DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

STATISTICAL REVIEW AND EVALUATION

BLA – ADDENDUM

BLA/Supplement Number: 125354/0

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

Indication(s): For detection of delayed type hypersensitivity to *Coccidioidies immitus*

Applicant: Allermed Laboratories, Inc.

Date(s): Letter Date: May 26, 2009

Action Due Date: July 29, 2011

Review Priority: Standard

Statistical Branch: FDA/CBER/OBE/DB/VEB

Primary Statistical Reviewer: **Jingyee Kou, Ph.D** _____
Mathematical Statistician Date

Concurring Reviewer (1): **Tammy Massie, Ph.D.** _____
Lead, Bacterial & Allergenic Team Date

Concurring Reviewer (2): **A. Dale Horne, Dr. PH** _____
Chief, Vaccine Evaluation Branch Date

Medical Office/Division: OVRR/DVRPA

Clinical Reviewer(s): Ann Schwartz, MD

Project Manager: Holly Wieland, RN, MPH

Jon Daugherty, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

1. There are insufficient safety data provided in this submission to review. However, this is a product that has been licensed before and the reviewer has not been notified of any serious adverse reaction reports. Thus it appears that this product may not have any unacceptable safety profile.

2. The studies included in this BLA report high estimated positive and negative response rates. However, since the trials were conducted in subjects with known disease history, it is not clear how the product will perform when the disease condition is not known. If licensed, a second confirmatory test study may be considered, depending on the clinical reviewers' judgment.

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 Coccidiodomycosis"
- Study S104-2: "Skin Test Specificity of 1.27µg 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 1.27µg per 0.1mL Spherule-Derived Coccidioidin in Adult Volunteers With a History of Pulmonary Histoplasmosis"

1.3 Major Statistical Issues and Findings

1. The applicant provided acceptable support based on one dosing study for using 1.27 µg/0.1mL as the dose concentration for this product.

2. The applicant provided reasonable estimates and supportive data for the positive response rate among people with a history of pulmonary coccidioidomycosis and the negative response rate among people without a history of pulmonary coccidioidomycosis.

3. The applicant provided evidence that twelve adults with a recent history of pulmonary histoplasmosis failed to react to Coccidiodin, but were positive to either Candin or Trichophyton Extract, which served as positive controls. This supports the

conclusion that the product did not cross-react in persons with past exposure to *H. capsulatum*.

2. INTRODUCTION

2.1 Overview

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

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

There were two Complete Response Letters issued by CBER on March 26, 2010 and on August 26, 2010 for this product. Please see the two previous reviews for background information.

2.2 Data Sources

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

- Original submission
- Amendments 1, 2, 3, 4, 5, 6, 7, 8, 9, 11.

This review includes discussion on the statistical analysis plan for study S101A, which was submitted on December 12, 2001 to IND -(b)(4)- and should have been included in this 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 been diagnosed with coccidioidomycosis. Current --(b)(4)-- manufactured by Allermed is made ----------(b)(4)----------
---
----------. The dose-response study reported in this submission was designed to evaluate the cellular hypersensitivity response to four doses of ----------(b)(4)----------
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According to the applicant, the original statistical protocol (SAP) was written by -(b)(4)- ---------- dated September 28, 2001. The study started on June 4, 2002 and was completed on January 14, 2003. The data obtained from this study was analyzed by ---(b)(4)--- according to the protocol he had written. The statistical protocol and the analysis results submitted to the BLA were summarized in the original review dated March 12, 2010.

In this SAP, -----(b)(4)----- used the induration response data collected from 19 subjects. Each subject was treated with three dose concentrations: 0.4, 0.8, and 1.6, to build a linear regression model expressed as:

E(induration | concentration) = -------(b)(4)------ concentration

For a concentration of 1.27, the predicted induration is 22.24mm.

In the first Complete Response (CR) letter issued on March 26, 2010, CBER commented that the analysis did not follow the statistical protocol and requested additional analysis be performed by excluding 4 subjects: one subject had no results that could be determined, two subjects responded to the placebo (thimerosal), and one subject had a non-linear response with increasing dose, which is one of the exclusion criteria specified in the statistical protocol.

In response to the first CR letter, the applicant informed CBER that --------(b)(4)-------- had replaced -----(b)(4)----- as the statistician for this product. The applicant requested that the original statistical protocol be withdrawn and provided, instead, a revised report by ----(b)(4)---. In the revised report, ----(b)(4)--- followed CBER's request and used the induration data from 16 subjects. However, in this analysis, he performed a linear regression for each subject using the logarithm base 10 of the 3 dose concentration as the covariate. Thus, the mean of the 16 estimated responses for log(1.27) was reported as 23.5 mm.

In the first CR letter, the reviewer had also included a comment that the regression was performed on the mean induration for each dose which reduces the variability arbitrarily. The statistical reviewer performed a simple linear regression using all the induration data from 16 subjects on the 3 dose concentrations, and obtained the following equation:

E(induration | concentration) = ------(b)(4)------ concentration

Thus, based on this calculation, the estimated induration for 1.27 is 22.6 mm.

