



<i>Coccidioides immitis</i> spherule ------(b)(4)----- -----	-(b)(4)-	Allermed Laboratories, Inc.	ITY7G7Q744
Water for Injection, -(b)(4)-	Q.S. --(b)(4)--	Allermed Laboratories, Inc.	059QF0K00R

Allermed performs -----(b)(4)----- monograph identity test for -----(b)(4)-----  
----- . Full --(b)(4)-- monograph testing is performed on --(b)(4)-- lot of -(b)(4)- 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)----- 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 Spherusol 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), and were satisfactory.

**Method of Manufacturing:**

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<u>Component</u>	<u>Specification</u>	<u>SOP</u>
-(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) -----  
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**Lot Release Testing:**

<u>Parameter</u>	<u>Specification</u>	<u>SOP#</u>
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:**

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

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

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**Animal care**

The guinea pig potency assay and general safety tests are performed at Allermid 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**

**Stability of the final product**

SOP 949-021 describes the stability test program for the Spherusol skin test product. The stability of the final product was evaluated during a (b)(4)- period. Vials will be tested at 0, 3, 6, 9, 12, 18, 24, 36, ---(b)(4)---. 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 36 months at 2 – 8 °C.

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

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3. *In the validation of accuracy of the relative potency test method, please discuss why an acceptable result for percent recovery was (b)(4) percent.*

Response summary:

Accepted practice for validation studies uses a range of (b)(4). Allered established (b)(4) criterion, and the data obtained in the validation process were within the (b)(4) range and supported the accuracy of the method.

**The sponsor's response about the validation studies is not adequate. However, the (b)(4) relative potency criteria for this skin test antigen is acceptable.**

4. *Please discuss the actions that will be taken if a decline in the potency of the (b)(4) is detected.*

Response summary:

A protocol to evaluate the potency of the (b)(4) in patients with a history of coccidioidmycosis will be submitted to the FDA for review. (b)(4)

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**The proposed actions that will be taken in response to a decline in the potency of the (b)(4) will be reviewed by the Agency after submission of the sponsor's proposal.**

5. *SOP 910-104 (Coccidioidin Internal Reference Standard relative Potency Test method) states that an investigation will be triggered if the (b)(4). Please explain why the (b)(4) value of (b)(4) was selected.*

Response summary:

This was a typo and should have read that " (b)(4) will trigger an investigation".

**Response to question #5 is adequate.**

6. *As we discussed during our August 27, 2008 pre-BLA meeting with you, based upon the data provided at the time, an expiration dating period of at least three years when stored at 2-8°C is being considered; however, we note that the most recent clinical lot of Spherusol was manufactured in 2007. Since the current lot is already 3 years old, please discuss your plans for manufacturing a new lot of Spherusol for eventual distribution.*

Response summary:

A new lot will be manufactured at the request of the FDA, or after approval has been received to manufacture and distribute Spherusol.

**Response to question #6 is adequate.**

7. *On page 2, you indicate that testing for bioburden and excipients is done -----(b)(4)-----, while Figure 1, page 3 indicates that this in-process testing is done -----(b)(4)------. Please clarify the stage of manufacture when these tests are performed.*

Response summary:

The reference to bioburden testing in Figure 1, page 3 is correct (and performed -----(b)(4)-----). In-process testing for excipients and sterility is performed -----(b)(4)-----.

**Response to question #7 is adequate.**

8. *SOP 969-000 (NaCl assay) states that -----(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.*

Response summary:

SOP 969-000 requires that -----(b)(4)----- of NaCl from a product sample be used in testing from -(b)(4)- of --(b)(4)--. The explanation of the acceptance criteria was incomplete and only applied to samples containing -(b)(4)- NaCl. Formula 2 listed above the Acceptance Criteria Section takes the -----(b)(4)----- into account and provides a result based on the % NaCl in the product, ---(b)(4)--- used in testing. The SOP has been corrected to remove the allowable NaCl limits, while maintaining the other sample acceptance criteria.

**Response to question #8 is adequate.**

9. *Please provide the concentrations of the negative fungal controls (----(b)(4)----) used in the validation of the identity testing for Spherusol.*

Response summary:

The concentration of each fungus extract was at -----(b)(4)-----.

**Response to question #9 is adequate.**

10. *Please provide data supporting the stability of the ---(b)(4)--- used in the identity test under the storage conditions chosen.*

Response summary:

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------(b)(4)-----  
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**Response to question #10 is adequate.**

11. *Please provide data using more than one lot of Spherosol for the validation of the specificity of the Identity Test.*

Response summary:

Data was provided for three lots of Spherosol (------(b)(4)-----  
-----). The data indicates that the identity test was specific for all three  
lots, clearly distinguishing Spherosol from -(b)(4)- fungal negative controls.

**Response to question #11 is adequate.**

**Additional Points:**

- On May 27, 2011, in response to an FDA letter dated May 11, 2011, Allermed submitted a revised version of the Product Release Protocol. This revised version addressed the issues outlined in the FDA letter and is acceptable.
- Since Spherosol is manufactured by a relatively straightforward procedure involving the ------(b)(4)-----, CBER will not require the submission of samples from lots for FDA testing.
- A new lot of Spherosol was manufactured on May 11/2011 (Lot #------(b)(4)-----). The product release test results were submitted to the FDA on June 20, 2011. All lot release tests yielded results that were within specifications and passed (-(b)(4)-, sodium chloride, sodium borate, identity, sterility, potency, and general safety). This new lot has an expiration date of 5/11/2014.

**Conclusion**

Allermed Laboratories, Inc., has provided acceptable responses to all CMC deficiencies outlined in the CR letter. There are currently no CMC issues to prohibit licensure.