

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)
LT Thomas J. Maruna, MSc, MLS(ASCP), OBRR/IOD/RPMS

Cc: Alexey Khrenov, PhD, Review Committee Chair, Laboratory of Hemostasis (LH), Division of Hematology Research and Review (DHRR)/OBRR

From: Natalya Ananyeva, PhD, LH/DHRR/OBRR

Through: Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR
Basil Golding, MD, Division Director, DHRR/OBRR/CBER

Subject: Final Review of the CMC Information (Cell Bank System) in the Original Biologics License Application from CSL Behring Recombinant Facility AG for Antihemophilic Factor (Recombinant), Single Chain [AFSTYLA]

INTRODUCTION

CSL Behring Recombinant Facility AG (CSLB) submitted an original Biologics License Application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant), Single Chain*. The proprietary name of the product to be marketed in the U.S. is AFSTYLA.

AFSTYLA is indicated for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes;
- Perioperative management of bleeding;
- Routine prophylaxis to reduce the frequency of bleeding episodes.

AFSTYLA is not indicated for the treatment of von Willebrand disease.

**The company's codes for the product are CSL627 and rVIII-SingleChain which are used interchangeably in this review for consistency with the documents submitted in the BLA.*

DESCRIPTION

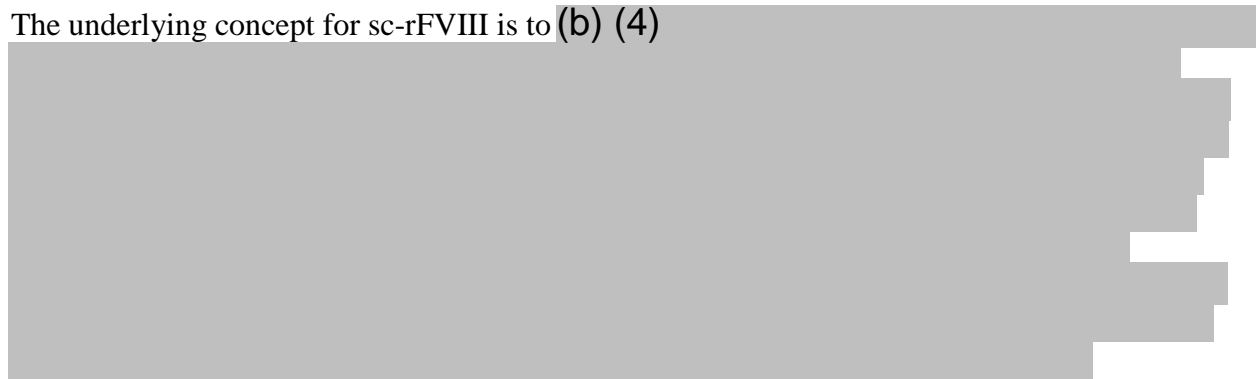
The active ingredient in AFSTYLA is a recombinant analogue of human Factor VIII (rFVIII) produced in Chinese hamster ovary (CHO) cells. The specific feature of the molecule (the

company code: CSL627) is that it is secreted as a single-chain (sc) polypeptide, in contrast to plasma-derived FVIII (pd-FVIII), which circulates as a heterodimer composed of the heavy and light chains (HCh and LCh) generated by a site-specific cleavage of the sc-polypeptide precursor. A modification of the CSL627 molecule involves deletion of most of the B-domain (b) (4), and 4 amino acids in the adjacent $\alpha 3$ acidic region of the LCh (amino acids 765 to 1652 of full-length FVIII). It results in the removal of the (b) (4) HCh and the LCh and the formation of a new N-glycosylation site at the junction. CSL627 molecule has (b) (4) amino acids in a single chain glycopeptide with a molecular weight of approximately (b) (4)

Figure 1: Domain structure of sc-rFVIII



The underlying concept for sc-rFVIII is to (b) (4)



AFSTYLA is a preservative-free, sterile, non-pyrogenic, lyophilized powder to be reconstituted with sterile Water For Injection (sWFI) for intravenous injection. AFSTYLA is available in single-use vials containing nominally 250, 500, 1000, 2000 or 3000 international units (IU) of FVIII potency per vial.

The scope of my review included information on the generation of cell substrate for expression of sc-rFVIII; establishment, characterization and testing of the cell bank system, and stability program.

REVIEW SUMMARY

3.2.S.2.3.2 Source, History and Generation of the Cell Substrate

The recombinant CHO cell line expressing sc-rFVIII protein was originally generated at (b) (4). The project for sc-rFVIII, including the expressing cell line, was licensed by CSLB from (b) (4). The design and experimental approach taken to generate the amino acid sequence for the sc-rFVIII protein, the construction of the expression vector and the generation of the expressing cell line at (b) (4) are described in:

- (b) (4)
- CSLB Report 050200013 “*Development of a Recombinant Single-Chain Human Factor VIII - Cell Line Development and Characterization at (b) (4) - Summary Report*” (dated February 23, 2012).

History of the CHO (b) (4) Host Cell Line

CHO (b) (4) is the host cell line used to create the sc-rFVIII cell substrate. The CHO (b) (4) cell line was generated from a CHO strain by a (b) (4)

no other raw materials of animal origin were used during preparation of the CHO (b) (4).


Design of the rFVIII-SingleChain Amino Acid Sequence

(b) (4) for full-length human FVIII was obtained from (b) (4). The (b) (4) for B-domain deleted FVIII (deletion of amino acids 765-1652) with a linker containing an N-linked glycosylation site at the HCh-LCh junction was produced by (b) (4). The (b) (4) sequence encoding the engineered sc-rFVIII amino acid sequence was designated as (b) (4) reports and was re-designated by CSLB as rVIII-SingleChain.

Construction of the rFVIII Expression Vector

(b) (4)

(b) (4)




(b) (4)






3.2.S.2.3.3 Cell Banking System, Characterization and Testing




CSL627 (b) (4) was tested (b) (4) for viability, sterility, bacteriostasis/fungistasis, and mycoplasma prior to its release, (b) (4)



(b) (4)



(b) (4)

RECOMMENDATION

The information provided in the original BLA and in the responses to the IRs adequately qualifies the MCB and WCB as the starting material for the manufacture of drug substance for AFSTYLA and confirms the identity, safety and genetic stability of the cell substrate throughout the production process. The revised stability program for the MCB and WCB is acceptable. Therefore, I recommend **APPROVAL** of this BLA, STN 125591/0, for AFSTYLA from the cell bank system perspective.