



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION BLA

BLA/Supplement Number: 125354/0

Product Name: *Coccidioides immitis* Spherule-Derived Skin Test Antigen

Indication(s): For detection of delayed type hypersensitivity to *Coccidioides immitis*

Applicant: Allermed Laboratories, Inc.

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Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES	5
1.3 MAJOR STATISTICAL ISSUES AND FINDINGS	6
2. INTRODUCTION	6
2.1 OVERVIEW	6
2.2 DATA SOURCES	6
3. STATISTICAL EVALUATION	7
3.1 EVALUATION OF EFFICACY	7
3.2 EVALUATION OF SAFETY	23
3.3 GENDER, RACE, AGE AND OTHER SPECIAL/SUBGROUP POPULATIONS	23
4. SUMMARY AND CONCLUSIONS	24
4.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	24
4.2 CONCLUSIONS AND RECOMMENDATIONS	24
APPENDICES (IF NEEDED)	26
DISTRIBUTION LIST.....	27

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The reviewer has the following questions for the applicant:

Study S101A

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

2. In section VII, Data Analysis, you state: “Based on our experience with other skin test antigens, we believe that a 20% variance in the induration response associated with cellular hypersensitivity is indicative of equipotency.” In the same section, you obtained an acceptable range of 17.6 to 26.4 mm by subtracting and adding 4.4 mm (20% of 22 mm) to 22 mm which was considered the corresponding mean response for the dose concentration 1.27 μg from the linear regression. Then using the same data and the SAS MIXED procedure, you fit a mixed linear model. In the same section, you state: “From the ... model, the estimated mean induration for a 1.27 concentration is 22.24mm and the associated 95% confidence interval computed through the MIXED procedure is between 19.383 and 25.091 mm. The 95% confidence limits fall well within the acceptable range of 17.6 and 26.4.” We have the following comments:
 - a. Please provide documentation to support your statement that 20% variance in induration response associated with cellular hypersensitivity is indicative of equipotency for this product.
 - b. You use the same data to determine an acceptable range and to fit the mixed linear model. Please provide data from independent sources to support your claim that the mean induration response corresponding to a dose concentration of 1.27 μg is about 22 mm. Please also provide independent sources to support your proposed acceptable range. For example, these independent sources may be either historical data or information in the published literature.

3. This study was conducted under IND -(b)(4)-. When you submitted the original submission to the IND (received by CBER on December 12, 2001), you included a document titled: “Statistical Protocol for Skin-Test --(b)(4)--- Dose/Response Study” as part of the study protocol. In this document, a detailed analysis plan was provided. We have determined that you did not follow the steps outlined in that document and you did not submit the document to the current BLA. We recommend that you re-analyze your data following the steps outlined in the statistical protocol and submit the results as well as the statistical protocol to the BLA. Furthermore, we consider that the following four subjects should not be included in the analysis:
 - Patient ID -(b)(6)-: Due to results that could not be determined
 - Patient ID --(b)(6)--: These two subjects responded to the placebo, thimerosal, which makes other results uninterpretable since the reactions might be due to the thimerosal in the placebo.
 - Patient (b)(6): Due to the subject having a non-linear response with increasing dose, which does not satisfy the criterion for inclusion in the analysis.
4. In the afore-mentioned statistical protocol, you state: “The mean induration response from the -----(b)(4)-----.” In order for CBER to verify, please submit the -----(b)(4)----- data to the BLA.

Study S104-1

1. In the section of Efficacy Results of the Synopsis (page 7 of 37), you state: “A total of 50 subjects out of 51 valid subjects were skin test positive to *Coccidioidin SD*.” However, in section 10.4.1, Analysis of Efficacy, you provided a table that indicates 52 out of 53 subjects responded to *Coccidioidin SD*. Please revise your report to make your results consistent or explain explicitly why the number of subjects varies.
2. In section 10.4.2 Statistical/Analytical Issues, you indicated that 25 subjects were treated with antifungal medication and 26 were not treated. However, in the dataset, Untreated.xpt, only 22 subjects were found. Please submit the complete dataset for the untreated subjects to the BLA or provide a rationale for this missing data.
3. In section 11, Safety Evaluation, you provided a summary table of the adverse events (AEs) that occurred during this study. In Table 12.1.2, you provided the individual data for adverse events in terms of event score and duration. The durations of AEs were expressed as categories A = 0-48 hours, B = 48-72 hours, C => 72 hours, and D = Occurred mid-study. This data presentation does not provide detailed information as to when an AE started, stopped, and how it was resolved. Please provide detailed safety data in electronic format.

Study S104-2

1. In section 10.4.1, Analysis of Efficacy (page 15 of 31), you state: “Negative DTH skin tests to *Coccidioidin SD* in 58 of 59 study subjects ...” However, in this study report no statistical testing results are included or reported. Please revise this section so that the statistical hypotheses, summary of the data, the results of the data analysis, and the conclusions obtained from the results are included.
2. In section 11, Safety Evaluation, you provided a summary of the adverse events (AEs). In Table 12.1.1, you provided the individual data on adverse events in terms of event score and duration. The durations of AEs were expressed as categories A = 0-48 hours, B = 48-72 hours, C => 72 hours, and D = Occurred mid-study. This data presentation does not provide detailed information as to when an AE started, stopped, and how it was resolved. Please provide detailed safety data in electronic form.

