

MEMORANDUM



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



To: Administrative File for BLA (STN 125591/0)
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Through: Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR

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Subject: Final CMC Review of CSLB's BLA for Antihemophilic Factor (Recombinant),
Single Chain [AFSTYLA]

Contents

1. Executive Summary	2
2. Background	3
3. Review History	4
4. Manufacturing Process.....	5
4.1. Manufacturers	5
4.2. Bulk Drug Intermediate and Bulk Drug Substance	7
4.3. Final Drug Product.....	8
4.4. Controls of Critical Steps and Intermediates	9
4.5. Analytical Methods, Release Specifications and Reference Standards	10
4.6. Control of Excipients	20
5. Process Development, Validation and Qualification	20
5.1. Cell Substrate	20
5.2. Process Development.....	20
5.3. Process Validation	22
6. Elucidation of Structure, Function and Impurities.....	23
6.1. Structure and Function Studies	23
6.2. Characterization of Impurities	25
7. Methods Used in Clinical Trials	26
8. Stability	26
8.1. Drug Substance	26
8.2. Drug Product	27
8.3. Post-Approval Stability Protocol	28

9. Post Marketing Commitments	29
10. Chemistry, Manufacturing and Controls - Conclusion	29
APPENDIX.....	30

1. Executive Summary

STN 125591/0 is an original biologics license application (BLA) submitted by CSL Behring Recombinant Facility AG (CSLB) for Antihemophilic Factor (Recombinant), Single Chain with the proprietary name AFSTYLA. The active ingredient of AFSTYLA is a recombinant analogue of human Coagulation Factor (F) VIII with genetic mutations that removed most of the FVIII B-domain and 4 amino acids of the adjacent acidic a3 domain. The genetic manipulation, which will be described in detail below, also resulted in the expression of the protein as a single chain versus a heterodimer found in wild-type FVIII. The protein is expressed in a Chinese Hamster Ovary (CHO) cell line, and purified using traditional manufacturing methodologies. The product is supplied as a preservative-free, lyophilized formulation presented in 5 dosage strengths of 250, 500, 1000, 2000 and 3000 IU in single-use glass vials of 6 mL (250, 500 and 1000 IU) or 10 mL (2000 and 3000 IU) nominal capacity. AFSTYLA is reconstituted with sterile Water for Injection (sWFI) using a needleless transfer device, Mix2vial™, giving volumes of 2.5 mL (for 250, 500 and 1000 IU) and 5 mL (for 2000 and 3000 IU).

AFSTYLA is indicated to treat children and adults with hemophilia A (congenital FVIII deficiency) for: (1) On-demand treatment and control of bleeding episodes, (2) Routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and (3) Perioperative management of bleeding.

STN 125591/0 was reviewed under the standard review schedule of the PDUFA V Program. CSLB submitted the BLA on 29 May 2015 and the PDUFA V action due date is 28 May 2016.

The scope of this review covers all CMC product topics except the Cell Bank System (reviewed by Dr. Natalya Ananyeva), evaluation of safety regarding adventitious agents (reviewed by Dr. Ze Peng), and Endotoxin and Bioburden test methods (reviewed by reviewers from the Division of Biological Standards and product Quality (DBSQC) in the Office of Compliance and Biologics Quality).

All substantive CMC issues were resolved during the review of the AFSTYLA BLA. In addition, CSLB made post-marketing CMC commitments to i) assess data after producing (b) (4) commercial scale GMP batches to revise the acceptance criteria of the (b) (4) specification, ii) investigate (b) (4)

, and iii) develop and validate an (b) (4) method in which the (b) (4)

Conclusion

The CMC data support the quality and safety of AFSTYLA to be used in the treatment of children and adults with hemophilia A. Therefore, approval of the BLA is recommended from a CMC perspective.

2. Background

AFSTYLA was developed for the U.S. market under IND 14791 for the on-demand treatment and control of bleeding episodes (BE), peri-operative management of bleeding, and routine prophylaxis to prevent or reduce the frequency of BE in children and adults with hemophilia A.

Hemophilia A and hemophilia B (FIX deficiency) affect 1 in 5,000 male births. The exact number of people living with hemophilia in the United States is not known, but currently the number is estimated to be about 20,000, of which 80% have hemophilia A.

Several FVIII products are licensed in the United States for the treatment of people with hemophilia A. These products include several recombinant full-length and B-domain deleted FVIII products, one recombinant FVIII-Fc Fusion Protein product, one PEGylated recombinant FVIII product, and several plasma-derived FVIII products.

For the purpose of consistency, the name AFSTYLA is used throughout the memo. In the BLA, the product is referred to by the name “*recombinant single-chain coagulation factor VIII*”, company code “CSL627” or acronym *rVIII-SingleChain*. The FDA proper name is “*Antihemophilic Factor (Recombinant), Single Chain*”. The recommended INN as published in the World Health Organization’s (WHO’s) List 73 is “*lonoctocog alfa*”.

After the activation of AFSTYLA and the removal of its (b) (4) B- and a3-domain, the activated rFVIII (rFVIIIa) molecule formed has an amino acid sequence identical to that of the FVIIIa formed from the endogenous, full-length FVIII. Therefore, AFSTYLA shares the same mechanism of action with other licensed FVIII products in hemostasis.

Figure 1 shows the structure of AFSTYLA: its domain structure, linkage between the heavy and light chains of FVIII, thrombin cleavage sites, and N-glycosylation sites. The new glycosylation site is indicated by a glycan structure shown in red. The amino acid numbering is based on the mature, full-length FVIII.

