

Analytical Procedures and Methods Memo - RiaSTAP

MEMORANDUM

To: File (STN 125317/0), Vasantha Kumar & Laura Wood

From: Ze Peng

Through: Timothy Lee , Acting Chief, LH/DH/OBRR

Subject: Final review of analytical procedures and methods validation in a BLA submitted by CSL Behring for Human Fibrinogen Concentrate, Pasteurized

This memorandum summarizes the review of analytical procedures and methods validation in a BLA under STN 125317 submitted by CSL Behring for Human Fibrinogen Concentrate, Pasteurized. The proposed trade name is Riastap. Upon review, I find the information provided to be satisfactory, and the data of the analytical procedures and methods validation to be supportive of the approval of this original BLA.

Summary of Review

3.2.R.2 Analytical procedures

The major methods used in these analytical procedures are as follows:

1. Practicability and ---(b)(4)--- test (determination of -----(b)(4)-----)
2. Quantitative protein determination in the -----(b)(4)----- (-----
----- (b)(4)-----
-----)
3. ----(b)(4)---- protein determination
4. Test of proteins for identity and purity.
5. -----(b)(4)----- for identity test following Ph.Eur.
6. Identification of chloride, citrate, sodium, and L-arginine monohydrochloride.
7. Determination of --(b)(4)- activity
8. Determination of fibrinogen (clottable protein)
9. Determination of ---(b)(4)---.
10. Determination of residual water in dry substance by means of --(b)(4) - according to --
--(b)(4)----.
11. Determination of the count of reproductive aerobic microorganisms including -----
(b)(4)----- And --(b)(4) --- species in starting material and in-process samples.
12. Determination of endotoxin of Gram-negative bacteria in -----(b)(4)-----.
13. Testing for pyrogens. (in Rabbits)
14. Sterility test. (----- (b)(4) -----)
15. General safety test. (in guinea pigs and mice)

3.2.R.3 Analytical procedures validation

1. *Testing proteins for identity and purity.*
----- (b)(4) ----- by the method (Q-04-010-07) of ----- (b)(4) ----- is a sensitive and specific method for the detection and identification of -(b)(4)- proteins. The proteins

are separated by -----(b)(4)-----
----(b)(4)-----

-----.

The characteristics of analytical validation basically include Specificity and Robustness. Regarding the Specificity, CSL Behring detected a fibrinogen -----(b)(4)----- in Haemocomplettan HS samples by the use of an -----(b)(4)----- . These ---- --(b)(4)----- of Haemocomplettan HS samples are detectable and identical to a comparative lot. Integrity of samples at -(b)(4)-C is validated until -(b)(4)- weeks in term of Robustness.

Comment: The test method was validated to be suitable for the specific detection of human plasma proteins including fibrinogen in Haemocomplettan HS. The acceptance criteria of all parameters were fully met.

2. Testing of presence or absence of human and -(b)(4)- protein.

The -----(b)(4)----- technique called -----(b)(4)----- (Q-04-040) enables the detection of a possible occurrence of foreign proteins in aqueous protein solutions of complex matrices (e.g., cryoprecipitate) as well as non-complex matrices (e.g., final product).

Comment: According to the requirements of the European Pharmacopoeia, this method is the current procedure to verify the presence of proteins of human origin in a protein solution and in addition to give negative results with anti-sera specific to the plasma proteins of each species of domestic animal commonly used in the preparation of materials of biological origin in the country concerned.

----- (b)(4) ----- is fully validated for all Aventis Behring products/drugs derived from the cryoprecipitate via method validation reports MVR-04-040-P666/P664/P650-01 (performed for cryoprecipitate) and MVR-04-040-Q666/Q664-01 (performed exemplary with --(b)(4)-- as a “non-complex protein matrix product”).

3. Determination of --(b)(4)-- activity.

The method Q-10-004-04 is the current procedure for the detection of --(b)(4)- as in-process control. This method is fully validated for Specificity, Detection Limit, and Robustness. This assay is specific for the detection of --(b)(4)- and the detection limit --- -----(b)(4)----- . Regarding Robustness, the maximum deviation of the data is - (b)(4)- during the storage time of up to -(b)(4)- hours, within -(b)(4)- of the starting concentration.

Comment: It was proved to be suitable for the determination of --(b)(4)- in the in-process intermediate “----- (b)(4) -----” of ----- (b)(4) -----.

