

Late-Cycle Meeting Summary, April 3, 2014

- Eloctate

•
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Late-Cycle Meeting Summary

Application type and number: STN BL 125487/0
Product name: Antihemophilic Factor (Recombinant), Fc Fusion Protein
Applicant: Biogen Idec, Inc.
Meeting category: Late Cycle Meeting (LCM)
Meeting date & time: April 3, 2014, 1:30 p.m. to 3 p.m.
Meeting format: Face-to-face
Meeting Chair/Leader: Paul D. Mintz, MD
Meeting Recorder: Leigh Pracht
LCM package sent: March 20, 2014

FDA Participants:

Natalya Ananyeva, PhD, Senior Staff Fellow, Division of Hematology, OBRR
Lokesh Bhattacharyya, PhD, Chief, Laboratory of Analytical Chemistry and Blood Related Products, Division of Biological Standards and Quality Control, OCBQ
Karen Campbell, Regulatory Coordinator, Division of Biological Standards and Quality Control, OCBQ
Wambui Chege, MD, Medical Officer, Division of Epidemiology, OBE
Christine Drabick, Consumer Safety Officer, Division of Inspections and Surveillance, OCBQ
John Eltermann, RPh, MS, Director, Division of Manufacturing and Product Quality, OCBQ
Lisa Faulcon, MD, Medical Officer, Division of Hematology, OBRR
Basil Golding, MD, Director, Division of Hematology, OBRR
Jie He, MS, Consumer Safety Officer, Division of Manufacturing and Product Quality, OCBQ
Patricia Holobaugh, Branch Chief, Division of Inspections and Surveillance, OCBQ
Ellen Huang, Consumer Safety Officer, Division of Manufacturing and Product Quality, OCBQ

Nisha Jain, MD, Chief, Clinical Review Branch, Division of Hematology, OBRR
Nancy Kirschbaum, PhD, Chemist, Division of Hematology, OBRR
Tim Lee, PhD, Acting Chief, Laboratory of Hemostasis, Division of Hematology, OBRR
Judy Li, PhD, Mathematical Statistician, Division of Biostatistics, OBE
Ginette Michaud, MD, Deputy Director, OBRR
Paul D. Mintz, MD, Deputy Director of Medical Affairs, Division of Hematology, OBRR
Loan Nguyen, PharmD, Regulatory Review Officer, Division of Case Management, OCBQ
Ze Peng, PhD, Staff Fellow, Division of Hematology, OBRR
Anne M. Pilaro, PhD, Chief, Pharmacology and Toxicology Branch, Division of Hematology, OBRR
Leigh Pracht, Regulatory Project Manager, Division of Blood Applications, OBRR
Renee Rees, PhD, Mathematical Statistician, Division of Biostatistics, OBE
Andrey Sarafanov, PhD, Chemist, Division of Hematology, OBRR
Christopher Sese, Independent Assessor, Eastern Research Group, Inc.
Destry Sullivan, MS, Team Lead, Division of Manufacturing and Product Quality, OCBQ
Carl-Michael Staschen, MD, PhD, Pharmacologist, Division of Hematology, OBRR
Craig Zinderman, MD, Deputy Director, Division of Epidemiology, OBE

Biogen Idec Inc Attendees:

Amin Abujoub, Vice President, Global Quality Control
Aoife Brennan, Senior Director, Medical Research
Ray Cardin, Consultant, CMC
Eliana D. Clark, Team Director, CMC
Paula Cobb, Vice President, Program Management
Caroline Coots, Senior Manager, CMC Regulatory Affairs
Mariana Dimitrova, Director, Technical Development
Ann Dodds-Frerichs, Vice President, CMC Regulatory Affairs
Ann Ferentz, Senior Manager, Regulatory Affairs
Eric Finley, Staff Associate, Product Quality Management
Arun Gaur, Director, Quality
Edward Goodreau, Vice President, Manufacturing Sciences
Canping Jiang, Senior Engineer III, Manufacturing Sciences
Gene Mehr, Senior Engineer II, Technical Development
Glenn Pierce, Senior Vice President, Hematology
Stephen Raso, Senior Scientist, Technical Development
Heidi Reichert, Team Director, CMC
Debra Segal, Director, Regulatory Affairs
Alasdair Shepherd, Vice President, Quality
Jurg Somers, Director, Research
Suzanne Stella, Director, CMC Regulatory Affairs
Elijah Tan, Associate Director, CMC Regulatory Affairs
Nicola Wilson, Associate Director, Contract Manufacturing

