Inspections, Compliance, Enforcement, and Criminal Investigations

Sanquin Plasma Products 8/29/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville, MD 20852-1448

WARNING LETTER

August 29, 2013

CBER-13-04

VIA FACSIMILE AND UPS

Robert F. Tiebout, MD
Managing Director
Sanquin Plasma Products &
C.A.F. – D.C.F.
Plesmanlaan 125
1006 CX, Amsterdam, Netherlands

Dear Dr. Tiebout:

The Food and Drug Administration (FDA) conducted an inspection of Sanquin Plasma Products, located at Plesmanlaan 125, 1006 CX Amsterdam, Netherlands, from May 27 - June 4, 2013, and CAF-DCF located at 120 Brussels, Neder-over-Heembeek, Belgium from May 15 - May 23, 2013. During the inspections, FDA investigators documented significant deviations from current good manufacturing practice (CGMP) requirements in the manufacture of the licensed biological product Cinryze. Deviations from CGMP include the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), Section 351(a) of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210 and 211. At the close of each inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to each facility's compliance with CGMP. Significant deviations observed during the inspections include, but were not limited to, the following:

Sanquin Plasma Products

1. You failed to withhold from use each lot of components until the lot was sampled, tested, or examined, as appropriate, by the quality control unit [21 CFR 211.84(a)]. Specifically, no procedures have been put in place for bioburden testing of the incoming **(b)(4)** batches from supplier C.A.F.-D.C.F., as was originally noted during the 2011 inspection of your facility.

2. You failed to follow test procedures, or other laboratory control mechanisms established to

assure that in-process materials and drug products conform to appropriate standards of identity, strength, quality, and purity. [211.160 (a) and (b)]. For example,

a. As per **(b)(4)** 14425, the wrong request code was entered into the Laboratory Information Management System (LIMS) and, as a result, the wrong test was performed on stability sample **(b)(4)**.

b. **(b)(4)** records 2961 and 8368 dated April 25, 2013, and December 18, 2013, respectively, document Out of Specification (OOS) amino acid test results for finished product. Both OOS results were attributed to human error in sample handling and preparation for testing.

3. You failed to follow your written testing program designed to assess the stability characteristics of your drug product [211.166(a)]. For example:

a. As per **(b)(4)** Event Record 1453, Stability Study SSP036 (037) did not start within **(b)(4)** after filling.

b. As per **(b)(4)** Event Record 4735, Stability Study SSP036 (022) missed the 3 month testing time point.

Additionally, significant deviations in the manufacture of your intermediates were observed during the inspection. These deviations violate Section 501(a)(2)(B) of the FD&C Act and Section 351(a) of the PHS Act. Specific areas of concern include, but are not limited to:

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FAILURE INVESTIGATIONS

4. Blockages that lead to excessive filtration times during the **(b)(4)** blockages of the Planova nanofilters, were noted during the current inspection (14 U.S. batches), as well as during the 2011 inspection (7 U.S. batches). No root cause has been found for these filtration issues.

5. Recurring errors and/or deviations during production have not been thoroughly investigated or effectively corrected. For example:

a. **(b)(4)** containers are shipped from the contract manufacturer in **(b)(4)**. Since the previous inspection, 93 Cinryze **(b)(4)** container leaks have occurred, compared to 12 container leaks from 2009-2011 as noted during the previous inspection.

b. Corrective and preventive actions (CAPAs) taken to prevent deviations at the **(b)(4)** step have not been effective. Specifically, several manufacturing deviations have occurred since the prior inspection, including: a broken stirrer on the **(b)(4)** that could result in **(b)(4)** problems, due to inadequate mixing. Similar errors were also noted during the 2011 inspection.

6. There is no procedure in place for conducting an investigation when adjustments need to be made to **(b)(4)**, when **(b)(4)** action limits are exceeded, or for long filtration times, all during the Planova nanofiltration step, and, as such, no product impact assessments have been conducted for Cinryze batches with long filtration times **(b)(4)**.

PRODUCTION AND PROCESS CONTROLS

7. You failed to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material. For example:

a. Planova nanofiltration time or **(b)(4)** parameters have not been validated.

b. The process of changing filters due to blockage has not been validated.

c. The mixing and stirrer speed at the **(b)(4)** step has not been validated.