4. Determination of clottable protein.

According to the currently valid quality control procedure (Q-16-003) of Haemocomplettan, fibrinogen is tested ----- (b)(4) ----- lots, not in --(b)(4)- -----, because ----- (b)(4) ----- do not affect the measurement of this parameter. The validation results are shown as below:

Validation parameters	Acceptance criteria	Results	Evaluation
Accuracy	Recovery rate --(b)(4)--	---(b)(4)--	Pass
Repeatability	RSD -(b)(4)--	-(b)(4)-	Pass

Validation parameters	Acceptance criteria	Results	Evaluation
Intermediate precision	RSD --(b)(4)--	-(b)(4)-	Pass
Specificity	----- (b)(4) -----	----- (b)(4) -----	Pass
Linearity	Correlation coefficient --(b)(4)--, ----- (b)(4) -----	-(b)(4)- ----- (b)(4) -----	Pass
Range	For lower and upper concentration of accuracy RSD - (b)(4)- For the 3 concentrations of accuracy, recovery rate --- (b)(4) - - Correlation coefficient --(b)(4)-- ----- (b)(4) -----	---- (b)(4) ---- --- (b)(4) --- --- (b)(4) --- ----- (b)(4) -----	Pass
Robustness			Pass

Comment: Since all acceptance criteria were met, the validated method Q-16-003 is applicable to determine the clottable protein content in Haemocomplettan and its preliminary stage “--(b)(4)-- and final adjustment of fibrinogen active ingredient solution” accurately, precisely, and linearly.

5. *Determination of L(+)-Arginine and ----- (b)(4) ----- by means of -(b)(4)- -----*
--.

According to test instruction, the method Q-16-087 was revalidated for the characteristics except detection limit on a -(b)(4)- and a ----(b)(4)---- ----- equipped with ----- (b)(4) -----.

A -(b)(4)- method calibration for the -(b)(4)- and a --(b)(4)- method calibration for the -(b)(4)- were established. The method Q-16-087 is suitable for the quantitative detection of L-Arginine-hydrochloride between ----- (b)(4) ----- mg/L on the ----- (b)(4) ----- and between ----- (b)(4) ----- on the ----- (b)(4) ----- in the product Haemocomplettan HS 1g/2g. All results met the acceptance criteria.

Comment: All results comply with the acceptance criteria. However, the method was validated for L-Arginine only because --- (b)(4) --- is not present in the product.

6. *Determination of residual moisture by ----- (b)(4) -----.*

Method Q-16-345 (----- (b)(4) -----) operating in a commercially available --- (b)(4) --- and Method Q-11-091 (----- (b)(4) -----) in a non-commercial --- (b)(4) --- employed for this study. The validation data are as follows:

Validation parameters	Acceptance criteria	Results	Evaluation
Accuracy (Q-16-345)	Recovery rate of the mean value for injection volumes of --- (b)(4) ----- -----	--(b)(4)--	Pass
Repeatability (Q-16-345)	RSD -(b)(4)-	-(b)(4)-	Pass

Validation parameters	Acceptance criteria	Results	Evaluation
Intermediate (Q-16-345/Q-11-091)	Confidence interval of mean value (for pair differences of the two methods compared) contains -(b)(4)--	-(b)(4)-	Pass
Quantitation limit (Q-16-345)	Recovery rate of the mean value for one individual concentration: --- (b)(4)--, RSD -(b)(4)-	--(b)(4)-- ----(b)(4)---	Pass
Linearity (Q-16-345)	Correlation Coefficient -(b)(4)- for Interval -(b)(4)-	-(b)(4)- --(b)(4)--	Pass
Range (Q-16-345)	Recovery rate of the mean value for one individual concentration -(b)(4)--, RSD -(b)(4)-, Correlation Coefficient -(b)(4)- for Interval -(b)(4)-	----- (b)(4) ----- ----- ----- -----	Pass
Robustness (Q-16-345)	RSD -(b)(4)-	-(b)(4)-	Pass

Comment: This study showed that the method Q-16-345 met all validation criteria to determine residual moisture content in lyophilized Haemocomplettan HS. Additionally, it has been shown that both methods (Q-16-345 and Q-11-091) in connection with the two described detection units are interchangeable without altering the result significantly. Thus, both systems are suitable for their intended use.

7. *Total aerobic counts in the in-process sample* - ----- (b)(4) -----.

The total aerobic microorganisms in the In-Process sample "----- (b)(4) -----" of the Haemocomplettan production are quantified by ----- (b)(4) ----- . The method Q-24-050 was validated in terms of its accuracy, repeatability, intermediate precision, specificity, and robustness. On the --(b)(4)--- medium --(b)(4)-, the colonies found in test 3 were morphologically identical with the product derived microorganisms found in test 2. It is confirmed to be ----- (b)(4) ----- by ----- (b)(4) ----- (likelihood of identification: 99.9%).