Figure 1: AFSTYLA structure.



3. Review History

The application was submitted on 29 May 2015. The BLA was reviewed under the standard 12-month schedule of the PDUFA V program.

An Information Request (IR) regarding the (b) (4) assay was sent to the company on 15 December 2015, and CSLB response was received on 23 December 2015 as amendment 125591/0.13. An extensive IR was sent on 18 December 2015 with questions regarding the justification of specifications and validations of analytical procedures. Partial responses from CSLB were received on 8 January 2016 as amendment 125591/0.15, with subsequent responses received on 29 January 2016 as amendment 125591/0.18 and on 29 February 2016 as amendment 125591/0.24. Some responses were found to be insufficient and a follow-up IR was sent on 17 February 2016. CSLB responses were received on 8 March 2016 as part of amendment 125591/0.27 and were found to be acceptable. In this amendment, CSLB also agreed to a Post-marketing Commitment (PMC) to establish (b) (4) acceptance criteria when the number of (b) (4) batches sufficient for statistical analysis is manufactured, which is acceptable to us.

An IR regarding an (b) (4) observed in the in-support testing of 250 IU DP by (b) (4) was sent on 20 January 2016. CSLB responses were received on 3 February 2016 as amendment 125591/0.21, but were found to be insufficient and a follow-up IR was sent on 17 February 2016. CSLB responses were received on 8 March 2016 as part of amendment 125591/0.27 and were found acceptable. CSLB also agreed to a PMC (the text was submitted on 15 April 2016 as part of amendment 125591/0.35) to further investigate this issue and develop a (b) (4) method, which is acceptable to us.

Other minor IRs were sent on 10 March 2016 and 11 April 2016 with satisfactory responses received on 18 March 2016 in amendment 125591/0.29 and on 20 April 2016 in amendment 125591/0.36, respectively.

The texts of all IRs are provided in the appendix of this memorandum.

Some review issues were also discussed with the company during the pre-license inspection (PLI) of the (b) (4) and during the Late-Cycle Meeting on 18 February 2016.

4. Manufacturing Process

4.1. Manufacturers

The manufacture of AFSTYLA is divided into two main stages (see Figure 2) conducted at two manufacturing facilities. Production of the Bulk Drug Intermediate (BDI) takes place at the contract manufacturer (b) (4), which was not previously licensed and was inspected during the review of this BLA. The productions of the Bulk Drug Substance (BDS) and Final Drug Product (FDP) are performed at the FDA-licensed facility of CSLB's subsidiary CSLB Behring GmbH in Marburg, Germany (Table 1).

Reviewer's Comments (all italicized text in the rest of the memorandum represents this reviewer's comments):

The split BDS manufacturing approach (BDI production by contract manufacturer and further manufacture to the BDS at CSLB in Marburg) is applied for all recombinant coagulation factor products developed by CSLB in recent years, which include AFSTYLA, Recombinant Coagulation Factor IX-Albumin Fusion Protein (IDELVION), (b) (4)

(b) (4) Split BDS manufacturing takes advantage of the (b) (4) expertise of specialized contractor companies and the extensive coagulation factor purification expertise in CSLB's plasma fractionating facility in Marburg, Germany.

Table 1: Manufacturing Facilities for AFSTYLA

Name/Address	FEI Number	DUNS number	Inspection/waiver	Justification /Results
<i>Drug Substance Intermediate</i> Manufacturing and Testing (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER DMPQ (b) (4) NAI
<i>Drug Substance</i> Manufacturing and Testing <i>Drug Product</i> Formulation, Fill/Finish, Labeling & Packaging, Testing CSL Behring GmbH (CSLB) Emil-von-Behring-Strasse 76 D- 35041 Marburg, Germany	3003098680	326530474	Waived	CBER DMPQ May 28- June 5, 2015 VAI

CBER conducted a PLI of (b) (4), the manufacturing and testing facility for the drug substance intermediate, from (b) (4). At the end of the inspection, no Form FDA 483 was issued. The inspection was classified as no action indicated (NAI).

The inspection team consisted of DMPQ inspector, LCDR Donald Ertel and OBRR product reviewer Dr. Alexey Khrenov. My overall impression was that the AFSTYLA BDI manufacturing process is well controlled, (b) (4) staff is well trained and the procedures are in place and adequate to handle any process deviations.

CBER conducted a PLI of CSLB in Marburg from May 28 - June 5, 2015 for the BLA of another product (IDELVION, reviewed under STN 125582/0). At the end of the inspection, a Form FDA 483 with 19 observations was issued. The deficiencies were related to the quality and manufacturing systems. The firm responded to the observations on July 1, 2015 and the corrective actions were reviewed and found to be adequate. All inspectional issues were considered to be satisfactorily resolved and the inspection was classified as voluntary action indicated (VAI).

Considering that the manufacturing and testing operations of AFSTYLA and IDELVION at the Marburg facility are performed in the same areas and laboratory facilities, the decision was made by DMPQ, and supported by DHRR, to waive the PLI for the CSLB Marburg facility for this BLA.

Batch and Scale Definition

(b) (4)

4.2. Bulk Drug Intermediate and Bulk Drug Substance

The AFSTYLA manufacturing process (Figure 2) is relatively standard for a coagulation factor product manufactured using recombinant DNA technology. AFSTYLA is purified using a (b) (4) steps designed to reduce the levels of product- and process-related impurities.

