



## MEMORANDUM

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

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To: File (STN 125566/0)  
Yu Do and Edward Thompson, Regulatory Project Manager, OBRR/IOD/  
RPM Staff

From: Ze Peng, PhD, OBRR/DHRR/LH

Through: Mark Weinstein, PhD, Assoc. Dep. Dir. for Science, OBRR/IOD  
  
Basil Golding, MD, Division Director, OBRR/DHRR

Subject: Final Review of CMC information in Baxalta's original BLA for  
Antihemophilic Factor (Recombinant), PEGylated

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### Executive Summary

This memorandum summarizes the review of CMC information in an original Biologics License Application (BLA) under STN 125566/0 submitted by Baxter (now Baxalta US Inc., abbreviated as Baxalta in this memo) for Antihemophilic Factor (Recombinant), PEGylated. The proposed proprietary name, *ADYNOVATE*, is found acceptable based on the review by Dr. Loan Nguyen in the Advertising and Promotional Labeling Branch. This product is proposed for 1) on-demand treatment and control of bleeding episodes; and 2) routine prophylaxis to reduce the frequency of bleeding episodes in adolescent and adult patients (12 years and older) with Hemophilia A (congenital factor VIII deficiency).

As described below, the information provided in the original submission and Baxalta's responses to our information requests (IRs) are sufficient to support the identity, quality, purity, safety, and potency of the product for the proposed indication; therefore, we recommend approval of the BLA under STN 125566/0.

### Background

*ADYNOVATE* is a PEGylated full-length recombinant FVIII (rFVIII) manufactured by modifying the U.S.-licensed rFVIII product, *ADVATE*, with a 20-kDa branched polyethylene glycol (PEG) reagent. The U.S. licensed rFVIII bulk drug substance (BDS), *ADVATE*, is produced by recombinant DNA technology from Chinese hamster ovary (CHO) cells. rFVIII is then covalently conjugated with PEG, which targets lysine residues mainly in the (b) (4). The product consists of a mixture of rFVIII molecules

modified with varying degrees of PEGylation, and contains on average (b) (4) moles of PEG per mole of rFVIII. This product is formulated as a sterile lyophilized powder only for intravenous administration. When reconstituted with its diluent, sterile Water for Injection (sWFI), each container of *ADYNOVATE* final product contains nominally 250, 500, 1000, or 2000 IU of rFVIII.

### Summary of Review

The manufacture of *ADYNOVATE* drug substance (DS) and *ADYNOVATE* drug product (DP) is performed at Baxalta's (b) (4) facility and (b) (4) facility, respectively. Labeling and secondary packaging for *ADYNOVATE* DP is performed at Baxalta's (b) (4) facility. The address for each facility is listed as follows:

Baxter Health Corporation

(b) (4)

Baxter (b) (4)

Baxter (b) (4)

### DRUG SUBSTANCE

#### 1. Flow diagram of the manufacturing process

##### ADVATE bulk drug substance

(b) (4)

##### ADYNOVATE bulk drug substance

(b) (4)



(b) (4)

**Product reviewer's comment:** The manufacturing processes are comparable between the production of these clinical batches and the conformance batches as discussed in the sections of *Control of Materials* and *Manufacturing Process Development*. Therefore, the (b) (4) stability data from the clinical batches under the (b) (4) storage are qualified to support the shelf-life of ADYNOVATE BDS. Together with the available stability data from conformance batches, they support the shelf-life of ADYNOVATE BDS proposed by Baxalta: ADYNOVATE BDS can be stored at (b) (4).

## DRUG PRODUCT

### 1. Description and Composition of the ADYNOVATE drug product

ADYNOVATE is full-length form of rFVIII consisting of 2332 amino acids covalently conjugated with PEG reagent. It is supplied in single-use vials containing nominal potencies of 250, 500, 1000, or 2000 IU of PEGylated rFVIII after reconstitution with 5 mL sWFI. Each vial of ADYNOVATE is labeled with the actual value of FVIII potency, which will be within (b) (4) of the targeted one. Tris, Calcium chloride, Mannitol, Sodium chloride, Trehalose, Glutathione, Histidine, and Polysorbate 80 serve as excipients and/or stabilizers.

