



MEMORANDUM

Date: January 15, 2013

To: File for STN 125430/0

From: Catherine Poole, HRM-680
Regulatory Coordinator, Division of Biological Standards and Quality Control (DBSQC)

Through: William McCormick, Ph.D., HFM-680
Director, Division of Biological Standards and Quality Control (DBSQC)

Subject: STN 125430 – Varicella Zoster Immune Globulin (Human), Review of the lot release protocol template submitted by Cangene Corporation

CC: Nannette Cagungun
Pei Zhang
Karen Campbell
Douglas Frazier
Liza Virata
Cheryl Hulme
Hyesuk Kong
Alfred Del Grosso
Karen Campbell
Lokesh Bhattacharyya

Background:

On June 29, 2012, Cangene Corporation submitted a Biologics License Application (BLA) for Varicella Zoster Immune Globulin (Human). A lot release protocol template was submitted in amendment 125430/0.6 on October 18, 2012 and was reviewed by Cheryl Hulme, Doug Frazier, Malgorzata Norton, Hyesuk Kong, Alfred Del Grosso, Pei Zhang, Liza Virata, Lokesh Bhattacharyya, Karen Campbell and Catherine Poole. Comments on the lot release protocol were sent November 20, 2012. Comments were sent to Cangene on November 20, 2012 and a revised lot release protocol was received in amendment 125430/0.12 on November 27, 2012. Comments from Cheryl Hulme and Hyesuk Kong on the 125430/0.12 lot release protocol template were sent to Cangene on December 3, 2012. CBER received a revised lot release protocol in amendment 125430/0.14 on December 7, 2012. The lot release protocol was updated in amendment 125430/0.16 on December 12, 2012 due to a typo in the appearance specification.

Submissions Reviewed in this Memo:

- 125430/0.6 Lot Release Protocol Template in section 3.2.R Varizig™ lot release protocol
- 125430/0.12 Lot Release Protocol Template in section 3.2.R Varizig™ lot release protocol
- 125430/0.14 Lot Release Protocol Template in section 3.2.R Varizig™ lot release protocol
- 125430/0.16 Lot Release Protocol Template in section 3.2.R Varizig™ lot release protocol

Conclusion:

The lot release protocol template submitted in 125430/0.16 (received December 12, 2012) is acceptable for use.

Review:

Cangene Corporation submitted a lot release protocol amendment 125430/0.6 on October 18, 2012. Comments were sent on November 20, 2012. A second draft was received on November 27, 2012. Comments on this draft were sent on December 3, 2012. The final draft was received on December 7, 2012. Cangene's responses to CBER's comments received in amendments 125430/0.12 and 125430/0.14 are in *italics*. CBER's review of responses and conclusion are provided in **bold font**.

Lot release protocols may not be submitted electronically on CD-ROMs until after licensure. Please submit as a paper copy until approval is given. You may not submit lot release protocols through the Gateway at this time.

Please remove the Electronic Protocol Filename on page 1. This should be completely removed until Electronic submissions are approved.

Please remove the signature and date from page 6 and move these to page 1. The signature and date should be completely removed from page 6 and should not be left as a place keeper.

Please remove the second "Lot No." designation that is under the company letterhead since it is located on every page. A template for page 1 has been provided at the end of this document.

Please add "Lot No." to the header of page 3 as done in other pages.

Conclusion: Responses are acceptable. Pages 1, 3 and 6 were edited as requested.

For Section 1 Chemical Assays, please include a column for Test Date in the table.

In table 2 on page 3, --b(4)-----, please include a column for Test Date in the table.

In table 3 on page 3, Potency, please include a column for Test Date in the table.

Conclusion: Responses are acceptable. Test Date columns were added to requested sections.

For Section 1 Chemical Assays, please remove the test item pH and report only the pH (1%) measurement. 21CFR 640.101(b) only calls for the 1% protein dilution. You may continue to perform the –b(4)– pH measurement, but CBER does not need to see it on the lot release protocol.

Conclusion: Response is acceptable. pH was removed from the table in Section 1.