Study S104-3

1. In the section of Statistical Methods in the Synopsis (Page 6 of 21), you reported “Observed Specificity” as 100%. Then in section 10.4.1, Analysis of Efficacy, you reported “Observed Sensitivity” as 1.000. Since this study was exploratory in nature, the terminologies “sensitivity” or “specificity” are not applicable. Please revise your report to include your findings in the form of proportions and corresponding 95% confidence intervals of subjects who had induration response ≥ 5 mm for each of the 5 skin test reagents.
2. In section 11, Safety Evaluation, you provided a summary of the adverse events (AEs). In Table 12.1.1, you provided the individual data on adverse events in terms of event score and duration. The durations of AEs were expressed as categories A = 0-48 hours, B = 48-72 hours, C => 72 hours, and D = Occurred mid-study. This data presentation does not provide detailed information as to when an AE started, stopped, and how it was resolved. Please provide detailed safety data in electronic form.

1.2 Brief Overview of Clinical Studies

Four studies are included in this BLA submission:

- Study S101A: “A Dose-Response Study of --(b)(4)--- Skin Test Antigen”
- 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”
- Study S104-2: “Skin Test Specificity of 1.27 μg per 0.1mL Spherule-Derived Coccidioidin in Adult Volunteers Without a History of Pulmonary Coccidioidomycosis Study Report of Phase III Clinical Trial”
- Study S104-3: “Skin Test Specificity of 1.27 μg per 0.1mL Spherule-Derived Coccidioidin in Adult Volunteers With a History of Pulmonary Histoplasmosis”

1.3 Major Statistical Issues and Findings

1. In the dose response study, the applicant used the same data to fit a statistical model and to verify the results. It is standard practice to fit a model using one set of data, and then verify its validity by applying it to a different set of data. Moreover, the analysis was not performed according to the procedures outlined in a statistical analysis plan submitted to the IND before the study was conducted. Analyses that deviate from those pre-specified in the statistical analysis plan are generally reviewed as exploratory rather than confirmatory.
2. The synopsis and the comprehensive study report contained conflicting information so that the sensitivity and specificity cannot be established until further clarification from the applicant is obtained.

2. INTRODUCTION

2.1 Overview

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

------(b)(4)----- In this submission, four study results are included to support the dose choice, the sensitivity, the specificity, and the cross-reaction of Spherule-Derived Coccidioidin in adults with a history of pulmonary histoplasmosis.

2.2 Data Sources

The BLA submission is stored in the CBER Electronic Document Room (EDR). This review covered the following sections:

- Section 3 – Summary
- Section 8 – Clinical
- Section 9 – Statistical

The original paper submission of IND -(b)(4)- is considered and included in this review because the statistical analysis plan for study S101A was included in IND -(b)(4)- submitted Dec. 12, 2001 but is not included in the BLA submission.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study S101A

Study S101A: “A Dose-Response Study of --(b)(4)--- Skin Test Antigen”

Introduction

This study was conducted to identify an appropriate dose of --(b)(4)--- as a skin test antigen in persons who have had coccidioidomycosis. -----(b)(4)-----

----- The dose-response study reported in this submission was designed to evaluate the cellular hypersensitivity response to four doses of -----(b)(4)-----

Study Cohort

Twenty adults between the ages of 22 and 54 were enrolled in the study. The mean age was 36. The group consisted of 8 males and 12 females.

Study Drug

The study was designed to evaluate the 48 hour skin test response to a Placebo Control and four different strengths of ---(b)(4)--. The materials used were:

1. Placebo Control: Diluent used to prepare --(b)(4)--- contains 0.4% phenol and thimerosal at the same concentration as the residual thimerosal in 2.4 µg/0.1 mL --(b)(4)---.
2. --(b)(4)--- 0.4 µg/0.1 mL with 0.4% phenol
3. --(b)(4)--- 0.8 µg/0.1 mL with 0.4% phenol
4. --(b)(4)--- 1.6 µg/0.1 mL with 0.4% phenol
5. --(b)(4)--- 2.4 µg/0.1 mL with 0.4% phenol (*)
(*) Note: Highest dose discontinued after 6 subjects

Study Deviations

Following the first day of testing on 06/04/02, two subjects had accelerated responses to the 2.4 µg dose of --(b)(4)---. The study was stopped and the results were reported to the Institutional Review Board (IRB), and MedWatch and were discussed with members of the CBER IND Review Committee. In conjunction with the IND committee, the decision

was made to delete the 2.4 µg dose from the protocol and continue the study with the Placebo Control and the 0.4 µg, 0.8 µg, and 1.6 µg doses of --(b)(4)---. Skin testing recommenced on 07/16/02 following the modified protocol and was completed on 01/14/03.

Adverse Reactions

Two subjects -(b)(6)- had accelerated reactions to the skin test antigen. Subject -(b)(6)- had large local reactions that were difficult to read. Subject -(b)(6)- showed a 50 x 55 mm response to the highest dose (2.4 µg) which, by itself, would not be considered an adverse reaction.

Since this response was observed at the same time that the larger reactions that developed in Subject -(b)(6)- were observed, it was considered prudent to report this finding to the IRB and IND ultimately leading to the removal of the highest dose. The 18 remaining subjects responded to the antigen in a predictable manner and did not experience unnecessarily large reactions or adverse outcomes to the remaining 3 dose levels.

