



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: 06/22/11
FROM: Siobhán Cowley, Ph.D., DBPAP
SUBJECT: STN 125354.0
TO: Sheldon Morris, Ph.D., DBPAP
THROUGH: Jay Slater, M.D., Director, DBPAP

Introduction: Spherusol is manufactured from a bulk concentrate of spherule-derived coccidioidin -----(b)(4)-----
-----.

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

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

Chemistry, Manufacturing and Control:

Manufacturing components:

Spherusol is manufactured according to the following formulation:

Components	Quantity	Supplier(s)	UNII code
Sodium chloride, (b)(4)	-(b)(4)-	----- (b)(4) ----- -----	451W47IQ8X
Sodium borate, ----- (b)(4) -----	-(b)(4)-	----- (b)(4) ----- -----	91MBZ8H3QO
--- (b)(4) -- phenol, (b)(4)	-(b)(4)-	----- (b)(4) -----	339NCG44TV

<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.	059QF0KO0R

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 Spherosol 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:

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

----- (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) -----

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) -----

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

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.

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

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

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

Consistency of manufacture

Three lots of Spherusol were manufactured (----- (b)(4) -----
-----) and submitted to lot release and stability testing protocols that assessed visual clarity, pH, sterility, and potency, as well as measurement of the final sodium chloride, sodium borate, and phenol concentrations. The results from these tests had minimal variation and were within specifications, demonstrating that Allermed can manufacture the product consistently.

The Sponsor's Responses to CBER's March 26, 2010 CR Letter:

In CBER's March 26, 2010 CR letter, the sponsor was asked to address the following product-related questions:

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.*

Response summary:

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

The description of the spherule killing procedure is adequate.

2. *If the guinea pigs are not adequately sensitized, the animals are boosted with either ----- (b)(4) ----- . Please discuss the factors involved in the decision to boost with ----- (b)(4) -----
-----.*

Response summary:

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

The criteria for boosting is adequately discussed and acceptable.

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 Spherosol.*

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:

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

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

Response to question #10 is adequate.

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

Response summary:

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