Background and Objectives:

FDA contacted Biogen Idec, Inc. (Biogen) on December 4, 2013, to provide the revised date for the Late Cycle Meeting. The purpose of the meeting is to share information, to discuss substantive review issues, and to communicate our objectives for the review cycle of STN BL 125487/0 for Antihemophilic Factor (Recombinant), Fc Fusion Protein for the treatment of adults and children with Hemophilia A for the following indications:

- Control and prevention of bleeding episodes
- Perioperative management for surgical prophylaxis
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

FDA conveyed the Late Cycle Meeting package to Biogen on March 20, 2014.

DISCUSSION SUMMARY:

I. Introductory Comments:

FDA introduced the agenda items:

1. Discussion of Substantive Review Issue(s) – 50 minutes
 - a. CMC/Product Questions 1 and 2: In-process Microbial Control
 - b. CMC/Product Question 3: Process Hold Times
 - c. CMC/Product Question 4: Averaging Out-of-Specification Results with In-specification results to obtain a reportable result
 - d. FDA comments on Biogen's responses to information requests
2. Labeling Discussion – 15 minutes
 - a. Any labeling issues for discussion
 - b. Questions from Biogen
3. Wrap up and Action Items – 10 minutes
 - a. Summary of discussion points
 - b. Questions and comments from Biogen

FDA explained that the meeting is not intended to discuss the pending regulatory decision on the application. After the meeting discussion, FDA may request that Biogen submit additional data or analysis.

II. Discussion of Substantive Review Issues:

CHEMISTRY, MANUFACTURING, AND CONTROLS:

In-process Microbial Control:

1. Your response in amendment 30 to item 18b from the September 11, 2013 information request was inadequate. Please revise the drug substance release specification for ----b(4)-----

Additional discussion:

As previously communicated through information requests for this product and for your rFIXFc product, FDA expects in-process specifications to reflect manufacturing capability in order to ensure continued manufacturing control.

Regarding Biogen's proposal to set in-process specifications (IPS) for --b(4)-----

----- drug product release specifications does not provide a high degree of confidence in your continued attention to manufacturing control in light of manufacturing experience that indicates your ability to control --b(4)-----

Biogen proposed to tighten the drug substance release limit for ---b(4)-----

Biogen further proposed to evaluate the release specification during -b(4)---- product review. FDA advised that the proposal will be considered internally and its decision conveyed to Biogen at a later date.

Note added in follow-up: FDA has completed its review of Biogen's proposal submitted in amendment 40 and finds it acceptable.

2. Your response in amendment 30 to item 19 from the September 11, 2013 information request was inadequate. Please align in-process specifications (IPS) for microbial control with those listed in Table CMC-1.

[b(4)]

--b(4)-----

----b(4)-----

Recommendations for --b(4)----- IPS in Table CMC-1 from the LCM document were based on action limits proposed by Biogen and submitted to amendment 30. This same approach was accepted by Biogen for the rFIXFc product. In particular, the IPS for --b(4)---- proposed in Table CMC-1 provides adequate flexibility in light of process validation data that indicated your ability to control --b(4)----- --. It is expected that IPS will be further adjusted after obtaining data from commercial manufacturing experience.

Biogen stated that they had observed intermittent low level --b(4)----- in some upstream process intermediates. Biogen agreed to propose tighter IPS similar to values concurred for rFIXFc process intermediates. FDA will convey their decision regarding Biogen's proposal after review.

Note added in follow-up:

FDA has completed its review of Biogen's proposal submitted in amendment 40 and finds it acceptable.