On page 2, three different measurements use the wrong definition for concentration; in each case the proper unitage is rendered inaccurate and confusing by adding “per fill volume”. These unit definitions and their concentrations are given in the following table:

Test	Given Unit Definition	Valid Unit Definition
Chloride	mM/per fill volume	mM [millimoles per liter]
Polysorbate 80	mg/mL per fill volume	mg/mL [milligrams per milliliter]
Glycine	M per fill volume	M [moles per liter]

Cangene’s response: VariZIG[®] is filled into the final vial presentation on the basis of potency and therefore there is a range of validated fill volumes used. The terminology “per fill volume” signifies that the product is reconstituted in the fill volume used for that specific batch in order to ascertain the true final excipient concentrations (polysorbate 80, glycine and chloride). For the Chloride test, the slash between mM and per fill volume has been removed, all other units were left as previously submitted based upon the rationale included.

Conclusion: The rationale in Cangene’s response is acceptable, the units are appropriate to use.

On page 2, the unit designation for the –b(4)– assay is not correct: –b(4)–. It should be in units of “–b(4)– of –b(4)–. The “per milliliter” is irrelevant; specific activity is defined as activity per mass, not as activity per volume per mass.

Cangene’s response: The method Cangene is using is based on the 1981 guide from the US Department of Health and Human Services –b(4)–
- In our method the –b(4)– is expressed as the amount of IgG required to activate –b(4)–. The specification was set based on the data generated from this method. This method has been previously approved by FDA for Cangene’s hyperimmune products.
(1) U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control. –b(4)–. Atlanta. 1981.

Conclusion: The rationale in Cangene’s response is acceptable, the unit is appropriate.

A test for –b(4)– as described in –b(4)– should be included. –b(4)– states that: –b(4)–

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

*Cangene's response: To date Cangene has not been required to perform b(4)-----
-----testing for b(4)----- on our products as they are Therapeutic
Protein Injections which are known to have particles inherent to them. The b(4)-----
----- has addressed this by revising the Injections b(4) section to
address b(4)----- in Therapeutic Protein Injections. Chapter b(4)- is
currently being written specifically to address b(4)--- testing in Therapeutic Protein
Injections. b(4)----- will be incorporated into b(4)-----
which becomes effective May 1, 2014. The inspection of the product for visible
b(4)----- is being done in compliance with the current b(4) Injections section b(4)*

**Conclusion: The rationale in Cangene's response is acceptable, a test for
b(4)----- will not be added.**

On page 2, please correct the spelling of the Polysorbate 80 test method. The correct
spelling is b(4)-----

*Cangene's response: The spelling of the test method for Polysorbate 80 has been
corrected to b(4)-----*

In table 2 on page 3 please change the words "b(4)-----

Conclusion: Responses are acceptable. Pages 2 and 3 were edited as requested.

On page 4, Bacterial Endotoxin, the endotoxin specification is b(4)-----.
Therefore, the average result should be converted to EU/vial as well.

In the product Test summary table for the Endotoxin test on page 4, the results should be
EU/mL. However, the average results should be converted to EU/vial as the specification
is b(4)-----

*Cangene's response: The individual endotoxin results in the product test summary table
(page 4) will be recorded as EU/mL; however the average results will be converted to
EU/vial for comparison to the product specification. Please refer to the revised lot
release protocol (eCTD section 3.2.R).*

Conclusion: Response is acceptable.

On page 5 (Sterility), please include the b(4) test date and Tested Quantity as shown in
the template below. A different format may be used as long as all of the data in the table
are provided.

*Cangene's response: Tables 5a and 5b for reporting Sterility results in the lot release
protocol have been modified to include to quantity tested for routine Sterility Testing as
shown in the tables below. The b(4) test date will be reported as the QA Final Approval
date on the b(4) Validation report.*

For the bulk type (Sterility test on page 5), the tested quantity for the sterility test using
b(4)----- was presented with b(4)- (Section) 3.2.P.5.2 analytical procedure
for sterility testing described "The sample volume requirements for the MF are outlined

in the compendial chapters.” According to 21 CFR610.12, the volume tested for Bulk shall be no less than –b(4)-. Please clarify.

Cangene’s response: Title 21 CFR610.12(g)(9) further states: “Immune globulin preparations. For immune globulin preparations, the test samples from the bulk material and from each final container need be no more than –b(4)-.” Cangene samples b(4) and -----b(4)-----

A recent revision to 21 CFR610.12 (effective June 4, 2012) eliminated the sterility test requirement for most bulk material. As a result, there is currently no specified volume for testing bulk product according to the CFR.

Conclusion: Repsonse is acceptable.