Comment: The quantification of test microorganisms required by European Pharmacopoeia (4 th edition), USP -(b)(4)- and one bacterium (--(b)(4)-- -----) found in routine-monitoring, is tested in absence and presence of the product. This validation study showed that the quantification of microorganisms is not affected by bacteriostatic or fungistatic activity of the product.

8. *Quantification of the endotoxins from Gram-negative bacteria using the --(b)(4)--.*

This method (Q-24-324) validation was performed with ----- (b)(4) ----- . However, it is also applicable for ----- (b)(4) ----- .

Validation parameters	Acceptance criteria	Results	Evaluation
Accuracy	The endotoxin recovery rate should be within --(b)(4)-	-(b)(4)-	Pass
Repeatability	RSD -(b)(4)-	-(b)(4)-	Pass
Intermediate precision	Including working days, analysts, and microplate-reader, each RSD -(b)(4)-	-(b)(4)-	Pass
Specificity	The test solution is considered free of interfering factors if the spike recovery for each spiked sample (-(b)(4)-) is within --(b)(4)-	---(b)(4)---	Pass
Detection limit	The certified detection limit of (b)(4)- ----- --- should be verified	----(b)(4)----	Pass
Quantitation limit	The acceptance criteria for the validation parameter "linearity" must be fulfilled to verify the quantitation limit of -(b)(4)- -----	----(b)(4)----	Pass
Linearity	Correlation coefficient: ----- (b)(4)----- Slope: -----(b)(4)-----	----- (b)(4) ----- - ----- (b)(4) ----- -	Pass
Range	Y-intercept: -----(b)(4)----- The acceptance criteria for accuracy, repeatability, and linearity have to be fulfilled for a working range of -(b)(4)- ----- for the diluted end product	----- (b)(4) ----- The range is from - ----- (b)(4) ----- -----	Pass

Comment: The -----(b)(4)----- test method Q-24-324 with the defined range is suitable to quantify the endotoxins of Gram-negative bacteria in -(b)(4)- -----

9. Microbial testing of raw material-sodium chloride.

This method validation was performed with material of "Sodium chloride".

Validation parameters	Acceptance criteria	Results	Evaluation
Accuracy	Mean value of -----(b)(4)----- ----- ----- ----- may not differ by more than a -----(b)(4)----- (Negative controls may not show microbial growth)	--(b)(4)--	Pass
		---- (b)(4)----	Pass

The cryoprecipitate is stored in a freezer (b)(4)- prior to packing into the (b)(4)- containers. The cryoprecipitate was then placed into a (b)(4)- container, which is an insulating shipping system. This (b)(4)- container was loaded into a truck and transported to (b)(4)-. After passing customs the pallet was loaded into an aircraft and transported to the (b)(4)- located in (b)(4)-. From there, the product was loaded into a truck and transported to CSL Behring Marburg, Germany manufacturing site.

Temperature monitoring device preparation and calibration: All temperature monitoring devices were in a calibrated state for the execution of this study and programmed to record temperature at (b)(4)- minute intervals. There were no discrepancies reported for this section.

Procedures verification: Verification of the Standard Operation Procedure (SOP) associated with product preparation and shipping was performed. The SOP existed in an “effective” state and was part of the documentation system. There were no discrepancies reported for this section.

Transport temperature monitoring verification: The temperature monitoring was complete when the pallets arrived at the Marburg, Germany manufacturing site. During the assessments of cryoprecipitate shipping validation between CSL Behring (b)(4)- and CSL Behring Marburg, Germany, The three validation runs have shown that the transport times ranged from (b)(4)- hours to (b)(4)- hours and the product temperatures ranged from (b)(4)-C.

Comment: All the product temperatures during the transport validation maintained a temperature range of (b)(4)-. The results met the acceptance criteria.

2. *Transport validation of finished product between CSL Behring manufacturing sites in Marburg, Germany and (b)(4)- in the temperature range of 2 to 25 degrees Celsius.*

The finished product is transported from CSL Behring Marburg, Germany with cool-truck to the (b)(4)-. The aircraft is loaded and the goods are transported to the (b)(4)-. After passing the customs, the goods are loaded on a cool truck and delivered to CSL Behring (b)(4)-. Truck loading activities in Marburg, Germany are performed at 2-8 °C in a cooling area, where the truck is segregated from the outside.