The presentation consists of one lyophilized drug product vial, and one diluent (sWFI) vial. A BAXJECT II Hi-Flow needleless transfer device is supplied to allow for the transfer of the diluent into the drug product vial for reconstitution. This device is a 510K cleared one (K092318) that is also used in Baxalta's another licensed drug product (i.e., FEIBA).

### Composition

Component	Function	Amount per vial for different dosage strengths			
		250 IU (nominal)	500 IU (nominal)	1000 IU (nominal)	2000 IU (nominal)
PEGylated rFVIII	Active ingredient	250 IU	500 IU	1000 IU	2000 IU
Mannitol	Excipient	160 mg	160 mg	160 mg	160 mg
Trehalose dihydrate	Excipient/Stabilizer	40 mg	40 mg	40 mg	40 mg
Sodium chloride	Excipient/(b) (4)	26.3 mg	26.3 mg	26.3 mg	26.3 mg
Histidine	Excipient	7.8 mg	7.8 mg	7.8 mg	7.8 mg
Tris	Excipient	6.1 mg	6.1 mg	6.1 mg	6.1 mg
Calcium chloride	Excipient/Stabilizer	1.2 mg	1.2 mg	1.2 mg	1.2 mg
Polysorbate 80	Excipient/(b) (4)	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Glutathione	Excipient/(b) (4)	0.4 mg	0.4 mg	0.4 mg	0.4 mg

### 2. Flow diagram of the manufacturing process

- 1) (b) (4) ADYNOVATE DS
- 2) (b) (4) ADYNOVATE DS
- 3) Formulation
- 3) Sterile filtration
- 4) Aseptic filling
- 5) Lyophilization
- 6) Capping
- 7) Packaging

3. *A brief description of manufacturing process*

ADYNOVATE DP is manufactured at Baxalta's (b) (4) facility. The (b) (4) ADYNOVATE BDS is (b) (4)

After the vials are filled and partially stopped, the product is lyophilized. The vials are fully stoppered after the completion of lyophilization and then capped with a flip off cap. The vials are shipped under controlled temperature (2 – 8°C) from Baxalta's (b) (4) facility to Baxalta's facility at (b) (4) (b) (4) for labeling, secondary packaging, and boxing.

4. *In-process control*

(b) (4)

The parameters established and their acceptance criteria are considered to be appropriate and acceptable.

5. *Process validation and/or evaluation*

Validation and evaluation studies on ADYNOVATE DP are listed as follows:

Studies	Report references
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(b) (4)

We defer the comments on the container closure system, lyophilization, media fill, and shipping validation to our DMPQ colleagues. For the (b) (4) validation studies, the preparation of Polysorbate 80, (b) (4)

(b) (4) the filter materials used in the manufacture of *ADYNOVATE* DP met all the acceptance criteria. Moreover, process validation was conducted through manufacture of: (b) (4) 250 IU lots, (b) (4) 500 IU (b) (4) (b) (4) 1000 IU lots, and (b) (4) 2000 IU lots, covering minimum and maximum lot sizes. Conformance lot information is listed as follows:

(b) (4)

Product quality attributes were further evaluated in the manufacture of these conformance lots (process validation study report No.2013-BAX855/FF-RFPPQ). The data on (b) (4) conformance lots are summarized as follows:

(b) (4)

(b) (4)

As part of the process performance qualification study, the conformance lot (b) (4) was manufactured with process holding times beyond the maximum limits allowed in the proposed commercial manufacturing process. As the above table shows, all the test results from this lot also met the acceptance criteria. These

data indicate that the extended holding times does not have a significant impact on the product quality.

In general, Baxalta conducted various validation studies regarding the manufacturing process of *ADYNOVATE* DP. Process and quality controls for conformance lot manufacture complied with prospectively defined acceptance criteria for successful process validation.

#### 6. Control of excipients

Tris, Calcium chloride, Mannitol, Sodium chloride, Histidine, Trehalose, Glutathione, and Polysorbate 80 serve as excipients, of which the last three are of (b) (4) origin. No excipients of human or animal origin are introduced in the manufacture of *ADYNOVATE* DP. All the excipients comply with the requirements of current (b) (4) (b) (4) except for Glutathione. Glutathione does comply with the requirements of (b) (4). Therefore, all the excipients used in the manufacture of *ADYNOVATE* are well controlled, and acceptable.