(b) (4)

(b) (4)

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4.3. Final Drug Product

(b) (4) is used to manufacture (b) (4) batches of FDP. The FDP batch size varies between approximately (b) (4) vials depending on which dosage presentation is manufactured. The FDP is provided as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000, 2000 and 3000 IU of FVIII activity (Table 2). There are no overages in the filling of AFSTYLA.

The sterilizing filtration of the DP (b) (4) All defined in-process control parameters (b) (4) sterilizing filtration have to fulfill all the requirements. The validation data were provided and discussed below.

The FDP is reconstituted with sWFI using a needleless device *Mix2vial*. Reviewer's comment: *The Mix2vial is cleared under 510(k) K031861. sWFI is manufactured by CSLB in Marburg. The same sWFI is co-packaged with 5 licensed products manufactured by CSLB, including plasma-derived FIX MonoNine®. CSLB has provided references to DMF(b) (4) under which the sWFI is manufactured.*

Table 2: Nominal composition of reconstituted AFSTYLA

Ingredient	Nominal composition after reconstitution with sWFI					Function
	250 IU vial	500 IU vial	1000 IU vial	2000 IU vial	3000 IU vial	
Factor VIII activity	100 IU/mL	200 IU/mL	400 IU/mL	400 IU/mL	600 IU/mL	Active Substance
Sodium chloride	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Polysorbate 80	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Calcium chloride	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucrose	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
L-Histidine	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

4.4. Controls of Critical Steps and Intermediates

The process control strategy was developed using a risk-based and science-based approach based on regulatory guidance provided by ICH Q8 – Q10 that ensures the consistency of the manufacturing process and product quality. The control strategy was developed to appropriately control sources of process variability such that the desired process performance and product quality (i.e., Critical Quality Attributes (CQAs)) are consistently achieved. For all operating parameters, assessments were undertaken to understand which parameters have the greatest potential to impact process performance and product quality.

The CQAs were defined based on the AFSTYLA Quality Target Product Profile (QTPP) and risk assessment of quality attributes, see Table 3 below.

I found these CQAs adequate and complete. The QTPP for AFSTYLA was consistent with typical development targets for coagulation factor products developed for hemophilia treatment .

Table 3: AFSTYLA CQAs for BDS and FDP

Quality attribute category	CQA
(b) (4)	(b) (4)

(b) (4)

CSLB defined critical process steps as those containing either a CPP, an In-Process Control (IPC), or In-Process Acceptance Criterion (IPAC) or both. The critical process steps were derived from extensive risk assessments, process characterization studies, manufacturing experience, and scientific rational. In-process testing is performed at each process parameter by process step.

BDS and FDP process parameters were assessed via a Failure Mode and Effect Analysis (FMEA). The purpose of this assessment was to evaluate all process parameters with regard to risk of failure (i.e., operating outside of the defined operating ranges) and to consequently identify a list of High Risk Process Parameters (further sub-categorized into Critical, Less Critical, Key, and Non-Critical based on a defined scoring system) according to a pre-determined set of FMEA scoring criteria.

I found that the controls of critical steps and intermediates are acceptable. The tiered classification system allows for better process understanding and facilitates risk management.

4.5. Analytical Methods, Release Specifications and Reference Standards

Due to the significant number of analytical methods used and the amount of information associated with them, this section outlines only the issues raised during the review and does not contain descriptive information. If the particular method is not mentioned, it is because no issues were identified.

DRUG SUBSTANCE AND DRUG PRODUCT SPECIFICATIONS

1. General Approach to Justification of Specification and setting of acceptance criteria

The original Justification of Specification documents submitted in the BLA did not provide data analysis and clear rationales for the setting of the acceptance criteria for the majority of the specification parameters for BDS and FDP. Most of the acceptance criteria were justified as (b) (4)

[REDACTED] CSLB was requested to review and revise the ranges and limits for all quantitative parameters in the specifications based on statistical analyses of the data acquired from testing of all FDP and BDS lots manufactured up to date and submit to the BLA the complete datasets used for the establishment of the revised specification ranges or limits; and the statistical analyses employed.

CSLB acknowledged the deficiency, performed the requested analysis and provided FDA with the data. They chose to establish the acceptance criteria based on the (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

As the number of the (b) (4) lots manufactured to date is limited due to the very high yield of the manufacturing process, CSLB claimed that revising the acceptance criteria for (b) (4) specification based on statistical analysis is not feasible. Instead, temporary alert limits were established as presented in Table 4 (proposed limits are listed in bold), and CSLB committed to revise or establish the acceptance criteria when data are available from (b) (4) batches manufactured by commercial process.

More data were available for the FDP as multiple FDP batches are produced from a (b) (4) [REDACTED], thus the FDP specifications were changed (mostly tightened) as presented in Table 5 below (revised specifications are listed in bold). In this reviewer's opinion, the current specifications are adequate to control the quality of AFSTYLA FDP and BDS.