The data of Truck loading, transport, and the unloading condition used in the process is summarized as follows:

Type of product	Step	Temperature	Qualification status
Finished product	Storage in Marburg	2-8 ° C, High bay warehouse (b)(4)-	Qualified by CSL Behring Marburg
Finished product packed and labeled in an outer carton	Storage in Marburg	2-8 ° C, Cooling area, (b)(4)-	Qualified by CSL Behring Marburg
Product in Pallet-Shipper (b)(4)-	Transport from Marburg to (b)(4)-	2-25 ° C, temporary storage areas with approx (b)(4)- at the --	Not applicable

Type of product	Step	Temperature	Qualification status
-----	----- - ----- -----	----- (b)(4) ----- -----	
Finished product packed and labeled in an outer carton	Storage in --- (b)(4) --	2-8 ° C, Cooling area Room - (b)(4) -, Cooling area Room - (b)(4) -	Qualified by CSL Behring --- (b)(4) -- -

The three transport validation runs have demonstrated that the maximum tolerable product temperature of 2-25 °C is maintained throughout the entire transport. The product temperature range in all runs was between 4.3 °C and 11.2 °C for -(b)(4)- hours.

Comment: Based on the results of all transportation validation runs it is considered that the current procedure for loading, transport, and unloading operations maintaining the product temperature of 2-25 °C is validated.

Review of CSL Behring's Response to the FDA's Information Request (IR)

At mid-cycle, I had one IR item, in *italics*, that was sent to CSL Behring on 15 October 2008. CSL Behring responded in an amendment on 29 October 2008.

With reference to page 4 of section 3.2.R.3-4, please provide the validation data for the ----- (b)(4) ----- technique (---- (b)(4) ---- test) used to verify the ----- (b)(4) ----- (human) protein and the ----- (b)(4) ----- protein in the samples.

CSL Behring's Response: Method validation report MVR-04-040-Q666/Q664-01 is provided in this amendment where the document provides validation data for the ----- (b)(4) ----- technique (---- (b)(4) ---- test) used to verify the ----- (b)(4) ----- (human) protein and the ----- (b)(4) ----- protein in --- (b)(4) -- samples. --- (b)(4) -- is used as an example for a “non-complex protein matrix product” derived from cryoprecipitate in this validation study.

Method validation report MVR-04-040-/Q636/Q636J/Q636U/Q637/Q658/Q660-01

“Testing of presence or absence of human and -(b)(4)- protein”, provided as part of the original BLA in CTD Module 3, Section 3.2.R.3-4, confirms that the test validation performed using --(b)(4)--- as an example, is fully valid for all CSL Behring products derived from cryoprecipitate, including Human Fibrinogen Concentrate, Pasteurized, HFCP.

Summary of the results of the validation study

Item	Validation parameter	Acceptance Criterion	Result	Evaluation
Specificity/ Identity test	---(b)(4)--- ----- ----- -----	A visible precipitate may only occur in the case that --- (b)(4) ----- was contaminated with ----- (b)(4) -----	Criterion fulfilled	Pass
	---(b)(4)--- -----	A visible precipitate may only occur in the case that	Criterion fulfilled	Pass

Item	Validation parameter	Acceptance Criterion	Result	Evaluation
	----- -----	---(b)(4)----- was contaminated with ---- (b)(4)-----		
	----- (b)(4)----- ----- -----	A visible precipitate may only occur in the case that ---(b)(4)----- was contaminated with ---- (b)(4)-----	Criterion fulfilled	Pass
	---(b)(4)--- ----- -----	A visible precipitate may only occur in the case that ---(b)(4)----- was contaminated with ----- (b)(4)-----	Criterion fulfilled	Pass
Detection limit	Detection limit of ---(b)(4)--- that is contaminated with -----(b)(4)--- -	A visible precipitate has to occur in all samples that were contaminated with --- --(b)(4)--- and ----- (b)(4)----- ----- -----	Detection limit ----- (b)(4)----- Criterion fulfilled	Pass
Robustness	Investigation of the shelf life of samples contaminated with -----(b)(4)--- - (storage time: ----- (b)(4)--- -----, storage temperature: -----(b)(4)-)	A visible precipitate has to occur in all samples that were stored at -(b)(4)- and contaminated with (b)(4)--- ----- ----- ----- -----	Detection limit ----- (b)(4)----- Criterion fulfilled for --(b)(4)--- -----	Pass

Comment: The response is adequate.

Recommendation

The information on analytical procedures and methods validation in this submission provided is acceptable , and supportive of the approval of this original BLA.