#### 7. Control of drug product

##### 1) Specification of the *ADYNOVATE* final drug product

Product quality attribute	Specification	Test method (Procedure number)
Appearance of lyophilized cake	White to off-white friable powder	Visual (NE-11-00052)
Appearance of reconstituted solution	Clear, colorless solution substantially free from foreign particles	
Reconstitution time	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Free FVIII subunits	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
FVIII Activity (b) (4)	Report for calculation	(b) (4)
FVIII Activity (Clotting)	200 – 2500 IU/vial; (b) (4) of the final targeted potency	One-stage clotting assay (NE-13-00032)
Total protein	Report for calculation	(b) (4)



Specific FVIII activity (Clotting)	2700 – 8000 IU/mg	Calculation
(b) (4)	(b) (4)	Calculation
Residual moisture	(b) (4)	(b) (4)
Particulate matter	(b) (4)	(b) (4)
Endotoxin	(b) (4)	(b) (4)
Sterility	Sterile	Membrane filtration (OR-12-00006)
Polysorbate 80	(b) (4)	(b) (4)
Calcium	(b) (4)	(b) (4)
Sodium	(b) (4)	(b) (4)
Mannitol	(b) (4)	(b) (4)
Trehalose-Dihydrate	(b) (4)	(b) (4)
Tris	(b) (4)	(b) (4)
Histidine	(b) (4)	(b) (4)
Total Glutathione	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4) binding	(b) (4)	(b) (4)
Free PEG	(b) (4)	(b) (4)
Total PEG	Report for calculation	(b) (4)
Degree of PEGylation	(b) (4)	Calculation
(b) (4)	(b) (4)	(b) (4)

Particulate matter, endotoxin, and sterility comply with the requirements of (b) (4). For other parameters, the specification limits are established based on the process capability and the evaluation of available preclinical/clinical data. Although the potency of PEGylated FVIII is determined by both One-stage clotting assay and (b) (4) assay, the ADYNOVATE DP will be labelled with the results determined by One-stage clotting assay (*Procedure No: NE-13-00032*).

**Product reviewer’s comment:** The specification limits of ADYNOVATE final product are acceptable except for that for Degree of PEGylation. We consider that the range for Degree of PEGylation set by Baxalta is relatively wide. To better control the consistency of the manufacturing process, we asked Baxalta to

revise the specification of this parameter for both *ADYNOVATE* (b) (4) DP based on a statistical analysis of all available batches or lots produced in the proposed commercial manufacturing process.

This IR was sent to Baxalta on 14 July 2015, and they responded in an amendment on 22 July 2015. The response is summarized as follows:

**Baxalta's response:** Baxalta produced additional (b) (4) post-conformance clinical batches of *ADYNOVATE* (b) (4) according to the proposed commercial manufacturing process so far. Together with previously qualified (b) (4) batches, (b) (4) batches of *ADYNOVATE* (b) (4) were used in the re-evaluation on the specification of Degree of PEGylation. Statistical analysis on the (b) (4) batches resulted in a lower limit of (b) (4) and an upper limit of (b) (4) for Degree of PEGylation. Therefore, Baxalta proposed to change the specification of this parameter to (b) (4) from previously defined (b) (4) for *ADYNOVATE* (b) (4).

Similarly, Baxalta did a statistical analysis on (b) (4) lots of *ADYNOVATE* DP produced in the proposed commercial manufacturing process. Based on the updated data, Baxalta proposed to change the specification of this parameter to (b) (4) from previously defined (b) (4) for *ADYNOVATE* DP.

**Product reviewer's comment:** The specifications of Degree of PEGylation for (b) (4) DP are tightened based on available *ADYNOVATE* (b) (4) DP lots produced in the proposed commercial manufacturing process. This change is more likely to reflect the capacity of the proposed commercial manufacturing process. Therefore, this response is acceptable.

Additionally, all the aforementioned test methods have been validated in the relevant validation reports. For the detailed review of the method validation on these analytical procedures for *ADYNOVATE* DP, please refer to the review memos from Drs. Alexey Khrenov, Hyesuk Kong, and Lokesh Bhattacharyya.