Table 4: Specifications and alert limits for the AFSTYLA BDS

(b) (4)

(b) (4)

Table 5: Specifications for the AFSTYLA FDP

Test	Parameter Monitored	Current Specification	Proposal for revised specification
Practicability and organoleptic properties	Quality	Lyophilized powder: White to slightly yellow powder (b) (4) Dissolution time: (b) (4) Reconstituted solution: Almost colorless, clear to slightly opalescent solution	(b) (4)
(b) (4)	Quality	(b) (4)	(b) (4)
(b) (4)	Quality	(b) (4)	(b) (4)
Residual moisture	Quality	(b) (4)	(b) (4)
Sodium	Quality	(b) (4)	(b) (4)
Calcium	Quality	(b) (4)	(b) (4)
Sucrose	Quality	(b) (4)	(b) (4)
Histidine	Quality	(b) (4)	(b) (4)
Polysorbate 80	Quality	(b) (4)	(b) (4)
(b) (4)	Purity	(b) (4)	(b) (4)
Protein composition (b) (4)	Purity	(b) (4)	(b) (4)

Test	Parameter Monitored	Current Specification	Proposal for revised specification
Chromogenic substrate (ChS) FVIII activity	Potency Identity	250 IU: (b) (4) 500 IU: (b) (4) 1000 IU: (b) (4) 2000 IU: (b) (4) 3000 IU: (b) (4)	(b) (4)
Protein concentration	Quality	(b) (4)	(b) (4)
(b) (4) FVIII activity	Purity	(b) (4)	(b) (4)
Sterility	Purity	(b) (4) 21 CFR, (b) (4)	(b) (4) .. (b) (4)
Bacterial endotoxins	Purity	(b) (4)	(b) (4)
Particulate matter	Purity	(b) (4)	(b) (4)
(b) (4)	Quality	(b) (4)	(b) (4)

2. Specifications found to be inadequate and non-informative

(b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

ANALYTICAL PROCEDURES

1. Approach to setting acceptance criteria in the validation of analytical procedures

During the review of the validation reports for the majority of the analytical procedures, I found the approach CSLB used to set the acceptance criteria for validation parameters to be statistically unsound. In particular, CSLB would define a single acceptance criterion for relative standard deviation (RSD) to be ^{(b) (4)} of the specification range while validating the precision or accuracy of the analytical methods.




The same issue was observed in the BLA for IDELVION and resolved during the review of that submission (the BLA for AFSTYLA was submitted before the issue for IDELVION was resolved). As the performance characteristics of a number of methods were established in the validation studies albeit with an inappropriately set acceptance criteria, we decided not to request revalidations of these methods, but rather to request CSLB to re-evaluate these performance characteristics along

with the revised specifications to ensure that the methods are still suitable for their intended purpose, which was done.


2. Deficiencies in Validation of Analytical procedures

a. Host Cell Proteins (HCP) (b) (4) assay

(b) (4)




(b) (4)



b. Determination of protein content (b) (4) Assay

(b) (4)



(b) (4)

CSLB addressed this concern by providing additional data on intermediate precision, performing supplemental validation and clarifying the language of the test instructions. These measures were found adequate.

c. Other issues

Multiple issues (incorrect range validated, incorrect versions of test instructions submitted, unclear validation reports) were identified in several analytical procedures, and were conveyed to the company through IRs, which are provided in the appendix. All the issues were successfully addressed by the company.

INCONSISTENCY BETWEEN BATCH ANALYSIS AND IN-SUPPORT TESTING FOR
(b) (4)

During in-support testing of 250 IU batches, an (b) (4)

(b) (4)

(b) (4)

Reference Standards and Materials

The respective reference standards and their maintenance program were established. A single primary product-specific potency standard calibrated against the (b) (4) WHO International Standard for Factor VIII Concentrate was developed from a (b) (4) of AFSTYLA manufactured at commercial scale and have been used since 08 December 2014 as the reference standard for all in-process and release testing of AFSTYLA. The structural and functional properties of this reference standard are extensively characterized. Prior to the development of this product-specific reference standard, the (b) (4) WHO International Standard for Factor VIII Concentrate and (b) (4) product standard (also calibrated against the (b) (4) WHO International Standard for Factor VIII Concentrate) were used for potency assignment.

The Working Standard for product-specific (b) (4) . It was used to generate the (b) (4) used in the assay and is employed as a reference at the protein concentration indicated on the corresponding certificate.

The remaining reference standards used for different assays are commercially available materials.

In-support testing

CBER has performed in-support testing of the following commercial scale AFSTYLA batches:.

1. (b) (4) (250 IU)
2. (b) (4) (250 IU)
3. (b) (4) (500 IU)
4. (b) (4) (1000 IU)
5. (b) (4) (1000 IU)
6. (b) (4) (3000 IU)

Test results were deemed consistent with the proposed commercial release specifications (except for (b) (4) assay as described above).

Exemption from CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (December 8, 1995), routine lot-by-lot CBER release is not required for AFSTYLA because it is a well-characterized recombinant product. *Reviewer's comment: Exemption of AFSTYLA from CBER Lot Release is consistent with all of the recently approved coagulation factor products.*

4.6. Control of Excipients

All excipients used in the preparation of AFSTYLA comply with the current compendial monographs.

All excipients are purchased from approved suppliers in accordance with written specifications, which describe the acceptance and release criteria. Prior to release, all excipients used in the manufacturing process are tested according to CSLB's in-house specifications and comply with international Pharmacopeial standards (e.g., USP-NF, Ph. Eur.). CSLB has qualified all analytical procedures described in the (b) (4) as well as validated all (b) (4) procedures.

5. Process Development, Validation and Qualification

5.1. Cell Substrate

The details of cell substrate regarding its development and controls are described in the memorandum from Dr. Natalya Ananyeva.

5.2. Process Development

The BDS manufacturing process was developed in 2 stages described in Table 6 below. Various process changes were implemented throughout the process development history in response to increased process knowledge and scale-up activities. Besides scale-up and (b) (4), only minor process adaptations were introduced in the commercial scale (CS) process to adopt the process to the facility with the larger equipment.