Results

Cellular hypersensitivity reactions at 48 hours to the --(b)(4)--- doses and the Placebo Control for 19 Subjects -(b)(6)- are summarized in Table 3. Ink tracings of the reactions are reported in the Appendix, Section 3. Data for Subject -(b)(6)- are omitted from the table for reasons discussed above under adverse reactions. The dose-response curve for the cohort is shown in Figure 1. Data points for the 2.4 µg dose are shown for Subjects -(b)(6)- only. These Subjects were skin tested before the decision was made to delete this dose from the study protocol. Data for the 2.4 µg dose were not used to develop the dose-response curve shown in Figure 1. Two Subjects -(b)(6)- did not react to the lowest dose of 0.4 µg and one Subject -(b)(6)- failed to respond to the 0.6 µg dose, but reacted to the lesser dose of 0.4 µg. Two Subjects -(b)(6)- reacted to the Placebo Control.

Data Analysis

The applicant developed the dose-response curve for --(b)(4)--- through the following steps:

- 1) The mean response at each dose was calculated and plotted against the dose concentration
- 2) The 2.4 µg dose was excluded from the curve because a complete data set was not available for this dose
- 3) The dose-response curve was obtained through the method of linear regression of the mean sizes of the induration responses
- 4) A dose of 1.27 µg corresponded to a mean response of 22 mm.

The applicant believed that a 20% variance in the induration response associated with cellular hypersensitivity is indicative of equipotency. Since 20% of 22 mm is 4.4 mm, the applicant believed that a mean induration response within the range of 17.6 and 26.4 mm is an acceptable range.

Then the applicant built a mixed linear model using the MIXED procedure in SAS, with concentration treated as fixed effects (0.4, 0.8, and 1.6) and subjects treated as random effects (19 total subjects) to obtain a linear equation. The equation was incorrectly stated in section VII, but was corrected in a later section titled “Verification of --(b)(4)--- Dose-Response Study Results.” The equation is expressed as:

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

The applicant then stated:

“From the above model, the estimated mean induration for a 1.27 concentration is 22.24 mm and the associated 95% confidence interval computed in SAS through the MIXED procedure is between 19.383 and 25.091 mm. Thus, we are 95% sure that the true mean induration produced by a 1.27 concentration of --(b)(4)--- is between 19.383 and 25.091. The 95% confidence limits fall well within the acceptable range of 17.6 and 26.4.”

The applicant concluded that the results of this dose-response study support the continued use of 1.27 µg/0.1mL as the appropriate dose for this product.

Note

This BLA was based on trials conducted under IND -(b)(4)-. In the original submission for this IND (Received on December 12, 2001), the study protocol had two parts for this study. The first part described the study design and conduct. The second part was titled: “Statistical Protocol for Skin-Test --(b)(4)--- Dose/Response Study” which may be considered as Statistical Analysis Plan (SAP).

The major contents of the SAP are summarized below:

- The *induration* of an injection area is the mean of the long and short axes of the reaction area surrounding the injection site.
- The mean induration response from the -----(b)(4)----- data was -(b)(4)- mm. Thus, 24 mm will be set as the target mean response.
- A 20% variance in DTH response is customarily considered to be indicative of equipotency of skin-test antigen. Therefore, a range for the target response was set to be between 19 mm and 29 mm.
- The *relative potency* is defined as the ratio of the induration elicited at a particular concentration and the reference mean of 24 mm. Therefore, the relative potency for a subject is the induration at the injection site divided by 24 mm. The *mean relative potency* is defined to be the ratio of the true mean indurations.

- Twenty eligible subjects each will receive 5 0.1 ml skin test injections with four different concentrations of antigen, at 0.4, 0.8, 1.6, 2.4 mcg/0.1ml and a placebo consisting of antigen diluent containing 0.4% phenol and thimerosal equal to the residual thimerosal present in the highest concentration of (b)(4) (2.4 mcg). Each injection will be randomly assigned to one of five injection locations and double-blinded.
- At 48 hours after injection, recordings of the long and short axes, in millimeters, will be taken from each of the five injection sites.
- Induration will be computed for each injection site and each subject.
- Only those subjects who are categorized as linear responders, i.e., subject's induration reaction must tend to increase linearly as the concentration increases, will be included in the analysis.
- A simple linear regression model (after adjusting for the within-subject variability using a mixed linear model approach) will be established between the relative potencies (RP) or natural-log of the relative potencies (lnRP) and the (b)(4) concentrations, 0.4, 0.8, 1.6, 2.4 mcg/0.1ml. Treat $y \equiv \ln RP$ as the dependent/response variable with concentration as the independent variable, x , and let \hat{y}_{ij} represent the fitted value for the i th concentration ($i=1,2,3,4$) and the j th subject ($j=1, \dots, 20$). Then the following represents the fitted linear model average over individuals:

$$\hat{y}^* = a + bx,$$

where a and b represent the intercept and slope of the fitted regression line, after adjusting for individual effects. This model represents the dose/response model for a general x contained in the interval $[0.4, 2.4]$.

- The estimated concentration, value of $x = x_0$, at which the average relative potency is equal to 1 yielding a $\ln RP = 0$ ($\bar{y} = 0$), i.e., (b)(4) formulation concentration which gives a mean-induration of approximately 24 mm, x_0 given

as,

$$x_0 = \frac{0 - a}{b} = \frac{-a}{b},$$

resulting from setting the previous equation equal to zero and solving for x .

Reviewer's comments:

- *Several issues were found in the current data analysis and they are listed in the Executive Summary (on pages 3-6) as part of the Complete Response (CR) letter to the applicant.*
- *The statistical analysis plan (SAP) for this study was included in the original submission to the IND (IND (b)(4)-) but is not included in the BLA submission. Furthermore, the applicant did not follow the steps in the SAP in analyzing the data. The reviewer would like the applicant to re-analyze the data by following the steps in the SAP.*

- Detailed questions to the applicant can be found in the Executive Summary section.