## 2) Batch analysis

Certificates of analysis for (b) (4) conformance lots manufactured at full-scale are included in the BLA. The release test results of these lots are listed as follows:

(b) (4)

(b) (4)

**Product reviewer's comment:** As the table shown above, all the results of these conformance lots met the release specifications of *ADYNOVATE* DP. However,

the test results of free PEG, total PEG, and Degree of PEGylation for all these conformance lots were absent in the original submission. Upon our request, Baxalta submitted these data in an amendment dated 13 August 2015. These data showed that all the test results for these three parameters met the acceptance criteria, and no significant trend was detected for each of these three parameters. These data confirm the consistency of the proposed commercial manufacturing process.

#### 4) Impurity profile

Please refer to the review of the impurity profile of *ADYNOVATE* DS, because all impurity profiles are identical between *ADYNOVATE* DS and DP.

### 8. Reference standards

The reference standards used are the same for the release and stability testing of *ADYNOVATE* (b) (4) except for that for the testing of free PEG.

(b) (4) reference material (lot (b) (4)) is used for the determination of free PEG in *ADYNOVATE* (b) (4) acid reference material (lot (b) (4)) is used for the determination of free PEG in *ADYNOVATE* DP.

These two reference materials were purchased from (b) (4) and passed all (b) (4) product release specifications and the in-coming material specifications established by Baxalta. Therefore, they are acceptable.

### 9. Container closure system

The primary container closure system for *ADYNOVATE* consists of a clear and colorless (b) (4) glass vial, a 20 mm gray (b) (4) butyl rubber stopper, and aluminum crimp-cap with a polypropylene flip-off disk. Vials are made of glass (b) (4) and meet the requirements of current (b) (4) (b) (4). Rubber stopper complies with the requirements of current (b) (4) (b) (4). (b) (4) Container closure safety and performance were qualified through extractables, leachables studies and container closure integrity testing other than final product monitoring in the established stability program.

**Product reviewer's comment:** We defer the review of this section to Cmdr Jeremy Wally from DMPQ.

### 10. Stability

Baxalta introduced a bracketing design in the stability studies for the following reasons. The design of a protocol that incorporates bracketing assumes that the stability of the intermediate condition samples is represented by those at the extremes. *ADYNOVATE* is supplied as nominal 250 IU, 500 IU, 1000 IU, and 2000 IU per vial. The composition of the *ADYNOVATE* is the same for four of the product

presentations except for the content of the active ingredient. The bracketing stability studies are designed in accordance with the International Conference on Harmonisation (ICH) guidance, *Guidance for Industry: Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*, January 2003.

Baxalta submitted additional stability data on 13 August 2015 according to the pre-BLA meeting minutes, and the available stability data are summarized as follows:

1) Stability study for the conformance lots of *ADYNOVATE* drug product

- Lots tested

DP lot No.	DP Strength (IU/vial)	DS batches used	Proposed storage condition	Data available (months)
(b) (4)	250	(b) (4)	5 ± 3°C	18
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)
	250	(b) (4)	5 ± 3°C	18
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)
	250	(b) (4)	5 ± 3°C	18
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)
	500	(b) (4)	5 ± 3°C	18
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)
	1000	(b) (4)	5 ± 3°C	18
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)
	1000	(b) (4)	5 ± 3°C	9
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)
	2000	(b) (4)	5 ± 3°C	18
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)
	2000	(b) (4)	5 ± 3°C	18
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)
	2000	(b) (4)	5 ± 3°C	18
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
			5 ± 3°C for 15 months + 30°C	(b) (4)

RH: Relative humidity

These lots are manufactured through the proposed commercial manufacturing process; therefore, the stability data from these lots are qualified to support the shelf-life of *ADYNOVATE* DP.