Table 6: Key stages of manufacturing processes development



(b) (4)

In order to establish that the early nonclinical and clinical data generated using material from the pilot scale (PS) process was supportive of conducting further clinical studies using material manufactured by the CS process, comparability studies were performed.

These comparability studies included comparison of process performance throughout the manufacturing process and comparison of specification test results and additional characterization assessments conducted at the BDI, BDS and FDP stages.

The comparison of process performance between the PS and CS processes included:

- Comparability of process parameters throughout the manufacturing process,
- Comparability of product quality attributes throughout the BDS manufacturing process, and
- Comparability of process performance attributes (performance parameters) throughout the BDS manufacturing process.

Product comparability was assessed by comparing product quality attributes of materials derived from the CS and PS processes, at the provisional specification stages of BDI, BDS and FDP. The analytical testing included routine provisional specification testing, as well as a range of characterization assessments conducted at these stages. The product comparability study assessed a wide range of product quality attributes including product-related substances/product composition, product- and process-related impurity profiles, posttranslational modifications (PTMs), and structural and functional properties.

FDP comparability comprised product safety attributes (b) (4) content),
filling and lyophilization performance attributes (b) (4)
, and product quality attributes (b) (4)

The following functional product attributes of the AFSTYLA FDP lots were assessed:

(b) (4)

In addition, the stability of process intermediates obtained at PS and CS was investigated and it was assessed whether these data support the comparability of both scales.

CSLB's data demonstrate that the PS and CS AFSTYLA BDS and FDP manufacturing processes are comparable with regard to consistency of manufacture, quality and stability of AFSTYLA.

5.3. Process Validation

Process Performance Qualification (PPQ) was accomplished in three separate parts, corresponding to the three major stages of production, BDI (b) (4) PPQ batches from (b) (4), BDS (b) (4) PPQ batches) and FDP (b) (4) PPQ batches). Although the PPQ batches for the BDI process and PPQ batches for the BDS process were performed in separate and independent PPQ campaigns, the corresponding non-PPQ portions of the processes were performed under representative commercial process conditions. PPQ for FDP consisted of the manufacture of (b) (4) consecutive batches covering each of the filling sizes. The PPQ data demonstrated that the manufacturing processes for AFSTYLA BDI, BDS and FDP were successfully qualified.

In addition to the PPQ studies, several ancillary validation studies were performed to support the consistency of the manufacture of AFSTYLA BDI and BDS. The studies included **In-Process Hold Time Validation**, (b) (4) **Validation**, **Mixing Validation**. For AFSTYLA FDP, the results of several validation studies were provided as well, including **Validation of filling**, **Validation of lyophilization cycles**, **Validation of (b) (4)**, **Validation of the mixing steps**, **Validation of hold times**, **Validation of (b) (4)** and **Final filter validation**.

CSLB requested, as part of the standard manufacturing process procedure, to allow the (b) (4)

*Such request is uncommon, and usually the permission to reprocess is submitted and reviewed as one-time exception request in a prior approval supplement. CSLB successfully validated the (b) (4) FDP batches and provided data in the report **Validation of (b) (4)**. I found the data acceptable and have no objection to the approval of this procedure.*

CSLB developed Continued Process Verification (CPV) plans at both (b) (4) CSLB Behring GmbH to ensure the validated state of the AFSTYLA manufacturing process throughout the product lifecycle. The CPV program is designed to collect process data and perform statistical evaluation of the dataset in order to routinely confirm the validated state and to identify and evaluate planned and unplanned changes in the manufacturing process.

I found no deficiencies in the process validation studies. The PPQ data demonstrate that the AFSTYLA BDI, BDS and FDP manufacturing processes were successfully qualified confirming the suitability of the Process Control Strategy.

6. Elucidation of Structure, Function and Impurities

6.1. Structure and Function Studies

The structure and function of AFSTYLA were characterized in a series of studies, which also examined the comparability of AFSTYLA batches manufactured at different sites and scales of the manufacturing process during product development. Functional characterization indicated similarity between AFSTYLA and licensed plasma-derived and rFVIII products in several parameters tested, except for the significant discrepancy between the results from the OS and ChS assays described below.

Minimal BDS lot-to-lot variability was observed between AFSTYLA batches produced at different scales or process iterations.

Potency

The potency of AFSTYLA is expressed in international units of FVIII activity and determined using an *in vitro* ChS assay. Comparison of the potency assignments for AFSTYLA using the ChS and OS assays revealed an approximate 2-fold difference, with the OS assay giving a lower value than the ChS assay. CSLB conducted non-clinical and *in vivo* investigation of the hemostatic effects of AFSTYLA and concluded from the data that a potency assignment using the ChS assay results in the most accurate assignment of 1 IU to an amount of protein that matches the hemostatic potential of FVIII in 1 mL of plasma in healthy individuals. Consequently, the materials used in all the clinical studies received a potency assignment based on the ChS assay.

To support the selection of a potency assay for AFSTYLA, several *in vitro* investigations were performed to examine the different aspects of FVIII potency testing and related functional characterizations of AFSTYLA:

(b) (4)

(b) (4)

As a result, the potency assignment by the OS assay will result in a significantly larger amount of FVIII protein in the vial and dose, whereas the ChS-assigned potency allows for a FVIII protein content comparable to those of currently licensed recombinant B-domain-deleted FVIII products.

There is no evidence to indicate that the (b) (4) of AFSTYLA (b) (4) affects its hemostatic function. All the materials used in the clinical studies received a potency assignment based on the ChS assay. The efficacy was demonstrated for all the proposed indications and no evidence of under-dosing was observed.

