



DATE: 01/25/10

FROM: Siobhán Cowley, Ph.D., DBPAP

SUBJECT: STN 125354.0

TO: Sheldon Morris, Ph.D., DBPAP

THROUGH: Milan Blake, Ph.D., Director, DBPAP

(b)(4)

Manufacturing components:

Coccidioidin SD is manufactured according to the following formulation:

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

Allermed performs -----(b)(4)----- monograph identity test for -----(b)(4)-----
----- monograph testing is performed on -----(b)(4)---- lot of each excipient
delivered.

Water for Injection, -(b)(4)-, is generated by in-house distillation and tested --(b)(4)-- in
accordance with full -----(b)(4)----- requirements.

The -----(b)(4)----- is tested ---(b)(4)--- year for potency and identity (no other tests
performed). There are no plans at this time to remanufacture the ---(b)(4)----.

Container Closure: The container closure system for *Coccidioidin SD* uses:

- 2mL glass serum vials (14 x 32mm -(b)(4)-, Class -----(b)(4)--- glass vials with 13 mm
finish, manufactured by -----(b)(4)-----).
- Stoppers -(b)(4)- with formulation -(b)(4)- gray (manufactured by -----(b)(4)-----).
- 13 mm aluminum seal (clear lacquered one piece with center tab; manufactured by
------(b)(4)-----).

Copies of the formulation of the -(b)(4)- glass and elastomeric stopper were provided for
the vials and stoppers. Further, a letter of authorization from -----(b)(4)-----
----- to allow FDA access to their DMFs for production of the glass vials and elastomeric
stoppers are included. Solvent loss testing and sterility (container integrity) tests were performed
(shown in Validation 1034).

Method of Manufacturing:

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

Component	Specification	SOP
-(b)(4)-	-(b)(4)-	-(b)(4)-
-(b)(4)-----	--(b)(4)--	-(b)(4)-
-(b)(4)-----	------(b)(4)-----	-(b)(4)-
-(b)(4)-	---(b)(4)---	-(b)(4)-
-(b)(4)----	------(b)(4)-----	-(b)(4)-

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

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

Lot Release Testing:

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

Lot release SOPs:

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

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

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

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

Two (2) Pages Determined to be Non-Releasable: (b)(4)

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

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

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

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

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

Animal care

The guinea pig potency assay and general safety tests are performed at Allermed in an on-site vivarium, where there are procedures in place to ensure compliance with the USDA, APHIS, and Federal Animal Welfare Regulations. The facility has not earned AAALAC accreditation, but the USDA conducts semi-annual inspections of the facility to ensure compliance to the laws and regulations found in the Animal Welfare Act. An Institutional Animal Care and Use Committee oversees compliance with written procedures.

Stability testing programs

Three stability testing protocols were submitted to the BLA. SOP 949-021 describes the stability test program for the *Coccidioidin SD* skin test product. Vials will be tested at 0, 3, 6, 9, 12, 18, 24, 36, ----- (b)(4) -----. During storage, the vials will be placed inverted at -(b)(4)-. The following tests will be completed during the stability assessments: pH, visual, sodium borate, sodium chloride, phenol, potency, and stability. Overall, the stability testing program for the final *Coccidioidin SD* product is adequate.

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

Stability of the final product

The stability of the final product was evaluated during a -(b)(4)- period. The parameters that were assessed were visual clarity, pH, sterility, and potency as well as sodium chloride, sodium borate, and phenol concentrations. Final containers were stored in upright and inverted positions at -(b)(4)- and 2 – 8 °C. The results of the studies showed that the product was extremely stable since the composition and potency did not change significantly during storage at ----(b)(4)--- for -(b)(4)- months and during storage for -(b)(4)- months at 2 – 8 °C. Based on these data, at least a 36 month expiration dating period would be appropriate for this exceedingly stable product.

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

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

The Sponsor’s Responses to CBER’s August 4 Letter

In CBER’s August 4 letter, the sponsor was asked to address the following product-related issues.

1. In the validation report for the *Coccidioidin SD* identity test, -(b)(4)- antigens are used as negative controls. However, in the SOP for the identity test, --(b)(4)-- antigens -----(b)(4)----- are listed. Please comment on this difference and describe the source of the -----(b)(4)-----.
2. In the Inter-assay studies of the identity test, the -(b)(4)- readings for *Coccidioidin SD* Lot -----(b)(4)----- are significantly different on days 1, 2 and 3. Please comment on the impact of the significant variability in -(b)(4)- readings may have on the performance of the identity test.
3. Please describe how the 95% confidence interval for the potency test was determined and submit data to the BLA supporting this confidence interval calculation.
4. For the relative potency studies, please clarify why the acceptance criteria within a lot is defined as -----(b)(4)-----

5. For the relative potency validation studies, please discuss why the acceptance criteria for the slope calculations on p. 8 and linearity calculations on p. 10 was selected to be between ---(b)(4)----.
6. Please identify the testing lab for the guinea pig potency and the general safety tests and indicate whether this lab has earned AAALAC accreditation.

Overall, the sponsor's responses to each of these items were appropriate and adequate.

Additional Comments for the Sponsor

1. Please describe the source of the killed *C. immitis* for the guinea pig sensitization procedure (SOP 910-101) and describe how the spherules are killed.
2. If the guinea pigs are not adequately sensitized, the animals are boosted with -(b)(4)-

Please discuss the factors involved in the decision to boost with -----(b)(4)-----
-----.
3. In the validation of accuracy of the relative potency test method, please discuss why an acceptable result for percent recovery was -----(b)(4)-----.
4. Please discuss the actions that will be taken if a decline in the potency of the ---(b)(4)--- is detected.
5. SOP 910-104 (Coccidioidin Internal Reference Standard relative Potency Test method) states that an investigation will be triggered if -----(b)(4)-----

Please explain why the -(b)(4)- value of -(b)(4)- was selected.
6. The latest clinical lot of *Coccidioidin SD* was manufactured in 2007. Given that the dating period for the product has not been defined, please discuss your plans for manufacturing a new lot of *Coccidioidin SD* for distribution.
7. Please clarify the time of -----(b)(4)----- for in-process testing (on page 2, it is written that testing is -----(b)(4)-----, while Figure 1 of page 3 indicates that testing is done -----(b)(4)-----).
8. SOP 969-000 (NaCl assay) states that the error percent for each sample is ----(b)(4)---- NaCl. Since the product specification is ----(b)(4)----, please comment on the ability of this assay to accurately determine NaCl concentrations in the product.
9. *Coccidioidin SD* Identity Test validation: Please comment on the concentrations of the negative fungal controls (----- (b)(4) -----
-----).
10. SOP 944-101 (Identity test): Please comment on the stability of the -----(b)(4)--- under the storage conditions chosen.
11. Please provide data using more than one lot of *Coccidioidin SD* for the validation of the specificity of the Identity Test.