- Parameters tested: Appearance Lyophilized, Appearance Reconstituted, Reconstitution Time, (b) (4) Total Protein, Residual Moisture, FVIII activity tested by both One-stage clotting Assay (b) (4) Assay, Specific Activity tested by One-stage clotting Assay, (b) (4) for Identity, (b) (4), Free PEG, Degree of PEGylation, and Particular Matter for Purity and Impurity, Free FVIII Subunits for Process Consistency, Endotoxin and Sterility for Microbiological Quality. The parameters selected are complete and acceptable in terms of the testing of stability of *ADYNOVATE* DP.
- Proposed shelf-life of the *ADYNOVATE* drug product

The *ADYNOVATE* DP is proposed to be stored at  $5 \pm 3^{\circ}\text{C}$  for up to 24 months. Within this period, the product is allowed to be stored at room temperature (i.e.,  $\leq 30^{\circ}\text{C}$ ) for up to 1 month not to exceed the expiration date.

- Stability results

Stability data for the long-term storage ( $5 \pm 3^{\circ}\text{C}$ ) are available for up to 18 months in the original submission and the amendment dated 13 August 2015. All the results were within the acceptance criteria. The potency data (One-stage clotting assay) for these lots stored at  $5 \pm 3^{\circ}\text{C}$  are listed as follows:

Lot No.	Strength (IU/vial)*	Storage time (months)						
		0	3	6	9	12	15	18
(b) (4)	250	100% (221 IU)	99%	95%	96%	102%	96%	95%
	250	100% (235 IU)	101%	99%	95%	98%	102%	96%
	250	100% (243 IU)	94%	93%	94%	97%	100%	92%
	500	100% (436 IU)	100%	103%	99%	96%	97%	98%
	1000	100% (933 IU)	100%	108%	101%	96%	99%	94%
	1000	100% (973 IU)	103%	96%	94%			
	2000	100% (1864 IU)	99%	102%	101%	99%	94%	95%
	2000	100% (1887 IU)	103%	104%	102%	109%	100%	99%
	2000	100% (1918 IU)	100%	98%	97%	100%	98%	102%

\*: Acceptance criteria, (b) (4) IU/vial and (b) (4) of Initial

A downward trend for FVIII potency was observed under the storage condition of  $30 \pm (b) (4)$ . However, the results for FVIII potency tested using One-stage clotting assay met the acceptance criterion for up to (b)(4) months. The results of other parameters also met the acceptance criteria at least for (b)(4) months.

Lot No.	Strength (IU/vial)*	Storage time (months)	
		0	(b)(4)
(b) (4)	250	100% (221 IU)	(b) (4)
	250	100% (235 IU)	
	250	100% (243 IU)	
	500	100% (436 IU)	
	1000	100% (933 IU)	
	1000	100% (973 IU)	
	2000	100% (1864 IU)	
	2000	100% (1887 IU)	
	2000	100% (1918 IU)	

\*: Acceptance criteria, (b) (4) IU/vial and (b) (4) of Initial

A slight increase in residual moisture was observed under the accelerated condition ((b) (4)). However, the test results for this parameter were (b) (4) still within the acceptance criteria (b) (4) during the (b)(4)-month storage period. The results of other parameters met the acceptance criteria for up to 1 month. The potency data (One-stage clotting assay) for these lots stored at (b) (4) are listed as follows:

(b) (4)

\*: Acceptance criteria, (b) (4) IU/vial and (b) (4) of Initial

**Product reviewer’s comment:** Baxalta did not provide the stability data on the parameters for free PEG and the degree of PEGylation for all conformance lots in the original submission. To complete our evaluation, we asked Baxalta

to take these parameters into account in the ongoing stability studies of the conformance lots of *ADYNOVATE* DP, and include the test results of these parameters when they submit updated stability data in our IR dated 21 May 2015.

They submitted these data in the amendment dated 13 August 2015, and the data are summarized as follows:

Baxalta missed the testing of Free PEG and degree of PEGylation at the beginning of stability for the conformance lots because these two assays had not been validated at that time. They provided the test results for these two parameters at the time points starting from 6 months of the long-term storage condition. Also, Baxalta provided 6 months stability data including these two parameters from (b) (4) additional lots manufactured in the proposed commercial process. As shown below, all the available data on these two parameters met the specification for the long-term storage condition and temperature excursion studies ( $5 \pm 3^\circ\text{C}$  for 15 months and then 30 (b) (4)

**Free PEG for the lots stored at  $5 \pm 3^\circ\text{C}$**

(b) (4)

**Degree of PEGylation for the lots stored at  $5 \pm 3^\circ\text{C}$**

(b) (4)



The updated stability data on *ADYNOVATE* DP provided in the amendment dated 13 August 2015 support a shelf-life of 18 months under the long-term storage condition of  $5 \pm 3^{\circ}\text{C}$ .