The applicant submitted a letter stating that a variance of +/- 20% in the potency of a test lot compared to an internal reference was accepted by the FDA in the licensure of Allermed's Candida albicans Skin Test Antigen for Cellular Hypersensitiviy (Candin). Therefore, the applicant proposes that a range of +/- 20% of the internal reference of -(b)(4)- is -------(b)(4)------.

Since all of the regression results show that the estimated induration values are well within the range regardless of the methods used, the statistical reviewer considers it is acceptable to keep the dose concentration at the 1.27µg/0.1mL level.

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 Coccidiodomycosis"

Clarification

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. Since the status of the disease is already known, the results from this study will provide an estimate of the positive response rate for people with a history of coccidioidomycosis but not evaluate the sensitivity of the skin test.

Results

In the first CR letter, the statistical reviewer commented that the results reported in the BLA submission were inconsistent between the synopsis and the main report body. The applicant submitted a revised version to correct the inconsistency.

The results provided in the revised report are provided in Table 1.

Table 1. Summary of the skin test response rates in subjects with a history of coccidioidomycosis.

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

Considering the results included in Table 1, the positive response rate is 50/51 = 0.98 with a 95% confidence interval of (0.90, 1.00).

3.1.3 Study S104-2

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

Clarification

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*. Since the status of the disease is already known, the results from this study provide an estimate of the negative response rate for people without a history of pulmonary coccidioidomycosis, but do not provide an estimate of the specificity of the skin test.

Results

Table 2 depicts the applicant's results for the skin test performed on subjects with no history of coccidioidomycosis.

Table 2. Summary of the skin test response rates in subjects with no history of coccidioidmycosis.

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

Since 58 out of 59 valid tests showed negative response, the estimated negative response rate is 0.98, with a 95% confidence interval of (0.91, 1.00)

It is of interest to note that in section 11.4.2, the applicant stated that 5 subjects failed to respond to all test articles, including the two positive controls. According to the applicant, the blood tests show that the subjects were not immuno-compromised but results were likely due to the absence of sensitivity to the test articles. Because these subjects failed to respond to all test articles, their true responses to the coccidioidin skin test are not attainable. The results should not be considered to imply that all subjects negatively responded as the applicant has assumed. In one possibility, they can be considered as not valid negative responses to the coccidioidin skin test. Hence, only 54

subjects should be considered as valid and the estimated negative response rate should be 53/54 = 0.98, with a 95% confidence interval of (0.90, 1.00). Alternatively, the worst case scenario would be that they had a positive response that was not manifested in the form of induration. In that case, the negative response rate would be 53/59 = 0.90 with a 95% confidence interval of (0.79, 0.96).

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"

Table 3 depicts the applicant's results for the subjects' reactions to reagents based on skin tests performed on subjects with a history of pulmonary histoplasmosis.

Table 3. Summary of reactions to reagents in subjects with a history of pulmonary histoplasmosis.

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

The applicant observed that all twelve adults with a recent history of pulmonary histoplasmosis failed to react to Coccidiodin, but were positive to either Candin or Trichophyton Extract, which served as positive controls. This finding supports the conclusion that the product did not cross-react in persons with past exposure to *H. capsulatum*.

3.2 Evaluation of Safety

Due to the small sample size for all the studies in this BLA submission, no statistical analysis based on safety data is performed. Please see the Clinical Review by Dr. Ann Schwartz for a more detailed evaluation.

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 analyses based on efficacy responses are performed. Additionally, since safety data were not provided in this submission, no subgroup analysis is performed on safety data as well.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

1. The applicant provided acceptable support based on one dosing study for using 1.27 μg/0.1mL as the dose concentration for this product.

2. The applicant provided reasonable estimates and supportive data for the positive response rate among people with a history of pulmonary coccidioidomycosis and the negative response rate among people without a history of pulmonary coccidioidomycosis.

3. The applicant provided an observation that twelve adults with a recent history of pulmonary histoplasmosis failed to react to Coccidiodin, but were positive to either Candin or Trichophyton Extract, which served as positive controls. This finding supports the conclusion that the product did not cross-react in persons with past exposure to *H. capsulatum*.

4.2 Conclusions and Recommendations

1. There are insufficient safety data provided in this submission to review. However, this is a product that has been licensed before and the reviewer has not been notified of any serious adverse reaction reports. Thus, it appears that this product may not have any unacceptable safety profile.

2. The studies included in this BLA report high estimated positive and negative response rates. However, since the trials were conducted in subjects with known disease history, it is not clear how the product will perform when the disease condition is not known. If licensed, a second confirmatory test study may be considered, depending on the clinical reviewers' judgment.

APPENDICES (IF NEEDED)

None

DISTRIBUTION LIST

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