8. You failed to perform leachable and extractable studies for the **(b)(4)** containers used in the storage of **(b)(4)** intermediates.

9. The sealing process for containers that are used for storage of **(b)(4)** intermediates has not been adequately validated. The validation did not include sufficiently broad parameters for **(b)(4)**. The validation studies were all performed under **(b)(4)**.

CONTROL OF COMPONENTS

10. Incoming intermediates for further manufacture, released in-process Cinryze intermediates, and "blocked" products are not adequately segregated to prevent mix-ups. For example, inspection of **(b)(4)** noted a lack of segregation and the comingling of "blocked" Cinryze batches stored among processed Cinryze products in containers tagged with "Quarantine." One of the storage container tags was noticed by the investigator on the floor of the freezer.

LABORATORY CONTROLS

11. You failed to follow Standard Operating Procedure (SOP) #M134-EN/17, dated May 20, 2013, titled "**(b)(4)** (Bioburden)," that requires the testing of manufactured products for bioburden within **(b)(4)**. 15 **(b)(4)**, 11 **(b)(4)**, and two final Cinryze bulk samples (**(b)(4)**) were not tested within the required **(b)(4)** from June 1, 2011, through May 31, 2013.

12. Procedures for laboratory testing are deficient or not followed in that operator errors continue to occur while processing/testing samples. For example, after detecting an OOS result for intermediate product sample **(b)(4)** for **(b)(4)**, the operator in question failed to initiate the OOS result in **(b)(4)**. A laboratory investigation was eventually conducted and ultimately revealed that the wrong sample was likely tested causing the OOS. Retests of sample **(b)(4)** yielded passing results.

13. In-process OOS investigations are not always initiated at the time of the event. Specifically, on February, 22, 2013, intermediate product sample **(b)(4)** from the Cinryze **(b)(4)** step tested OOS for **(b)(4)** OOS 11522 was not initiated until March 6, 2013 to investigate the OOS.

EQUIPMENT

14. There is no Preventive Maintenance (PM), or PM is inadequate for equipment used in the production or storage of Cinryze product intermediates. For example:

a. There is no procedure in place for the PM of the **(b)(4)** container sealing equipment.

b. The PM for the **(b)(4)** used for product storage is inadequate. During the inspection, the freezer was found with ice needle formation on the ceiling, floor, entrance floor, curtains of the freezer, and inside the open containers used for product container storage.

C.A.F. – D.C.F.

FAILURE INVESTIGATIONS

1. You failed to thoroughly investigate endotoxin failures that resulted in 44 rejected batches of **(b)(4)**. For example:

a. Investigation Report RA-QA-PR-0040-01 concluded that the cause of the endotoxin failures was a change made to the cleaning program. However, sampling of the implicated **(b)(4)** or any potentially suspected manufacturing equipment was negative for endotoxin and bioburden.

b. There was no documentation in the investigation report of the possibility that **(b)(4)** could have been contaminated by the visible leak on the **(b)(4)**.

c. There is no data to support the conclusion that the accumulation of endotoxin remaining in **(b)(4)** was the source of the contamination of the 44 batches of **(b)(4)**.

d. There was no extension of the investigation to include the 10 **(b)(4)** batches with action level endotoxin excursions over the licensed in-process specification of **(b)(4)**.

e. No manufacturing investigation was conducted for Event Report 3572 as a result of a confirmed OOS/OOL endotoxin result of 1.336 EU/ml for **(b)(4)** Batch **(b)(4)**.

f. Three of the first four batches manufactured immediately after the aforementioned 44 batches had action level endotoxin excursions for **(b)(4)** Batches **(b)(4)** all were processed in **(b)(4)**, were cleaned with the same **(b)(4)**, and were **(b)(4)** using the **(b)(4)** as the 44 **(b)(4)** batches that had been rejected. However, there was no additional investigation performed into these three excursions and the batches were released for further processing.

2. According to Event Report #2682, dated April 13, 2013, during production there was a visible leak found on the **(b)(4)**. Production continued and **(b)(4)** batches were manufactured from March 19, 2012, to June 15, 2012. These **(b)(4)** batches included 14 of the 44 batches that were rejected due to endotoxin failures.