2) Stability study for the Phase II/III clinical lots of *ADYNOVATE* drug product

- Lots tested

In addition to the abovementioned conformance lots, Baxalta also performed stability studies on the following clinical lots.

DP lot No.	DP Strength (IU/vial)	DS batches used	Proposed storage condition	Data available (months)
NEB00413	250	(b) (4)	$5 \pm 3^{\circ}\text{C}$	24
			$25 \pm 2^{\circ}\text{C}$ (b) (4)	(b) (4)
			30 (b) (4)	(b) (4)
			(b) (4)	(b) (4)
NEB00113	1000	(b) (4)	$5 \pm 3^{\circ}\text{C}$ for 18 months + $30^{\circ}\text{C}$	(b) (4)
			$5 \pm 3^{\circ}\text{C}$	24
			$25 \pm 2^{\circ}\text{C}$ (b) (4)	(b) (4)
			30 (b) (4)	(b) (4)
NEB00313	2000	(b) (4)	(b) (4)	(b) (4)
			$5 \pm 3^{\circ}\text{C}$	24
			$25 \pm 2^{\circ}\text{C}$ (b) (4)	(b) (4)
			30 (b) (4)	(b) (4)
NEB00513	2000	(b) (4)	(b) (4)	(b) (4)
			$5 \pm 3^{\circ}\text{C}$	18
			$25 \pm 2^{\circ}\text{C}$ (b) (4)	(b) (4)
			30 (b) (4)	(b) (4)

**Product reviewer's comment:** Although the manufacturing process is slightly different for the *ADVATE* bulk used for the production of the conformance lots and the clinical lots of *ADYNOVATE*, they are comparable as we discussed in the sections of *Control of Materials* and *Manufacturing Process Development*. Therefore, these four clinical lots can be used to support the proposed shelf life of *ADYNOVATE* DP.

- Stability results

All the results were within the acceptance criteria for these four clinical lots stored at  $5 \pm 3^{\circ}\text{C}$  for up to 24 months, and no significant trend was detected. A downward trend for FVIII potency was observed under the storage conditions of  $25 \pm 2^{\circ}\text{C}$  (b) (4) and 30 (b) (4). However, Stability data for storage at  $25 \pm 2^{\circ}\text{C}$  (b) (4) and 30 (b) (4) met the acceptance criteria for up to (b) (4) months and (b) (4) months, respectively. Stability data for storage at 40 (b) (4) also met the acceptance criteria for up to (b) (4).

**Product reviewer's comment:** Based on the stability data for the four clinical lots and the conformance lots aforementioned, they support a shelf-life of 24 months under storage at  $5 \pm 3^\circ\text{C}$ . Within this period, *ADYNOVATE* final product is allowed to be stored at room temperature (i.e.,  $\leq 30^\circ\text{C}$ ) for up to 1 month not to exceed the expiration date.

### 3) Reconstitution (in-use) stability

Baxalta submitted reconstitution stability data under Section 3.2.P.8.3. The conformance lots were stored at  $5 \pm 3^\circ\text{C}$  for 4 months, and then tested at the time points of 0, 3, (b) (4) hours after reconstitution. These data showed that *ADYNOVATE* DP is stable at room temperature within (b) (4) hours after reconstitution. Considering the risk of microbial contamination, we agree with Baxalta to use *ADYNOVATE* product within 3 hours after reconstitution.

### 4) Stability of the diluent, sterile Water for Injection

sWFI is manufactured by (b) (4), and this product (i.e., 5 mL sWFI in 6 mL colorless neutral (b) (4) glass vial sealed with a chlorobutyl rubber stopper with an inert coating) is currently used in Baxalta's other licensed products including ADVATE, RECOMBINATE, and RIXUBIS.