As a result of the assay discrepancy, under-estimations of FVIII activity in post-infusion plasma samples can be expected in clinical settings because the OS assay with a plasma reference standard for FVIII activity is customarily used in the majority of the clinical laboratories in the United States. This underestimation may potentially lead to patients receiving more AFSTYLA than is needed.

CSLB central laboratory characterized the relationship between the OS and ChS assays for AFSTYLA in the pharmacokinetics (PK) investigations of 130 subjects from the two clinical trials

used to support licensure. From these data, CSLB claims a strong linear relationship between the ChS and OS assay results, with the OS assay results consistently being 45% lower than the ChS assay results. Therefore, CSLB claims that the AFSTYLA FVIII activity data obtained using the OS assay can be aligned with that obtained using the ChS assay by multiplying the OS assay result by a correction factor of two. These results were confirmed in a field study involving (b) (4) clinical laboratories (including 13 from the United States). FDA agreed with CSLB's proposal to include the conversion factor, but noted that specific measures are required to adequately convey this information to the clinicians, the hemophilia community, and to all those involved in the care of patients with hemophilia A in order to facilitate adequate monitoring, and to prevent over-dosing of AFSTYLA. To address this issue, specific communication and labeling strategies were developed by CSLB.

The potency assay and the potency labeling are considered validated by the favorable hemostatic efficacy demonstrated by AFSTYLA in all clinical trials. The comprehensive functional studies performed by CSLB produce sufficient explanation for assay discrepancy and also support the claim that the ChS assay is reflective of hemostatic efficacy. Additionally, special government employee was consulted on the issue and answered positively to the question "Does the information provided support Sponsor's proposal to assign potency of their Factor VIII product by a chromogenic substrate (ChS) assay based on the potency assignment and the correlation with clinical outcomes?". Additionally, Biogen published similar findings regarding the functional characterization of single-chain FVIII form present in their product. While in this reviewer's opinion, CSLB presented strong argument for ChS potency labeling for AFSTYLA, some small under-dosing risk may exist. Ultimate decision to allow ChS-based potency labeling was made by OBRR management.

6.2. Characterization of Impurities

Relevant product-related impurities of AFSTYLA have been assessed including (b) (4)



I found that CSLB's impurity investigations were complete and their findings were acceptable. AFSTYLA does not contain unexpected impurities that may have a negative impact on the safety and efficacy. Based on the characterization studies and analysis of the study results, adequate release and in-process tests and acceptance criteria for the control of impurities were implemented.

7. Methods Used in Clinical Trials

The following assays were used and validated in house by CSLB for the evaluation of clinical study samples:

- Determination of FVIII activity in plasma samples: ChS assay
- Determination of FVIII activity in plasma samples: OS assay
- Determination of inhibitors against FVIII
- Determination of non-inhibitory anti-drug antibodies (ADAs)
- Determination of antibodies against CHO host cell proteins

Recognizing the potential of high variation in FVIII activity measurement in other laboratories outside of CSLB central laboratory, CSLB initiated a field study to investigate clinical laboratory performance measuring AFSTYLA and Advate (recombinant full-length FVIII) activity in blinded samples. The study results demonstrated consistent ChS/OS assay ratio despite differences in the methodology used in different laboratories.

CSLB used a tiered approach to test the presence of antibodies against CHO host cell proteins from the AFSTYLA (b) (4) in plasma samples. An initial screening (b) (4) assay is carried out to detect antibodies against HCP. To confirm the presence of anti-HCP antibodies in positive samples, a (b) (4) assay was developed.

An (b) (4) method was developed and validated to monitor the development of antibodies against AFSTYLA.


Anti-FVIII inhibitory antibody activity was measured by a traditional (b) (4) Bethesda clotting assay.

Review of pharmacokinetics and immunogenicity assays did not identify significant issues.

8. Stability

8.1. Bulk Drug Substance

(b) (4)



(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

8.2. Final Drug Product

Based on currently available real-time data for both PS and CS batches, a shelf-life of 3 years at +5°C including a single period of up to 3 months at +25 °C within the expiration date, is claimed for all dosage strengths.

If stored at room temperature, the package insert instructs the user to record the date that AFSTYLA is removed from refrigeration on the top flap of the carton. After storage at room temperature, AFSTYLA should not be returned to the refrigerator. The powder form for the product then expires after storage at room temperature for 3 months, or after the expiration date on the product vial, whichever is earlier.

This stability claim is supported primarily by long-term stability studies on CS batches that were called temperature shift studies to reflect the change from +5 °C storage to +25 °C in line with the shelf-life claim.

Two principle schemes were applied to reflect the different timing of the +25 °C storage window over the shelf-life:

(b) (4)

These primary studies are supplemented by additional stability studies at constant temperatures.

The stability data support the proposed storage regimen for AFSTYLA FDP.

To determine photostability, samples were exposed to light providing an overall illumination of not less than (b) (4)

As the reconstituted product does not contain a preservative, from a microbiological point of view, reconstituted AFSTYLA should be used as soon as possible after reconstitution and within 4 hours. The data provided demonstrated reconstituted product physicochemical stability for up to (b) (4) at a maximum of +25 °C.

The proposed in-use stability claim is appropriate.

8.3. Post-Approval Stability Protocol

(b) (4) follow-up stability studies will be performed for (b) (4) of each AFSTYLA presentation. Detailed stability protocol is provided in the BLA.