3.1.2 Study S104-1

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*”

Objective

This study was conducted to evaluate the Delayed-type Hypersensitivity (DTH) skin test response to *Coccidioidin SD* in persons with a history of pulmonary *coccidioidomycosis* confirmed by laboratory findings.

Study Design and Endpoints

Eligible participants were skin tested on Visit#1 with five reagents in a blinded, randomized manner and asked to complete a diary of adverse events (AEs) for the next 48 hours. The results of skin tests were read after 48 hours (± 4 hours) on Visit#2.

Subjects were asked to continue to keep a diary to monitor AEs until they returned to the physician’s office one week later. Vital signs were measured during each visit.

Table 3.1 The skin test reagents used on each subject.

Reagent	Color	Code	Purpose
<i>Coccidioidin SD</i> (1.27 µg/0.1mL) Lot # XSN04220301	Green	4101	Evaluate DTH response in subjects with a history of pulmonary <i>coccidioidomycosis</i>
Thimerosal Control Lot # ------(b)(4)-----	Red	6849	Evaluate DTH response to residual thimerosal (1:1,000,000) in <i>Coccidioidin SD</i> from -----(b)(4)----- -----
Placebo Control Lot # XDf06020301	Black	3546	Evaluate DTH response 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
Thichophyton Extract Lot # Mm11080401	Yellow	5461	Evaluate subject’s ability to elicit a positive DTH response

Blinding

The five skin test reagents that were used in the study were color coded. Each reagent was assigned a clinical code (lot) to ensure the identity of the article. This code was different from the lot number. Neither the investigational staff nor study subjects were aware of the contents of reagent containers (vials).

Measurements

Efficacy

Efficacy 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.

Safety

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.

Patient Disposition, Demographic and Baseline Characteristics

This study has two sites: Tucson, AZ and Bakersfield, CA.

Forty three subjects signed informed consent documents at the Tucson site; one subject did not qualify. Thirteen subjects signed informed consent documents at the Bakersfield site; one subject did not qualify. The one subject at Bakersfield forgot to return for skin test readings at 48 hours and this subject was excluded from the analysis of the results. Total of fifty three subjects completed the study and fifty one subjects had valid data.

Volunteers included thirty eight males and fifteen females. Ages ranged from 23 to 64. Thirty-seven (37) subjects were Caucasian, six (6) Hispanic, six (6) African-American, one (1) Asian, one (1) Native American and two (2) subjects did not specify ethnicity.

The inclusion and exclusion criteria were provided in the protocol. However, due to the lack of available participants, two criteria were amended:

- the age range changed from 18-60 years of age to 18-65 years of age
- to allow persons receiving antifungal treatment for the disease were allowed to enroll in the study

Statistical Methodologies

Product sensitivity was analyzed by the Fisher’s Exact Test. The 95% two-sided confidence limits were calculated for product sensitivity. The *Student’s t-test* was used to compare the means of the induration response to *Coccidioidin SD* in persons who were not treated with the antifungals versus persons who received antifungal therapy.

Results and Conclusions

Table 3.2 Induration ≥ 5mm at 48 hours to Skin Test Articles

Negative Controls		Positive Controls		Product
Placebo Control	Thimerosal Control	<i>Candin</i>	Trichophyton	<i>Coccidioidin SD</i>
2/53	1/53	45/53	46/53	52/53

Coccidioidin SD elicited positive skin tests in 98% of study volunteers. The two Negative Controls (Placebo Control and Thimerosal Control) did not elicit positive DTH reactions in over 95% of subjects. Subject (---(b)(6)---) at the Bakersfield site had a 8.0mm response to the Placebo Control and a 10.5mm response to the Thimerosal Control. However, this subject had large reactions to all other skin test reagents which could indicate a high degree of skin sensitivity to any intradermally injected substance. Subject (--(b)(6)--) at Tucson had a 7mm induration response to the Placebo Control. Reactions < 5mm (3-4mm) to the Placebo Control were observed in two subjects in the Bakersfield cohort. Although thimerosal (at a concentration of 1 part in 10,000) is known to elicit DTH-like reactions, the residual thimerosal in *Coccidioidin SD* (1 part in 1,000,000) did not cause a DTH-like response in most individuals. The single 10.5mm reaction observed at Bakersfield is similar to the 8.0mm response to the Saline Placebo Control observed in the same volunteer. Subjects -----(b)(6)----- were excluded in the analysis of sensitivity to *Coccidioidin SD*.

Positive skin tests to *Candin* and *Trichophyton Extract* were observed in approximately 85% of subjects. The mean size and range of the DTH response to these antigens compared to *Coccidioidin SD* are shown in the table below:

Table 3.3 DTH Response to Positive Controls and to *Coccidioidin SD*

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

Several large reactions to *Trichophyton Extract* (42.0, 51.0, 55.0, 71.0mm) were primarily responsible for the higher mean response to this antigen. The mean response to *Coccidioidin SD* was 17.0mm, which the applicant considered acceptable for a DTH

antigen for the following reasons: (1) induration of 17.0mm is easy to interpret as a positive DTH response, and (2) a 17.0mm response usually does not result in vesiculation or necrosis.

Statistical/Analytical Issues

At the time the protocol was amended to include volunteers who were receiving treatment with antifungal medication, the FDA asked Allarmed to provide a separate analysis of the data obtained from treated versus non-treated subjects. With the exception of subject (-)(b)(6)-, who had a negative DTH skin test to Coccidioidin SD (4.0mm) and who had received treatment with isoniazide in 1999, all other subjects were DTH positive to Coccidioidin SD, regardless of treatment history.

