

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: File STN Number 125354/0

From: Deborah Trout, BLA Committee Member, OCBQ/DMPQ, HFM-675

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ, HFM-675

Subject: Review of Biologics License Application (BLA) from Allermed Laboratories Inc. for the manufacture, formulation, fill and packaging of Coccidioidan Skin Test; STN Number 125354/0

cc: Sheldon Morris, BLA Committee Chair, OVRP/DBPAP/LMDCI, HFM-431

My review includes an evaluation of the following sections (reference is made to Comprehensive Table of Contents): Item 3 Summary (section A), Item 4 CMC (environmental assessment, biological substance, biological product, batch records and CMC SOPs), Item 15 Establishment (entire section), and Amendment 125354/0/3 received October 15, 2009 in response to request for additional information (see filing memo dated June 18, 2009).

Section I: Recommended Action.

Resolve all issues identified in Section II below. Once issues are resolved, I will prepare an approval recommendation memo.

Section II: Outstanding Issues that can be addressed in an Information Request, Deficiencies or Complete Response letter.

It is unclear from your response dated October 15, 2009 whether a process validation protocol was executed for critical manufacturing steps. Please note the objective of process validation is to ensure that the manufacturing process will consistently yield product with specific quality attributes. Further, a process validation protocol is a prospectively written plan pre-approved by the quality unit that specifies critical steps, controls, and measurements. The process validation protocol states how validation will be conducted, identifying sampling, assays, specific acceptance criteria, production equipment, and operating ranges. Results obtained for each study described in the protocol should be evaluated in an associated process validation report. Please comment.

It appears from your response dated October 15, 2009 that the media fill procedure does not include the -----(b)(4)----- . Please provide validation data to

support the -----(b)(4)-----.

Please provide data demonstrating that you have achieved -----(b)(4)-----
-----.

There is no description of the container closure system used in Validation 1036 “Validation Report for Holding Time of ----(b)(4)---- Allergenic Extract Bulks” dated June 21, 1999. Please describe how you determined that this study adequately represents the container closure system used for the Coccidioidan bulk drug substance.

Please provide method validation for the -----(b)(4)----- Test used to test container closure integrity.

The regulation cited under Section 4, Environmental Assessment for your Categorical Exclusion made in pursuant to 21 CFR 25.31(f), is not appropriate. Please correct and resubmit.

Section III: Pre-license Inspection Issues

See Inspection Waiver memo dated February 16, 2010.

Section IV: Review Narrative (Review Date: 8/13/08).

Coccidioidomycosis is a fungus infection which is acquired by the inhalation of the spores of the fungus *C.immitis*. The disease is usually a self-limiting pulmonary infection characterized by flu-like symptoms. In a small percentage of individuals, the primary pulmonary infection may progress to pneumonia, or disseminate to other parts of the body, including the skin, bones and central nervous system. In some cases the outcome is fatal.

Coccidioidin SD is manufactured from a -----(b)(4)-----

----- During the early stages of development at Allarmed, Coccidioidin SD -----(b)(4)-----, SOPs and clinical protocols. The name was changed to avoid confusing the current product preserved with phenol -
----(b)(4)---- -----.

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

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

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

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

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

Container/Closure System

Stopper

- 13 mm -----(b)(4)----- gray stoppers manufactured by -----(b)(4)-----.

Seal

- 13mm aluminum seals manufactured by -----(b)(4)-----.

Vial

- 2 mL glass serum vials manufactured by -----(b)(4)-----
-----, 14 x 32 mm Type -----(b)(4)----- glass.

Protection: Solvent loss and microbial contamination/sterility testing have been performed to demonstrate the integrity of the seal between the container and the closure which protects the product from contamination and evaporation of the liquid portion of the product. Allermed has performed solvent loss testing and sterility (container integrity) as per Validation 1034

Safety Glass Vial: The Certificate of Compliance indicates that the glass meets specifications as indicated in items "I-IV" of the C of A which includes glass type certification, ---(b)(4)---
----- certification, ----(b)(4)---- certification, and product certification.

Elastomeric Stopper: Allermed provided the chemical composition of the stopper along with the test results of the stopper resin in accordance with -----(b)(4)----- requirements. The extraction properties of the drug product vehicle may not reasonably be expected to differ from that of -(b)(4)- since the product -----(b)(4)----- range, and there are no solubilizing excipients present. Therefore Allermed has accepted results where -(b)(4)- has been used as the extraction medium. The extraction profile has been obtained on stopper material that has been exposed to -----(b)(4)----- as expected by their current sterilization practice.

Container-Closure Integrity

To assure that container-closure integrity maintains a microbial barrier throughout the shelf-life of Coccidioidin SD, Allermed has reviewed their sterility data and container-closure testing sensitivity.

The -(b)(4)- methods that were employed to demonstrate the absence of leakage from containers were the -----(b)(4)----- Test.
The methods and specifications of the tests were provided in the application (Protocol VP1034).

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

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

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

The application indicates that the sensitivity of the -----(b)(4)----- test demonstrates -(b)(4)--
----- when containers were subjected to -----(b)(4)-----

Environmental Assessment Exclusion

Alarmed request categorical exclusion based on 21 CFR 25.31 provides for a categorical exclusion from an environmental assessment for this product under paragraph (f).