The original submission lacked a detailed post-approval stability protocol which was provided per FDA request. The stability protocol presented allows sufficient control of FDP stability post-approval.

9. Post-Marketing Commitments

The following post-marketing commitments not subject to the reporting requirements under section 506B were agreed to by CSLB:

- i) CSLB commits to assess data after producing (b) (4) commercial scale GMP batches to revise the acceptance criteria of the (b) (4) CSLB commits to perform an interim statistical re-assessment of the alert limits after evaluating commercial scale GMP batches manufactured by May 31, 2017 and submit the interim report as a Changes Being Effected **Supplement contains PMR/PMC Submission – Final Study Report** by July 31, 2017 and submit the final acceptance criteria as a Prior Approval **Supplement contains PMR/PMC Submission – Final Study Report** by September 30, 2018.
- ii) CSLB commits to investigate the (b) (4) , and agrees to submit a Supplement containing the Post-marketing Commitment – Final Study Report by May 31, 2017.
- iii) CSLB commits to develop and validate an (b) (4) method in which the (b) (4) , and agrees to submit a Supplement containing the Post-marketing Commitment - Final Study Report by May 31, 2017.

10. Chemistry, Manufacturing and Controls - Conclusion

The manufacturing process of AFSTYLA is considered to be adequately validated and sufficiently controlled to ensure consistent manufacture of the commercial product that meets the release specifications. The CMC data support the quality and safety of AFSTYLA to be used in the treatment of children and adults with hemophilia A.

I found the CMC information to be supportive of the quality, identity, purity, potency and safety of AFSTYLA, and recommend approval of this BLA.

APPENDIX

INFORMATION REQUESTS SENT TO THE COMPANY.

IR sent on 15 December 2015.

With reference to testing instruction Q-16-410, version 4.0, (b) (4)

recombinant factor VIII”:

1. The testing instruction mentions an “accuracy control sample” prepared by (b) (4). Please provide the following information, missing from the testing instruction: a. How results from analysis of the “accuracy control sample” are used and what are the acceptance criteria for the “accuracy control sample”; b. If the “accuracy control sample” is being prepared from each lot analyzed or if a single “accuracy control sample” sample is used for the analysis of multiple lots.

2. Lot (b) (4) is reported with (b) (4) in the batch analysis. Please provide the results and acceptance criteria for analysis of the “accuracy control sample” for this lot.

IR sent on 18 December 2015.

1. Please revise the release specifications, including the “Justification of Specifications,” for bulk drug substance (BDS) and final drug product (FDP). Specifically,

a. Please review and revise acceptance ranges or limits for all quantitative parameters in the DS and FDP release specifications based on statistical analyses of the data acquired from release results of all FDP and DS lots manufactured, to date. Please submit the complete datasets used for establishment of the revised specification acceptance ranges or limits and the statistical analyses employed.

b. The current specification for (b) (4) is not informative and does not allow sufficient control for potential changes in the (b) (4). The Agency considers a (b) (4) to be a critical quality attribute. Please revise the specification to establish quantitative acceptance criteria for (b) (4) analyses to ensure continued product quality and manufacturing consistency.

c. The current specification for (b) (4) is not justified. The (b) (4) used for identity confirmation are found in all FVIII (b) (4) studied and their presence is not sufficient to confirm identity of rFVIII-Single Chain (see question 3b). Please establish an identity test specific for rFVIII-Single Chain.

d. Please establish a drug substance release specification for (b) (4), which may be in addition to or *in lieu* of in-process control testing for (b) (4).

2. As we discussed during the pre-license inspection for BLA 125582, the (b) (4) " was used inappropriately to set the acceptance criteria in the validation studies. While the use of (b) (4) of the specification range as an assay range may be appropriate in some situations, the use of this value as the standard deviation of the analytical method is not justified. However, the performance characteristics of a number of methods (except for those listed in item 3 below) were established in the validation studies albeit with inappropriately set acceptance criteria. Therefore, please re-evaluate these performance characteristics along with the revised specifications to ensure that the methods are suitable for their intended purpose.

3. The following issues were identified in the validations and/or testing instructions for the specified analytical methods. Please address each item accordingly, and submit the amended documents to the FDA.

(b) (4)

i. Please submit complete Testing Instruction-42-052 including attachments.

ii. Method validation used a different procedure from the testing instruction. (b) (4)

Please re-establish the specification and re-validate the method, accordingly.

(b) (4) analysis

i. Please re-validate the assay for the intended purpose as described under 1(b) above.

ii. Please consider qualifying a suitable reference standard for this assay.

(b) (4)

d. CHO Host Cell Protein assay by (b) (4)

i. It is not clear from the report 030200111 if the HCP preparation used for the production of (b) (4) was produced with the pilot or commercial scale process. It is also not clear if the verification of (b) (4) performance was done using commercial scale or pilot scale sample. Please provide this information.

ii. The quality of (b) (4) used to determine the (b) (4), and does not allow reliable calculation of (b) (4). Please repeat the experiments using commercial scale samples and submit the results.

e. Protein composition by (b) (4)

The claimed range of the method, (b) (4) is inferred from results of the validation of the linearity and accuracy. However, there is no evidence in the validation report that accuracy was validated over the range of the method. Please provide data establishing the accuracy of the method in the range of (b) (4)

(b) (4)

g. Determination of protein content by (b) (4) Assay

Validation of intermediate precision is insufficient. The data demonstrates significant difference (b) (4) analysts who analyzed samples on different days. Due to the limited amount of data and lack of matrix approach in the validation study design, it is impossible to estimate intermediate precision of the method and determine its suitability for intended purpose. Please perform supplemental validation of this parameter.

