.2.1, page 16/21.

Adverse events documented at 48 +/- 4 hours after skin test placement.

The number of subjects reporting adverse events is not provided in the submission.

Serious Adverse Events

There were no serious adverse events reported during the course of the study.

8.4.10 Comments & Conclusions for Study S104-3

In this small study enrolling 12 subjects with a documented previous case of pulmonary histoplasmosis, there appears to be no cross reaction between *C. immitis* and *H. capsulatum* for the skin test antigen. All skin tests with *Coccidioidin SD* were negative (< 5mm induration). No local adverse events were seen for *Coccidioidin SD*.

The following general comments are for communication to the Applicant regarding the studies submitted to the license application:

- In letters dated 21 June 2004 and 18 November 2004, CBER requested that you specify the proposed clinical indication which would be supported by the studies which you have now completed. We did not receive a response to this inquiry. The proposed indication presented in your BLA submission of detection of delayed type hypersensitivity following exposure to *C. immitis* may be relevant within a clinical setting, but further information is required to make this determination. Without evidence of how the product will be used in a clinical setting we are unable to assess the risks and/or benefits of the use of this product. Please present in your response, data to support the clinical use of your product. If this information is not available or is not sufficient to support an indication for this product, further discussion and clinical studies may be necessary.

- In each of the studies presented in the application, please indicate the dose administered of each of the skin test antigens, Candin and Trichophyton and the negative controls, --(b)(4)-- saline and thimerosal diluent.
- 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.

An overview sections to be completed upon receipt of information in response to the CR letter.

9 Overview of Sensitivity and Specificity Across Trials

9.1 Indication

9.1.1 Methods

9.1.2 General Discussion of Efficacy Endpoints

9.1.3 Study Design

9.1.4 Efficacy Findings

9.1.5 Efficacy Conclusions

10 Overview of Safety Across Trials

10.1 Safety Database - Number of Subjects, Types of Subjects and Extent of Exposure

10.2 Safety Assessment Methods

10.3 Significant/Potentially Significant Events

10.3.1 Deaths

10.3.2 Other Significant/Potentially Significant Events

10.3.3 Dropouts

10.4 Other Safety Findings

10.4.1 ADR Incidence Tables (Local & Systemic Events)

10.4.2 Laboratory Findings, Vital Signs, ECGs, Special Diagnostic Studies

10.4.3 Product-Demographic Interactions (e.g., Age, Gender, etc.)

10.4.4 Product-Disease Interactions

10.4.5 Product-Product Interactions

10.4.6 Immunogenicity (Therapeutic Proteins) (if relevant)

10.4.7 Carcinogenicity

10.4.8 Withdrawal Phenomena/Abuse Potential (if relevant)

10.4.9 Human Reproduction and Pregnancy Data

10.4.10 Assessment of Effect on Growth (if relevant)

10.4.11 Overdosage Exposure (if relevant)

10.4.12 Post-marketing Exposure

10.5 Safety Conclusions

11 Additional Clinical Issues

11.1 Directions for Use

11.2 Dose Regimens and Administration

11.3 Special Populations

11.4 Pediatrics

Product has been granted Orphan drug status therefore PREA regulations do not apply.

11.5 Other

12 Conclusions – Overall

The materials provided in the original BLA submission are not sufficient to assess the safety of the product, *Coccidioidin SD* for licensure. Safety data, where submitted, are unevaluable in their current presentation. For Study S101A, no safety data are included in the study report. For Study S104-1 the reported local adverse events are not presented in relationship to the product received. Study S104-2 did not include the results of safety monitoring that was pre-specified in the protocol. Insufficient data are included to fully assess the statistical sensitivity or specificity of the product (Please see Statistical review). No information is included regarding the clinical use of the product in any population.

Clinical use(s)

The Applicant has not presented information to support the clinical use of the product in any population. No studies were performed in a general population or in a population with active disease caused by *C. immitis*. From review of the submitted data, the product may be useful as an epidemiological tool, but has not been studied as a diagnostic tool in an acutely ill or convalescing population. Per the U.S. Federal Code, Title 21, Chapter 9, subchapter II, section 321(g) (1) (B), a drug is defined as an article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man. [In this case “drug” refers to all products that are subject to regulation under Title 21]. The materials provided in the original submission are not sufficient to assess the safety of the product, *Coccidioidin, SD* for licensure. Insufficient data is included to fully assess the sensitivity or specificity of the product. No information is included regarding the clinical use of the product in any population.

13 Recommendations

13.1 Approval, Non-approval, Conditions

Recommend that a “Complete Response” letter be sent to the Sponsor requesting data that will allow for the evaluation of safety in already completed studies, to assess sensitivity and specificity of the product and an assessment of clinical use of the product. It may be necessary to complete further clinical studies to ascertain the clinical use for the product. It is not clear at this time what studies might support licensure of the product. The Applicant will need to determine the indication for which the product will be used prior to this determination.

13.2 Recommendation on Postmarketing Actions

None at this time. Please see the Pharmacovigilance reviewer’s review.

13.3 Labeling

Review of the label to be completed after the complete response is returned from the Sponsor. Preliminary review of the submitted label and carton shows many deficiencies.

The submitted label does not include:

- An age range for use of the product
- Information on a dosing regime for clinical use of the product

The Sponsor has included a “Black Box Warning” in the label that should be deleted. Multiple other issues concerning format and included data will be addressed during the review of the complete response.