

Information Request, September 2, 2013- Eloctate

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

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

Our Reference: BL STN 125487/0

Biogen Idec, Inc.
Attention: Nadine Cohen, PhD
September 11, 2013
Sent by email

Dear Dr. Cohen:

We are reviewing your March 7, 2013 biologics license application (BLA) for Antihemophilic Factor (Recombinant), Fc Fusion Protein [rAHFFc]. We are providing the following comments and requests for additional information to continue our review.

Chemistry, Manufacturing and Controls (Facilities and Equipment)

1. Regarding -----b(4)-----
 - o Please provide the -----b(4)----- validation studies for the --b(4)----- of vials used for the drug product, and for the syringe barrel and plunger used for the diluent.

- Please provide a description of all of the -----b(4)----- that will be used for the vials, syringe barrel and plunger.

2. Regarding sterilization:

- Please provide a description of all autoclaves used for sterilization of product contact equipment and/or components. Please provide the sterilization validation studies.
- Please provide a description of the autoclave used to sterilize the diluent. Please provide the --b(4)-----sterilization validation studies for the diluent.

3. Regarding lyophilization:

- Please provide the study report(s) for validation of the lyophilization process and a description of the lyophilizer(s).
- Please explain your approach to validating the lyophilization cycle. Required information will include the results of empty chamber temperature mapping studies for each lyophilizer you intend to employ to manufacture drug product. Please provide a summary of those studies. Please also ensure you describe your sampling method (e.g., extended sampling, sampling pattern, which shelves sampled and sample locations, number of samples taken at each location), lot size of each run, fill volume of each run, product strength of each run, and testing results (e.g., residual moisture, potency, reconstitution time).
- Please clarify if validation studies were performed using vials from each qualified vendor. If not, please justify why this is acceptable.
- Please confirm that the lyophilization cycle is fixed. Please provide detailed information on any changes made for any of the validation runs.
- Please provide your validation final report for the corresponding validation runs.
- Please clarify if a study was performed for each dosage strength and fill volume. If not, please provide a justification for why this is acceptable.
- Please provide the final fill volumes and vial sizes for all dosage strengths.
- Please provide the drug product glass transition temperature for all dosage strengths.
- Please explain how the filled product is physically transported to the lyophilizer and how you prevent contamination of the product during this process.

4. Please clarify if there are any differences in the lyophilization cycle and product testing among drug product lots: ---b(4)-----

5. Regarding the --b(4)---- test for container closure integrity testing (CCIT):

- Please provide the validation report for CCIT of the drug product and diluent.
- You stated that the positive control was --b(4)-. Please provide your rationale on why this size was selected as the positive control and why it is appropriate.
- You stated the acceptance criterion for this study as, “--b(4)-----
----- Please clarify if you have qualified the

operators to be able to detect –b(4)--- approaching worst case and if the –b(4)-----
----- is sufficient to be detected by visual inspection.

- Please clarify if CCIT was done on vials from –b(4)- vendors for the drug product.
- Please clarify if any part of the container closure system that is product contact contains latex.
- For CCIT for stability testing, please provide the –b(4)-----.
- Please clarify why you used different test methods for CCIT for stability testing versus initial release.

6. Please clarify if –b(4)----- is used as an overlay during either drug product or diluent manufacture. Please also clarify if the drug product is stoppered –b(4)-----.

7. Regarding visual inspection:

- Please clarify if the inspection is manual, semi-automated, or automated.
- Please describe the visual inspection procedure performed for the drug product and diluent. Information provided should include, but not be limited to, defects evaluated, acceptance criteria, and criteria for accepting or rejecting a lot.
- Please provide the qualification of your visual inspection process.

8. You state, “equivalent equipment may be used,” for the manufacturing of the drug product and diluent (module 3.2.A.1). Please clarify which equivalent equipment will be used and if those pieces of equipment are also validated for manufacturing rAHFFc.

9. Regarding hold time validation for drug product, --b(4)-----
-- were studied (module 2.3.P. Table 23) and product intermediates were held for significantly less time than the claimed maximum. Please adjust maximum hold times to reflect conformance lot manufacturing experience.

10. Please provide your drug substance and drug product process validation protocols.

Chemistry, Manufacturing and Controls (Product)

11. Please provide a study report describing the *complete* validation of the commercial Factor VIII potency assay, to include testing of multiple commercial drug substance batches and drug product lots.

12. Please provide complete validation of the ---b(4)----- test against the accepted, compendial –b(4)----- test to cover the shelf life specification and all dosage strengths.