Treated subjects were from Tucson, AZ and Bakersfield, CA. Subjects who did not receive treatment were from Tucson, AZ only. Two subjects, one from Tucson, AZ and one from Bakersfield, CA were disqualified from the analysis, because both subjects had > 5mm induration to the Negative Controls.

To evaluate the potential effects of treatment with antifungal agents, subjects who had received treatment were divided into two groups based on the length of time that had elapsed between treatment and skin testing with Coccidioidin SD. A cut-off period of approximately 6 months prior to skin testing was used to separate the groups.

Group 1: Subjects who received treatment with antifungal medication after January 2006. This date covered the time period approximately 6 months prior to the start of the study and during the course of the study. The influence of antifungal drugs might be expected to be most pronounced on the DTH skin test response during this time period.

Group 2: Subjects who received treatment with antifungal medication before January 2006.

Table 3.4 depicts the summary statistics of the responses for the treated and un-treated group submitted by the sponsor.

Table 3.4 Summary statistics of the responses for the treated group and un-treated group.

N	Treated Subjects	Not Treated Subjects
N	25	26
Mean	19.32	14.15
SD	10.42	7.87
Median	16.50	10.75
Min	4.00	5.00
Max	39.50	35.00

In the applicant provided dataset (Untreated.xpt), there are only 22 subjects included in the data file for the un-treated group, therefore, the results included in the submission cannot be verified.

Applicant’s Efficacy Conclusions

In the BLA submission, the applicant states: “*Coccidioidin SD* elicited a positive DTH skin test response in 98% of persons with a history of pulmonary coccidioidomycosis confirmed by laboratory findings. As a skin test antigen, *Coccidioidin SD* exhibits a high degree of efficacy in detecting sensitivity to *C.immitis*.”

Note

The following statements are copied directly from the synopsis section of this study report. This information is not included in the main report:

“Statistical Methods: The trial was designed to show that the population sensitivity to Coccidioidin SD is greater than 80%, i.e. the null and alternative hypotheses were:

$$H_0: \text{Sensitivity} \geq 0.80 \quad \text{vs.} \quad H_A: \text{Sensitivity} < 0.80$$

Sensitivity is defined as the proportion of persons in a population with a history of pulmonary coccidioidomycosis who would test DTH positive with Coccidioidin SD if tested using the procedure given in this protocol. In this study the two participating sites within coccidioidomycosis endemic regions were Bakersfield, CA and Tucson, AZ. To confirm if sensitivity is at least 80%, the 95% two-sided Confidence Limits (CL) were calculated using the Fisher’s Exact Test.

Efficacy results: The results of intradermal skin tests with the study reagents are tabulated below:

	Bakersfield	Tucson	Desired Outcome
Coccidioidin SD	11/11	41/42	Positive
Positive Congtrolls:			
Candin	10/11	31/42	Positive
Trichophyton	11/11	31/42	Positive
Negative Controls:			
Trimerosal	1/11	0/42	Negative
Placebo	1/11	1/42	Negative

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

Sensitivity of Coccidioidin SD

Sites	Total Tests	Invalid Tests	Total Valid Subjects	Valid Tests	
				Coccidioidin SD Positive	Coccidioidin SD Negative
Bakerfield, CA	11	1	10	10	0
Tucson, AZ	42	1	41	40	1
Total	53	2	51	50	1

A total of 50 subjects out of 51 valid subjects were skin test positive to Coccidioidin SD. The 95% two-sided confidence limits for the sensitivity are shown in the following table:

Site	Valid Tests	Positive Tests	Observed Sensitivity	95% Confidence Limits	
				Lower Limit	Upper Limit
Bakerfield/ Tucson	51	50	0.980	0.896	1.000

Summary – conclusions

Fifty subjects with valid test results reacted to Coccidioidin SD with a positive DTH response (induration ≥ 5 mm). Positive DTH tests also were observed to one or both positive controls in two subjects. However, the two negative controls failed to elicit a positive DTH response in over 95% of subjects. The data obtained from this study support the following conclusions:

1. The observed sensitivity to Coccidioidin SD is greater than 95%. It can be said with 95% confidence that the two-sided lower confidence level is greater than 89% in persons with a history of pulmonary coccidioidomycosis.
2. Positive DTH skin tests to Coccidioidin SD and the two positive controls confirmed the immunocompetency of study volunteers.
3. Negative DTH skin tests to the Thimerosal and Placebo Controls in 98% of subjects demonstrated the absence of skin reactive substances in the diluent used to prepare Coccidioidin SD. Based on these findings, the occurrence of false-positive skin tests from product excipients is approximately 2%.”

Amendment:

In Study S104-1, the trial was designed to show that the population sensitivity to Coccidioidin SD is greater than 80%, i.e. the null and alternative hypotheses were:

$$H_0: \text{Sensitivity} < 0.80 \quad \text{vs.} \quad H_A: \text{Sensitivity} \geq 0.80$$

Since 50 subjects out of 51 valid subjects were skin test positive to Coccidioidin SD, the

95% two-sided confidence limits for sensitivity are (0.896, 1.000). Since the lower limit of this confidence interval is greater than 0.8, the null hypothesis is rejected in favor of the alternative that the sensitivity is $\geq 80\%$.

