

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125499Orig1s000

CHEMISTRY REVIEW(S)

From: Ennan Guan
Through: Juhong Liu and Susan Kirshner

Jan 7, 2014

Addendum to BLA 125499 Plegridy (peginterferon beta-1a)

Background

Biogen sent in the following responses to the Agency's information request at the time of the late cycle meeting and after the CMC review had been signed off. The most information request items has been discussed and resolved at the late cycle meeting except the following two items: 1) request regarding addition of receptor IFNAR2 binding assay to the DP release and stability testing and 2) [REDACTED] (b) (4)

[REDACTED] This addendum reviews the information about the two issues received after the late cycle meeting.

FDA Request F regarding receptor binding assay

You evaluated affinity of peginterferon to its receptor IFNAR2 as a characterization test but did not include this test in release and stability testing. Provide a scientific justification for your decision. Because this assay may be more sensitive to potential changes in product quality and may be less variable than the cell based CPE assay, we recommend that you consider including this assay in your release and stability testing.

Biogen Response

Interferon beta-1a belongs to type I interferon family. Effects of the type I interferon family members are mediated through interaction with a common type I IFN receptor composed of IFNAR1 and IFNAR2. As such, full functional biological activities mediated by IFN require both IFNAR1 and IFNAR2 binding. The CPE assay routinely used for peg interferon beta-1a release and stability testing is a full functional assay that assesses binding affinity to both IFNAR1 and IFNAR2 receptors. Since the IFNAR2 binding assay only provides one of the required biological functions of peginterferon beta-1a it is not suitable for product release and stability testing. The Biogen proposes to continue use of IFNAR2 binding as a characterization assay.

FDA Reviewer Comments

It is well-known in the literature that binding of both IFNAR1 and IFNAR2 is required for type I IFN full functional activity which is monitored in the current cell-based CPE potency assay. Biogen provided sound scientific justification to not include the IFNAR2 binding assay for release and stability testing because it only assesses IFNAR2 binding activity. Therefore, I concur with the sponsor's proposal to continue use of IFNAR2 binding assay as a valuable characterization assay and not to include it in routine release and stability testing.

Response to FDA Request F is satisfactory

The rest information request items were discussed at the later cycle meeting with the sponsor.

1) Regarding revising (b) (4)

The Agency did not agree with the proposed (b) (4) ppm stated in their response since this is much higher than the manufacturing experience of (b) (4) ppm. The sponsor agreed to revise (b) (4) according to manufacturing history and clinical experience.

FDA Reviewer Comments

In its response submitted on Feb. 20, 2014, Biogen proposed to revise (b) (4)

(b) (4) the proposed limits are adequate to ensure safety.

This issue has been addressed.

2) Regarding including accelerated stability testing to the DP post-approval stability protocol.

In their response, the sponsor believes that it is not necessary to include accelerated stability testing to the DP post-approval stability protocol because the DP has been demonstrated a good stability profile historically. At the late cycle meeting, the Agency stated that the accelerated stability testing was generally more sensitive to identify potential product quality issues. Accelerated stability testing should be an integral part of annual stability testing program and should stay with the product throughout its entire life cycle. The sponsor agreed to include accelerated stability test to their annual stability protocol.

3) Provide details about your potency assignment strategy and your assessment of how the strategy prevents drift.

The Agency agreed with the sponsor's strategies on potency assignment and potency draft prevention.

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/s/

ENNAN GUAN
03/10/2014

JUHONG LIU
03/10/2014

SUSAN L KIRSHNER
03/10/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From: Juhong Liu, Ph. D.
Division of Therapeutic Proteins (DTP)

Through: Susan Kirshner, Ph.D.
Review Chief
Division of Therapeutic Proteins (DTP)

Amy Rosenberg, MD
Director
Division of Therapeutic Proteins (DTP)

BLA Number: 125499
Product: Plegridy
Sponsor: Biogen Idec, Inc.
Date of Review: January 22, 2014

Due Date of CDTL Memo: January 23, 2014

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA125499 for Plegridy, manufactured by Biogen Idec, Inc. The data submitted in this application support the conclusion that the manufacture of Plegridy is well controlled, and leads to a product that is pure and potent. The processes used in manufacturing have been validated, and a consistent product is produced from different production runs, which helps ensure continued product safety and efficacy.