Three conformance lots (lots (b) (4)) are included in the stability studies. These lots are being investigated under the long-term storage conditions ( $5 \pm 3^\circ\text{C}$  (b) (4);  $25 \pm 2^\circ\text{C}$ /(b) (4);  $30^\circ\text{C}$  (b) (4))

and the accelerated condition ((b) (4)). The container closure system used in the stability study is identical to the one used commercially. The parameters used in the long-term stability study include Appearance of solution, (b) (4)

(b) (4), Extractable volume, (b) (4)  
(b) (4), Particulate matter, Bacterial endotoxins, and Sterility.

(b) (4) months of long-term stability and (b) (4) months of accelerated stability data are available. The test results were within the acceptance criteria for the samples stored at  $5 \pm 3^\circ\text{C}$  for up to (b) (4) months, and no significant changes were detected. No deviations were observed for the samples stored at  $25 \pm 2^\circ\text{C}$ /(b) (4) for (b) (4) months after the storage of  $5 \pm 3^\circ\text{C}$  for (b) (4) months. Additionally, for the samples stored at  $25 \pm 2^\circ\text{C}$  and  $30^\circ\text{C}$  (b) (4), the test results for (b) (4) substances were OOS after (b) (4) months. The test results for the samples stored at (b) (4) for up to (b) (4) months met the acceptance criteria.

**Product reviewer's comment:** The stability studies on these conformance lots are complete, and the data from these studies are sufficient to support Baxalta's proposed shelf-life of the diluent to be (b) (4) months under the storage of  $5 \pm 3^{\circ}\text{C}$ . Within this period, the diluent may be stored at room temperature ( $\leq 25^{\circ}\text{C}$ ) for up to (b) (4) months.

## 11. Virus safety

The starting material in the manufacture of *ADYNOVATE* is *ADVATE* bulk. No animal or human derived raw materials are used in the manufacture of *ADVATE* bulk as well as *ADYNOVATE*. Therefore, the viral safety evaluation on *ADVATE* bulk is fully applicable to *ADYNOVATE*. This evaluation is summarized as follows:

### 1) Testing of all mammalian cell banks for the absence of infectious viruses

Master Cell Bank (WCB) and WCB for the production of *ADVATE* are well controlled regarding the potential of viral contamination. *ADVATE* is produced in a genetically modified CHO cell line (b) (4). The MCB has been tested for viruses according to ICH Q5A(R1). All the tests were found negative for the presence of viruses except for the expected presence of retrovirus-like particles that were found through (b) (4). Furthermore, cells at the limit of *in vitro* cell age used for production were tested, and found negative for adventitious viruses. Baxalta routinely tests cell cultures used in the manufacturing process for *in vitro* adventitious viruses to ensure that viruses are below their detectable levels.

**Product reviewer's comment:** Baxalta conducted the full tests for viral safety according to the ICH guidance Q5A. All the tests were found negative for the presence of viruses except for the expected presence of retrovirus-like particles. These retrovirus-like particles are considered to be non-pathogenic. Moreover, there is one dedicated virus inactivation step in the manufacturing process. Together with the other (b) (4) purification steps (i.e., Immunoaffinity Chromatography (b) (4)), the potential of the *ADVATE* bulk to be contaminated with viruses is minimized.

### 2) Control of materials used in the manufacturing process

The potential risk of adventitious virus or transmissible spongiform encephalopathy agent contamination is minimized in the manufacturing process of *ADYNOVATE*. The cell line for the production of *ADVATE*, the starting material in the manufacture of *ADYNOVATE*, has been adapted in a culture medium that does not contain additives of human or animal origin. No animal or human derived raw materials are added in the PEGylation process. Additionally, no raw materials or ingredients of human or animal origin are used in the formulation of *ADYNOVATE* final product.

3) Testing the capacity of the ADYNOVATE purification process to clear viruses

No additional viral clearance steps are qualified in the manufacture of *ADYNOVATE* other than those included in the manufacture of *ADVATE* bulk.