Reviewer's Comment:

- *In the Synopsis, applicant reported that 50 out of 51 subjects had positive response to Coccidioidin SD. However, in the main report, the applicant reported 52 out of 53 subjects had positive response.*
- *The applicant reported 26 subjects who did not receive any antifungal medication. However, only data for 22 subjects were found in the dataset (untreated.xpt) submitted to the BLA.*
- *Detailed questions to the applicant related to this study can be found in the Executive Summary section.*

3.1.3 Study S104-2

Study S104-2: “Skin Test Specificity of 1.27 μ g per 0.1mL Spherule-Derived Coccidioidin in Adult Volunteers Without a History of Pulmonary Coccidioidomycosis Study Report of Phase III Clinical Trial”

Objective

This study was conducted 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*.

Study design

Subjects were screened prior to skin testing, which included a medical history questionnaire, informed consent, measurement of vital signs, pregnancy test (female), serologic evaluation for *C.immitis* and a residential and travel history. Eligible participants were skin tested on Visit# 1 with five reagents simultaneously in a blinded, randomized manner and asked to complete a diary of adverse events for the next 48 hours. The results of skin tests were read after 48 hours (± 4 hours) on Visit# 2. Subjects were asked to continue to keep a diary to monitor adverse events until they returned to the physician's office one week later. Vital signs were measured during each visit.

All female study participants were required to show medical documentation of surgical sterilization or take a urine pregnancy test within 24 hours before skin testing. All participants had a 10mL blood sample taken for serological analysis for *C.immitis* antibodies using the ELISA, Immunodiffusion, and Complement Fixation Methods. Serologic tests for *C.immitis* antibodies were performed by the -----(b)(4)-----

------(b)(4)----- . Persons who were skin test negative to all skin test reagents were tested for possible immunodeficiency by performing a lymphocyte subset analysis. This assay was performed by -----(b)(4)-----.

Each volunteer received one intradermal injection of each of five investigational products as those in study S104-1.

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.

The results obtained for the 60 subjects were analyzed as a single data set. One subject had invalid test results and was not included in the analysis of specificity.

Volunteers included twenty-two (22) males and thirty-eight (38) females. Ages ranged from 18 to 56 years. 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.

Results

Table 3.7 Induration \geq 5 mm at 48 hours to skin test articles

Negative Controls		Positive Controls		Product
Placebo Control	Thimerosal Control	<i>Candin</i>	Trichophyton	<i>Coccidioidin SD</i>
0/60	1/60	52/60	8/60	1/60

The Thimerosal Control elicited a 5mm response in one subject (-(b)(6)-) which was considered to be a positive test. Therefore, the individual was excluded from the specificity analysis of Coccidioidin SD. The residual thimerosal in Coccidioidin SD, 1 part in 1,000,000, did not cause a DTH-like response in over 98% of individuals.

The applicant concluded that positive skin tests to the Positive Controls (Candin and Trichophyton Extract) confirmed that study participants were capable of mounting a DTH response to one or both of these substances and, therefore, capable of responding to other antigen substances if sensitivity to the substance were present.

The applicant interpreted the results as the following (Page 15 of 31 of the S104-2-S- Study Reprint of the BLA submission):

“Negative DTH skin tests to Coccidioidin SD in 58 of 59 study subjects with valid test results demonstrated that the product does not evoke induration in persons who lack cellular hypersensitivity to *C.immitis*. The 5mm response observed to Coccidioidin SD in one subject (-(b)(6)-) could have been a non-specific response to the injection, or it is possible that the subject had been sensitized to *C.immitis*, since he had travel on a limited basis in AZ and CA.”

Applicant’s Efficacy Conclusions

The applicant provided the following summary and conclusion based on study S104-2: “Coccidioidin SD at a concentration of 1.27µg/0.1mL did not elicit positive DTH skin test reactions in over 98% of adult volunteers who: (1) lived in a non-endemic area for *C.immitis*, (2) had limited exposure to *C.immitis* from travel to endemic areas, (3) were serologically negative to *C.immitis* as determined by ELISA, Immunodiffusion and Complement Fixation Assays, and (4) had no history of pulmonary coccidioidomycosis. These findings support the specificity of the product in terms of its non-reactivity in non-sensitized individuals.”

Note

The following statements were from the synopsis section of this study report, but not in the main report body:

“Statistical Methods: The trial was designed to show that the population specificity to Coccidioidin SD is at least 85%, i.e. the null and alternative hypotheses were: H0: Specificity \geq 0.85 vs. HA: Specificity $<$ 0.85 Specificity was defined as the proportion of persons in the population without previous exposure to *C.immitis* who would test DTH negative with Coccidioidin SD if tested using the procedure given in this protocol. To confirm if specificity is at least 85%, the 95% two-sided confidence limits (CL) were calculated using the Fisher’s Exact Test. The results of the statistical analysis are summarized below:

Table: Specificity of Coccidioidin SD

Site	Total Tested	Invalid Tests	Total Valid Subjects	Valid Tests	
				Coccidioidin SD Positive	Coccidioidin SD Negative
Spokane, WA	60	1	59	1	58

A total of 58 subjects out of 59 valid subjects were skin test negative to Coccidioidin SD. The 95% two-sided confidence limits for specificity are shown in the following table:

Site	Valid Tests	Negative Tests	Observed Specificity	95% Confidence Limits	
				Lower Limit	Upper Limit
Spokane, WA	59	58	0.983	0.909	1.000

The observed specificity was 98.3%. Since only the lower limit is of interest it can be said with 97.5% confidence that the specificity is at least 90%. (See SAS Datasets Table 12.1.1 (S) DTH Spokane.xpt)

Efficacy Results: Coccidioidin SD did not elicit a positive DTH skin test in 58 of 59 naïve volunteers 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. A second subject (-(b)(6)-) showed an induration response of 4.5mm which was reported as negative. The Placebo Control (diluent, to which the *C.immitis* antigen is added) 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 subjects with valid tests that were included in the analysis of specificity to Coccidioidin SD.