13. For the –b(4)----- assay, please comment on whether or not you have tested cross-reactivity with BDD-rFVIII.

14. Please provide a representative –b(4)----- from analysis of polysorbate 20 in the drug product.

15. Please provide a representative –b(4)----- from analysis of rAHFFc drug product by –b(4)-----
16. Please explain which epitope on FVIII is recognized by the –b(4)----- affinity ligand.
17. Please add the following tests to the drug substance release specification:

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

18. Please revise acceptance criteria for the following release tests, as indicated:

- Please establish acceptance criteria for chromogenic assay determined –b(4)----- in accordance with clinical and commercial scale manufacturing experience, calculated according to an appropriate statistical paradigm. The proposed acceptance criteria of –b(4)----- and –b(4)----- - for drug product do not reflect historical manufacturing experience.
- Please establish an acceptance criterion for endotoxin that reflects manufacturing capability and is consistent with the drug product release specification. The proposed acceptance criterion of –b(4)----- neither reflects conformance batch results, –b(4)----- nor is consistent with the highest proposed drug product release specification of –b(4)-----
- Please establish a provisional acceptance criterion for percent non-processed form determined by –b(4)----- and drug product release since this was the statistically based, calculated value. Please commit to re-evaluation of the acceptance criterion after accumulating additional commercial release data, with the aim of lowering the value.

19. Please establish in-process specifications (IPS) for –b(4)----- that reflect manufacturing capability.

20. Please add an in-process test (IPT) for –b(4)----- ---- to confirm attainment of the validated range for virus inactivation.

21. Please add to the drug product release specification, tests for all excipients.

22. Please establish maximum process intermediate hold times based on conformance batch manufacturing experience, not laboratory studies, e.g.:

[b(4)]

23. Please commit to submitting a prior approval supplement for a one time exception to release any lot manufactured outside critical limits, including excursions to: (i) in-process specifications, (ii) maximum processing times/ process intermediate hold times, (iii) any parameter controlling viral inactivation by –b(4)-- treatment of –b(4)-----, (iv) any parameter controlling virus removal by –b(4)-- 15N filtration and (v) critical control parameters for the production –b(4)-----, sterile filtration, lyophilization or diluent –b(4)----- sterilization.

24. Process validation submitted to BL STN 125487/0 was inadequate in that designated process validation lots for 500 IU, 750 IU, 1000 IU, 1500 IU and 2000 IU were analyzed under a retrospective validation protocol. Retrospective validation is only applicable to legacy products with a long history of commercial manufacture. Please manufacture the following lots under a prospective validation protocol:

- 500 IU dosage, small –b(4)-----vial) lot size
- 1,000 IU dosage
- 2,000 IU dosage, large –b(4)----- vial) lot size

Please ensure that drug product conformance lots are manufactured from drug substance lots manufactured under a prospective validation protocol. Please ensure that all drug substance conformance batches and drug product conformance lots are monitored according to the approved, commercial stability program.

25. Please request from –b(4)-----, the submission to FDA of a master file to support continued quality and control of the –b(4)----- Ligand. Please submit a letter of authorization from –b(4)----- permitting reference to the applicable master file.

26. Please be advised that –b(4)-----of the –b(4)----- 15N viral filtration step will not be allowed.

27. Please provide the column lifetime limit (cycle number) provisionally validated for –b(4)----- column use.

28. Please provide operating ranges for flow rates for all chromatography steps.

29. Please be advised that only the manufacturing areas through which conformance batch/lot manufacture has been successfully performed will be licensed

30. Please be advised that an *in vitro* functional test for FVIII activation kinetics should be implemented for characterization and comparability.

Clinical/ Pharmacovigilance

31. Your current Pharmacovigilance Plan (PVP) is insufficient to evaluate the long-term safety and efficacy of rAHFFc, and the safety and efficacy in previously untreated patients (PUPs). Please expand the inclusion criteria for the ongoing pediatric study to include PUPs patients. Please classify the following ongoing studies as Post-marketing Commitment Studies (PMCs) and submit appropriate timelines for completion of study and submission of a final study report:

- a. "An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIII Fc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia, an extension to the Phase 3 study."
- b. "An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BII B031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A."

32. The following Important Potential Risks were identified on review of clinical trial data:

- o Development of anti-drug (rAHFFc) antibodies (ADA)
- o Thrombotic Events
- o Dosage errors

The following Important Missing Information was identified on review of clinical trial data:

- o Use in previously untreated patients

Please add the four safety concerns listed above to the PVP and planned action(s) to address each safety concern. If the planned action includes a clinical study, please provide a copy of the study protocol and interim study report, if applicable

The review of this submission is ongoing and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file by December 1, 2013 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is March 8, 2014.

If you have any questions, please contact me at (301) 827-6116.

Sincerely,

Leigh Pracht
Regulatory Project Manager
FDA/CBER/OBRR/DBA/RPMB