S/D treatment (b) (4)

(b) (4) ) is a dedicated virus inactivation step in the manufacture of *ADVATE*. Immunoaffinity Chromatography<sup>(b) (4)</sup> steps also contribute to viral removal. The enveloped viruses selected in the viral clearance studies for these steps at down-scale include (b) (4)

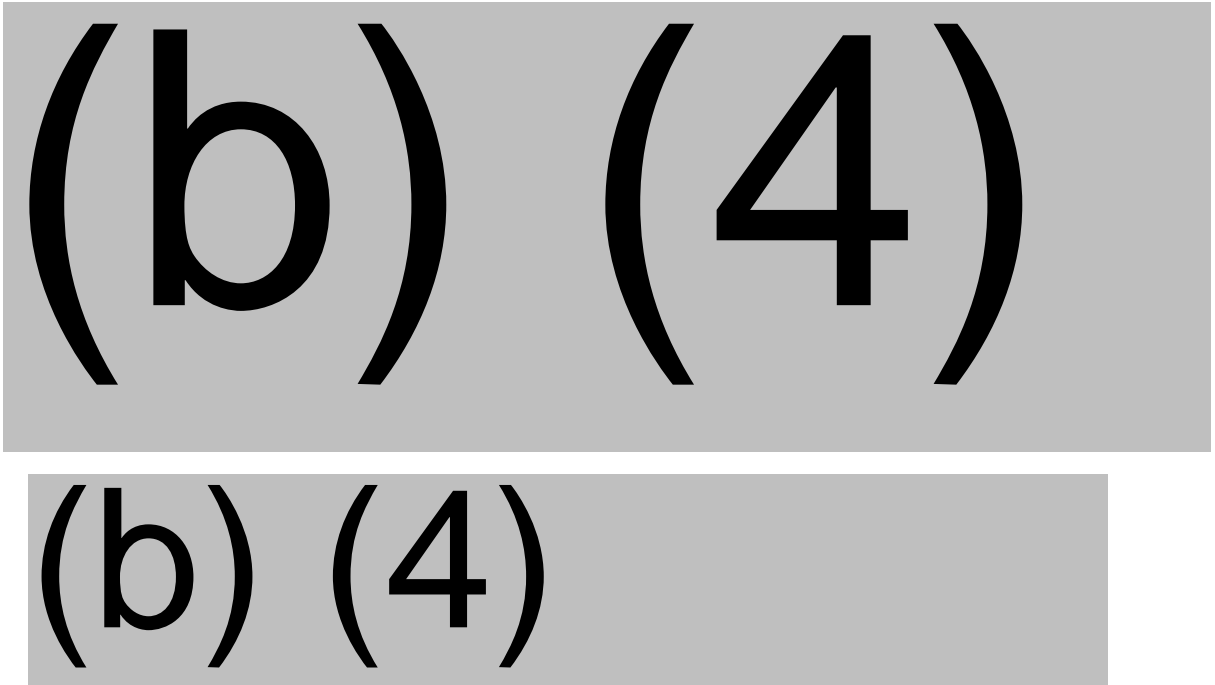
The studies on the viral clearance steps abovementioned have been evaluated under the review of the original BLA for *ADVATE*, and are considered to be sufficient by FDA. To avoid redundancy, Baxalta only summarized the following changes introduced in STN 125063/1089 for *ADVATE*, which have been implemented during the manufacturing process development of *ADYNOVATE*. These steps are related to (b) (4) steps in the manufacture of *ADVATE* bulk.

(b) (4)

(b) (4)

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## LABELING

For the drafted Prescribing Information (PI), we asked Baxalta to make the following revisions:

- a. Multiple edits were made regarding Section 11 "*Description*" in our IR dated 6 August 2015.
- b. Regarding Section 16 "*How supplied/storage and handling*", please add the sentence "Do not refrigerate after reconstitution. Use the reconstituted solution immediately or within 3 hours after reconstitution. Discard any remaining solution."
- c. Please change the proper name of the product Antihemophilic Factor (Recombinant), Pegylated back to Antihemophilic Factor (Recombinant), PEGylated in the product label.

They submitted their responses on 12 August 2015 and 24 September 2015, in which they fully agreed with our requests. The relevant PI, carton, and vial labels were updated accordingly. Therefore, their responses are acceptable.

## Recommendation

The manufacturing process of *ADYNOVATE* is considered to be adequately validated and sufficiently controlled to ensure consistent manufacture of the commercial product that meets the release specifications. The measures taken by Baxalta to control adventitious agents in the manufacture of *ADYNOVATE* are acceptable. We found the information to

be supportive quality, identity, purity, potency and safety, and recommend approval of this BLA.