Safety Results: No serious, expected or unexpected, local or systemic

SUMMARY – CONCLUSIONS

Sixty adults without prior exposure to *C.immitis* were skin tested with Coccidioidin SD concurrently with positive and negative control reagents. Fifty-nine subjects had valid test results. Fifty-eight subjects were skin test negative (< 5mm induration) to Coccidioidin SD. Only one subject reacted with a minimal 5mm response to the antigen. These data demonstrate that Coccidioidin SD does not elicit positive DTH skin reactions in over 98% of persons who have not been sensitized to *C.immitis*.

The absence of positive DTH skin tests to Coccidioidin SD in over 98% of adult volunteers without a history of exposure to *C.immitis* demonstrates that the antigen does not elicit a positive skin test response in naïve individuals. In addition, no serious adverse events occurred in study subjects which demonstrated that the product can be safely used as a DTH skin test antigen in a naïve population without previous exposure to *C.immitis*. The local and systemic adverse events that were reported were due to DTH control antigens, rather than Coccidioidin SD.”

Reviewer’s Comment:

The applicant reported that 1 of 60 subjects tested positive for Coccidioidin SD. However, in the synopsis, the applicant reported that 1 invalid test resulted in 58 of 59 subjects testing negative. A question to the applicant regarding this inconsistency can be found in the Executive Summary section.

3.1.4 Study S104-3

Study S104-3: “Skin Test Specificity of 1.27µg per 0.1mL Spherule-Derived Coccidioidin in Adult Volunteers With a History of Pulmonary Histoplasmosis”

Study Objective and Design

This study was conducted to evaluate the DTH skin test response to Coccidioidin SD in persons with a history of pulmonary histoplasmosis.

Subjects were screened prior to skin testing, which included a medical history questionnaire, informed consent document, measurement of vital signs, pregnancy test (female), serologic evaluation for *C.immitis* and *H.capsulatum*, residential and travel history. Eligible participants were skin tested on Visit# 1 with five blinded, randomized reagents and asked to complete a diary of adverse events 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 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 current status of their health.

All female study participants were required to show medical documentation of surgical sterilization or take a urine pregnancy test within 24 hours before skin testing. All participants had a 20mL blood sample taken for serological analysis for *C.immitis* and *H.capsulatum* antibodies using the ELISA, Immunodiffusion, and Complement Fixation Methods.

All members of the study cohort were employees of a -----(b)(4)----- where exposure to *H.capsulatum* occurred. The group consisted of twelve (12) Caucasian adults ranging in age from 33 to 60. Five (5) subjects were female, seven (7) subjects were male.

Table 3.8 Induration \geq 5 mm at 48 hours to skin test reagents

Negative Controls		Positive Controls		Product
Placebo	Thimerosal	Candin	Trichophyton	Coccidioidin SD
0/12	0/12	11/12	6/12	0/12

Table 3.9 The two-sided 95% confidence limits for *Coccidioidin SD* in this population

			95% Confidence Limits	
Histo. Subjects	Negative Tests	Observed Sensitivity	Lower Limit	Upper Limit
12	12	1.000	0.735	1.000

On page 15 of 21 of S104-3-B-Study Report in the BLA submission, the applicant concluded the following:

“The two negative control articles (Placebo Control and Thimerosal Control) did not elicit positive skin tests. Positive skin tests were observed to the Positive Control articles (*Candin* and Trichophyton Extract) which demonstrated that study subjects were capable of mounting a positive DTH response to a skin test antigen. Subjects were not skin test positive to *Coccidioidin SD* which demonstrated the absence of sensitivity to *C.immitis* or cross-reacting components in *Coccidioidin SD*.”

Applicant’s Efficacy Conclusions

Coccidioidin SD at a concentration of 1.27 μ g/0.1mL did not elicit positive DTH skin test reactions in study participants. At this concentration the product did not cross-react in persons with past exposure to *H.capsulatum*.

Note

The following statements were from the synopsis section of this study report but not in the main report body:

“Criteria for Evaluation:

Efficacy: Efficacy of Coccidioidin SD as a diagnostic skin test antigen was based on the outcome of the skin test response. Induration less than 5mm at 48 hours demonstrated product specificity and induration \geq 5mm at 48 hours demonstrated cross-reactivity or the absence of product specificity in the population studied.

Safety: The safety of Coccidioidin SD was based on the absence of local or systemic reactions associated with its use. Local reactions that were monitored included swelling, itching, pain, and necrosis. Systemic responses included flu-like symptoms, increased heart rate, nausea/cramps, fatigue, weakness, faintness, difficulty breathing. Statistical

Methods: The Fisher’s Exact Test was used to calculate the 95% two-sided confidence limits for specificity. These results are shown below:

Statistical Methods: The Fisher’s Exact Test was used to calculate the 95% two-sided confidence limits for specificity. These results are shown below:

Histo. Subjects (n)	Negative Tests	Observed Specificity (%)	Two-sided 95% Lower Confidence Limit (%)
12	12	100	0.735

SUMMARY – CONCLUSIONS Twelve adults with a recent history of pulmonary histoplasmosis were skin tested with Coccidioidin SD. All twelve subjects failed to react to Coccidioidin SD, but were skin test positive to either Candin or Trichophyton Extract which were administered concurrently as positive controls. Coccidioidin SD did not elicit local reactions and systemic adverse events did not occur. It is believed to be safe when used as a skin test antigen in persons with a history of pulmonary histoplasmosis.”