3. The investigation into the cause of leaking containers of **(b)(4)** that are shipped to the Netherlands is deficient. Specifically, 92 **(b)(4)** containers received at Sanquin had leaking seals from October 2011 - April 2013. CAPA # 1681 was not opened until there had been 55 separate reports of container leaks, and corrective and preventive actions have been ineffective, as an additional 21 leaks have occurred since the closure of the CAPA on August 7, 2012, with 10 of the 21 occurring in 2013.

4. Investigations into the root cause of recurring production deviations are inadequate. Specifically, from May 23, 2012, -January 25, 2013, several **(b)(4)** transfer errors were noted, which caused manufacturing delays and batches to be rejected and/or quarantined. Several CAPAs were initiated but **(b)(4)** transfer errors were still occurring as recently as April 10, 2013.

5. Several endotoxin OOS test results for **(b)(4)** were reported as Out of Limit (OOL) in laboratory documents and, therefore, not adequately investigated as per SOP #QC-013 Rev. 3. For example, Event Report #12381 documents **(b)(4)** batch **(b)(4)** which had an endotoxin test result of 3.407 EU/ml with a licensed in-process specification of **(b)(4)**. No assignable laboratory error was found and so this batch should have been investigated as an OOS with a full manufacturing investigation as per SOP #QC-013. Instead, it was recorded as OOL and only a limited laboratory investigation was performed.

EQUIPMENT CLEANING

6. The endotoxin **(b)(4)** and bioburden **(b)(4)** action limits for equipment after **(b)(4)** are not scientifically justified or based on historical values.

LABORATORY CONTROLS

7. In 2012, the stability time points for several batches were missed at the three month time point.

The deficiencies described in the Forms FDA 483 issued at the close of the inspections and in this letter are an indication that your quality control units are not fulfilling their responsibility to assure the identity, strength, quality, and purity of the licensed biological drug product and intermediates manufactured at Sanquin Plasma Products and CAF-DCF. FDA expects you to

undertake a comprehensive and global assessment of all of your operations to ensure that products conform to FDA requirements. Please describe in detail how you will attain CGMP compliance with regard to the above observations.

We acknowledge receipt of your written responses dated June 24, 2013, which address the inspectional observations on the Forms FDA 483 issued at the close of each inspection. We also acknowledge the commitments made in your responses to address the items listed on the Forms FDA 483.

We have reviewed your responses and we have determined that you are out of compliance with CGMP and are issuing this letter. Additionally, we have the following specific comments on your responses which are numbered to correspond to the observations listed on each Form FDA 483.

Sanquin Plasma Products

General Comments
We acknowledge your intent to continue to investigate the root cause for the filter blockages. Please provide a copy of the investigation report referenced in Action 1.1 (due date indicated as September 2013) for review.

Response to Item 2
Once complete, please provide a copy of your decision tree for release or rejection of a batch with extended filtration times (Page 13). Additionally, the risk assessment you mention as part of **(b)(4)** #11764 should include evaluating previously manufactured batches as well as future batches. Please provide the risk assessment for review.

Please note that several changes you plan to make may result in significant changes to in-process parameters and further downstream manufacturing steps. Your process validation could be affected by these changes and should be evaluated for the need to re-validate based on these changes and modifications. These changes should also be communicated to the license holder so that an evaluation may be made for the need to submit a supplement to the Cinryze BLA.

C.A.F. – D.C.F.

Response to Item 12
Please provide validation report R-CV-PR-0836.02.0 and **(b)(4)** Method Evaluation report R-CV-PR-0911.02.0 for review.

Neither the above deviations, nor the observations listed on the Forms FDA 483 presented to the firms at the conclusion of the inspection, are intended to be an all-inclusive list of deviations at Sanquin Plasma Products and CAF-DCF. It is your responsibility to ensure compliance with all requirements of the laws and regulations administered by FDA.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice.

To facilitate your remediation efforts, we request a meeting with you and other senior management at Sanquin Plasma Products, C.A.F. – D.C.F., and ViroPharma Biologics, Inc., to further discuss the issues cited in this letter and your proposed responses to address these issues.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that corrective action has been achieved. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N,

Rockville, Maryland 20852-1448. To schedule a meeting at your earliest convenience, please contact Robert D. McElwain, Consumer Safety Officer, in the Division of Case Management at (301) 827-6201.

Sincerely,
/S/
Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:
Paul J. Gil, PhD
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