Process Hold Times:

3. Process validation reports submitted to amendment 37 indicated that established process hold time limits far exceeded manufacturing experience for the validated process. Please align process hold time limits during drug product manufacture

with conformance lot manufacturing experience.

Additional discussion:

As previously communicated through information requests for this product and for your rFIXFc product, FDA expects process hold times to be directly validated. The established process hold times for drug product manufacture far exceeded hold times documented during conformance lot manufacture. Biogen agreed to propose revised hold times for the drug product manufacturing process based on manufacturing experience with the validated process. Biogen requested that the Agency consider a -b(4)-- maximum process time for the filling operation based on support from media fill studies. FDA will convey its decision after review of Biogen's proposal.

Note added in follow-up:

FDA has completed its review of Biogen's proposed process hold times for drug product manufacture submitted in amendment 40 and finds them acceptable.

4. -b(4)----- for an out-of specification (OOS) result for Factor VIII potency, associated with process validation report, -b(4)----- revealed the practice of averaging an OOS result with a result meeting specification to generate a reportable result within specification. Please be advised that this practice is unacceptable under any circumstance.

Additional discussion:

FDA acknowledged that the OOS reported in -b(4)----- from process validation study --b(4)---- was controlled by a -b(4)-----

----- . Nonetheless, FDA is conveying that in general, the practice of averaging an OOS result with an in-specification result to obtain a reportable result is an unacceptable practice. Biogen confirmed that no OOS data will be accepted for in-process, release or stability testing.

CMC/Facility and Equipment:

5. During empty chamber thermal mapping of the lyophilizer, --b(4)-----

-----Please comment.

Additional discussion:

Item not discussed in the meeting – resolved during previous telecon.

6. Please note that we are waiting for the re-qualification report for container closure integrity testing of the diluent syringe as committed in amendment 25.

Additional discussion:

Item not discussed in the meeting – resolved during previous telecon

7. Please note that the Final Rule for 21 CFR Part 4 – Regulation of Combination Products became effective July 22, 2013. The pre-filled diluent syringe is considered a combination product [21 CFR 3.2(e)]. It appears that you have chosen to demonstrate compliance with the drug CGMPs. Please ensure you have complied with the following provisions of the Quality System (QS) regulation for the pre-filled diluent syringe:

- a) 21 CFR § 820.20 Management responsibility
- b) 21 CFR § 820.30 Design controls
- c) 21 CFR § 820.50 Purchasing controls
- d) 21 CFR § 820.100 Corrective and preventive action

Additional discussion:

Item not discussed in the meeting – resolved during previous telecon.

Outstanding Information Requests:

- An information request was sent on March 18, 2014, requesting that Biogen label product vials of Antihemophilic Factor (Recombinant), Fc Fusion Protein with potencies determined using a one stage clotting assay.

Additional discussion:

Biogen summarized its rationale for implementation of the chromogenic substrate (CS) assay for control of commercial manufacture and vial labeling. Biogen maintains that the CS assay is more reproducible and more conservative. Biogen indicated that the one stage (OS) clotting assay reads out –b(4)- than the CS assay. A field study using mock patient samples yielded good recovery and there was not a problem with monitoring in clinical laboratories using OS assays with a variety of reagents. The ISTH/SSC guidelines give manufacturers the option to label with either assay. Data from over –b(4)- recent product lots yielded many OS values –b(4)- the -b(4)- nominal potency upper limit. Implementation of the OS assay at this time would negatively impact process validation, the product stability program and commercial supply. FDA advised that they will discuss this issue further but prefer labeling with the OS assay. FDA will consider and advise Biogen of the final decision.

Labeling:

Recommendations for the *Prescribing Information* and the vial and carton labels will be provided as part of the labeling review.

III. Issues requiring further discussion:

- Assay for potency labeling

IV. Action items:

1. Biogen will submit proposals for microbial control limits and drug product process hold times in an amendment to STN BL 125487/0.
2. The Agency will continue internal discussion regarding FVIII potency labeling.

3. Note added in follow-up: Biogen submitted amendment 40 on April 9, 2014, which contained responses to issues discussed at the Late Cycle Meeting.

End