Reviewer’s Comment:

- *The applicant used the term “observed sensitivity” in the main report and “observed specificity” in the synopsis section. Since this is an exploratory study on the cross-reaction of two reagents, these terms are not appropriate to describe the findings in this study.*

3.2 Evaluation of Safety

Reviewer’s Comment:

Safety data were provided in summary tables by the applicant. More details are needed for complete safety evaluation. Questions concerning safety data to the applicant are included in the Executive Summary.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

Due to small sample size for all the studies provided in this BLA submission, no subgroup analysis is performed.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

1. In the dose response study, the applicant used the same data to fit a statistical model and to check its validity. Moreover, the analysis was not performed according to the procedures outlined in a statistical analysis plan submitted to the IND before the study was conducted.
2. The synopsis and the main report body contained conflicting information, so that the determination of sensitivity and specificity of the skin test needs further clarification from the applicant.

4.2 Conclusions and Recommendations

The reviewer has the following questions for the applicant:

Study S101A

1. In this study, you have collected induration response data from 20 subjects, each of whom received 5 different dose concentrations. After eliminating the placebo dose, the highest dose due to incomplete data, and one subject for no data, you plotted the mean induration response of 19 subjects for each of the 3 doses against the dose concentration. In section VII, Data Analysis, you state: “The dose-response curve was analyzed by linear regression and it was determined that a dose of 1.27 μg corresponded to a mean response of 22 mm.” We have the following comments:
 - a. Please provide a rationale for using the mean induration response as the dependent variable. Note that by taking the mean, you have arbitrarily reduced the variation within each dose.
 - b. Please provide a rationale or justification illustrating how you determined that the relationship between induration response and dose is linear.
2. In section VII, Data Analysis, you state: “Based on our experience with other skin test antigens, we believe that a 20% variance in the induration response associated with cellular hypersensitivity is indicative of equipotency.” In the same section, you obtained an acceptable range of 17.6 to 26.4 mm by subtracting and adding 4.4 mm (20% of 22 mm) to 22 mm which was considered the corresponding mean response for the dose concentration 1.27 μg from the linear regression. Then using the same data and the SAS MIXED procedure, you fit a mixed linear model. In the same section, you state: “From the ... model, the estimated mean induration for a 1.27 concentration is 22.24mm and the associated 95% confidence interval computed through the MIXED procedure is between 19.383 and 25.091 mm. The 95% confidence limits fall well within the acceptable range of 17.6 and 26.4.” We have the following comments:

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

Study S104-1

1. In the section of Efficacy Results of the Synopsis (page 7 of 37), you state: “A total of 50 subjects out of 51 valid subjects were skin test positive to *Coccidioidin SD*.” However, in section 10.4.1, Analysis of Efficacy, you provided a table that indicates 52 out of 53 subjects responded to *Coccidioidin SD*. Please revise your report to make your results consistent or explain explicitly why the number of subjects varies.
2. In section 10.4.2 Statistical/Analytical Issues, you indicated that 25 subjects were treated with antifungal medication and 26 were not treated. However, in the dataset, Untreated.xpt, only 22 subjects were found. Please submit the complete dataset for the untreated subjects to the BLA or provide a rationale for this missing data.

3. In section 11, Safety Evaluation, you provided a summary table of the adverse events (AEs) that occurred during this study. In Table 12.1.2, you provided the individual data for adverse events in terms of event score and duration. The durations of AEs were expressed as categories A = 0-48 hours, B = 48-72 hours, C => 72 hours, and D = Occurred mid-study. This data presentation does not provide detailed information as to when an AE started, stopped, and how it was resolved. Please provide detailed safety data in electronic format.

Study S104-2

1. In section 10.4.1, Analysis of Efficacy, (page 15 of 31), you state: “Negative DTH skin tests to *Coccidioidin SD* in 58 of 59 study subjects ...” However, in this study report no statistical testing results are included or reported. Please revise this section so that the statistical hypotheses, summary of the data, the results of the data analysis, and the conclusions obtained from the results are included.
2. In section 11, Safety Evaluation, you provided a summary of the adverse events (AEs). In Table 12.1.1, you provided the individual data on adverse events in terms of event score and duration. The durations of AEs were expressed as categories A = 0-48 hours, B = 48-72 hours, C => 72 hours, and D = Occurred mid-study. This data presentation does not provide detailed information as to when an AE started, stopped, and how it was resolved. Please provide detailed safety data in electronic form.

Study S104-3

1. In the section of Statistical Methods in the Synopsis (Page 6 of 21), you reported “Observed Specificity” as 100%. Then in section 10.4.1, Analysis of Efficacy, you reported “Observed Sensitivity” as 1.000. Since this study was exploratory in nature, the terminologies “sensitivity” or “specificity” are not applicable. Please revise your report to include your findings in the form of proportions and corresponding 95% confidence intervals of subjects who had induration response ≥ 5 mm for each of the 5 skin test reagents.
2. In section 11, Safety Evaluation, you provided a summary of the adverse events (AEs). In Table 12.1.1, you provided the individual data on adverse events in terms of event score and duration. The durations of AEs were expressed as categories A = 0-48 hours, B = 48-72 hours, C => 72 hours, and D = Occurred mid-study. This data presentation does not provide detailed information as to when an AE started, stopped, and how it was resolved. Please provide detailed safety data in electronic form.

APPENDICES (IF NEEDED)

None

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