4. As was discussed during pre-license inspection of (b) (4) facility, please provide in an amendment to the BLA, the specifications for (b) (4)

5. With reference to the post-approval stability studies detailed in the original BLA submission:

a. Please modify section 3.2.P.8.2 Post-approval Stability Protocol And Stability Commitment, adding detailed stability protocol, including testing schedule

b. Please submit Stability Protocols for Master Cell Bank and Working Cell Bank, and specify tests to be performed and frequency of testing.

IR sent on 20 January 2016.

During in-support testing of lots (b) (4) (both 250 IU strength) by (b) (4) according to testing instruction Q-16-410 (version 5.0), both samples, when tested after reconstitution to a (b) (4), exhibited (b) (4) (b) (4)

(see Fig. 2 in this memo), which was not observed in samples of higher dosage strengths. (b) (4) (b) (4) failing the acceptance criteria for (b) (4)

Release limit and (b) (4) Shelf-life limit).

Please provide the following information to address this issue:

1. Please indicate if this (b) (4) has previously been observed in the testing of rFVIII-SC drug substance (DS) or drug product (DP).

2. If the (b) (4) was previously observed, please provide the information regarding the characterization and identity of the (b) (4), and the results of other relevant studies.
3. Please review the results of previous testing of DP lots (b) (4), and submit their (b) (4) to verify the (b) (4) in question.
4. Please provide the results of the latest time-points in the ongoing stability studies on the testing of DP lots (b) (4)

IR sent on 17 February 2016.

1. With reference to amendment STN 125591/0.15 dated 8 January 2016 (your responses to our Information Request (IR) dated 18 December 2015), please address the following:

a. In your responses, you committed to revise the acceptance criteria of the (b) (4) specification after the analysis of the results of (b) (4) (b) (4). Please provide a draft text of the Post-Marketing Commitment, which should include the date of the submission of the final study report.

b. In the modified (b) (4) test, the system suitability criterion of (b) (4) (b) (4) (b) (4). Please clarify how this acceptance criterion was established. Please provide the data for (b) (4) for the samples which were analyzed by date.

c. Regarding the determination of *Protein Content* by the (b) (4) Assay, please address the following:

i. You claim that the suitability of the assay for its intended purpose is demonstrated in the **Justification of Specification** section for the parameter (b) (4). Therefore, please provide the results of protein concentration measurements used to calculate the (b) (4) for each of the (b) (4) batches referenced in the **Justification of Specification** section. Please provide the sample dilution scheme used in the analysis of each dosage strengths of the rFVIII-SC Drug Product (DP). Please also provide the dates when the measurements were performed.

ii. The validated range of the (b) (4). With the working range of the assay after (b) (4). However, the validated range was based on the much lower (b) (4) than that of rFVIII-SC. The batch analysis data show that the protein concentrations (b) (4) (b) (4) which will require a (b) (4) (b) (4) (b) (4). Please perform supplemental validation to establish the assay capability for the analysis of samples with protein concentration (b) (4) i.e., in the concentration range typically found in the rFVIII-SC DP.

d. The stability program for Master and Working Cell Banks (MCB and WCB) described in the amendment was incomplete in that it is limited to the assessment of cell growth and viability during (b) (4) (b) (4)

Please include genetic characterization as recommended in ICH Guideline Q5(b), i.e., assessment of the integrity of the coding region, integration status and copy number for the rFVIII-Single Chain construct; and identify the testing intervals. Also, please explain in detail if your stability program includes testing for adventitious viruses and what tests are to be performed. Please submit an updated SOP for cell banks storage stability investigation.

2. With reference to amendment 125591/0.18 dated 29 January 2016 (your responses to our IR dated 18 December 2015), please provide the updated Section 3.2.S.4.1 **Specification** for the Drug Substance including the updated acceptance criteria for (b) (4).

3. With reference to amendment 125591/0.21 dated 3 February 2016 (your responses to our IR dated 20 January 2016), please provide the following information.

a. The original report of the investigation, referenced in your response, performed in 2013 by CSLB.

(b) (4)

IR sent on 10 March 2016.

1. In the document “Summary report on the structural characterization of recombinant single-chain Factor VIII (rFVIII-SingleChain)” in section 3.2.S.3.1-1, you included detailed structural characterization of the (b) (4). If available, please provide the (b) (4).
(b) (4)

IR sent on 11 April 2016.

1. With reference to section 3.2.P.8.1 Stability, to support 36 months shelf life for all dosage strengths of AFSTYLA Drug Product please provide updated stability report on ongoing stability studies and studies completed after submission of this BLA.

2. With reference to sections 3.2.S.5 and 3.2.P.6 Reference Standards or Materials:

a. Please provide the Certificate of Analysis for product-specific standard used for measuring FVIII activity in chromogenic substrate assay.

b. Please provide the information regarding the date when product-specific standard was introduced for release testing and the list of released batches specifying what potency standard was used for potency assignment.

IR sent on 11 April 2016.

We have included the following proposed Post-Marketing Commitments (PMCs) for your concurrence:

1. CSL Behring commits to investigate the (b) (4)

We commit to submit a Supplement containing the Postmarketing Commitment - Final Study Report by May 31, 2017.

2. CSL Behring commits to develop and validate an (b) (4) method in which the (b) (4)

We commit to submit a Supplement containing the Postmarketing Commitment - Final Study Report by May 31, 2017.