The Plegridy Phase I clinical trial was initiated with Plegridy Drug Product (DP) manufactured with the BIIB017-A process and was continued with Plegridy Drug Product (DP) manufactured with the proposed commercial BIIB017-B process. Process B is superior to process A because the process has (b) (4)

All products used in phase III trials were manufactured from the BIIB017-B process. The licensure of Plegridy is therefore supported by the safety and efficacy profile obtained in the clinical trials

It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture Plegridy drug substance at the Biogen Idec, Inc. facility in Cambridge, MA. The final formulated product will be manufactured at (b) (4). You may label your product with the proprietary name Plegridy and will market it at 63, 94 and 125µg dosages in prefilled syringes or pens.

The dating period for Plegridy prefilled syringes and pens shall be 36 months from the date of manufacture when stored at 2 to 8 °C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for your drug substance shall be (b) (4) months when stored at (b) (4) °C. Results of ongoing stability studies should be submitted throughout the dating period as they become available. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Plegridy to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Plegridy, or in the manufacturing facilities.

III. POST MARKETING COMMITMENTS/POST MARKETING/REQUIREMENTS

The following draft Post Marketing Commitments will be communicated to the sponsor during the late cycle reviews. The final completion dates will also be negotiated with the sponsor.

1. Drug Substance : To reevaluate release and stability specifications for the following: potency by the CPE assay, (b)(4), high molecular weight impurities by SEC-HPLC and (b)(4) for drug substances (DS) manufactured using the commercial process. The evaluation will be provided after thirty (30) batches are manufactured or within three (3) years, whichever is sooner. The revised specifications together with supporting information will be submitted to your BLA in accordance with 21 CFR 601.12.

Rationale: The current specifications are based on results from eight clinical (four of which are also process validation) lots. The four specifications mentioned above are sufficient to ensure that the safety and efficacy of commercial lots are within the favorable clinical safety and efficacy experience. However, due to lack of adequate commercial manufacturing experience, there are not sufficient data to assess whether these specifications reflect manufacturing capability. Biogen will re-assess these specifications after manufacturing adequate number of commercial lots.

2. Drug Product: To reevaluate release and stability specifications for potency by CPE, (b)(4) high molecular weight peginterferon beta-1a impurity by SEC-HPLC, (b)(4), and purity by RP-HPLC for drug product (DP) manufactured from Peginterferon beta-1a DP commercial process. The evaluation will be provided after thirty (30) batches or within three (3) years, whichever is sooner. The revised specifications together with supporting information will be submitted to your BLA in accordance with 21 CFR 601.12.

Rationale: Same as for PMC #1.

3. To evaluate levels of leachables for the components detected in the extractable studies for samples at the end of expiry.

Rationale: The sponsor requested 36 months expiry for Plegridy PFS but only provided leachable study results for up to 24 months at proposed storage condition of $5 \pm 2^\circ\text{C}$ and up to 12 months under accelerated condition ($25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$). Trending of the data indicate the leachables are likely to stay well below levels that cause any safety concern. Furthermore, DP stability data don't indicate any product degradation at the end of expiry. The lack of leachable data at the end of expiry doesn't indicate any safety concern but the Biogen should complete the leachable study to fully support the requested expiry of Plegridy PFS.

4. To conduct subvisible (2-10 microns) particulate testing of Plegridy PFS using orthogonal methods.

Rationale: Subvisible particulate testing is not included in release and stability testing but provides better quality control for the product. Biogen should perform a study to evaluate subvisible particles in stability samples and assess whether this testing should be included in release and stability testing.

Response to the following information requests are still pending. Based on the response, additional PMCs may be added.

1.  (b) (4)
Revise your  (b) (4) according to manufacturing history and in concordance with clinical trial material to ensure safety.
2. In your primary and working reference standard qualification, you state the potency of the references will be assigned based on a “rigorous protocol driven testing” but provided no details. Provide details about your for potency assignment strategy and assessment how the strategy prevents drift.
3. Your DP post approval stability protocol includes only real temperature stability testing. Revise your annual stability protocol to include stability testing under accelerated storage conditions.
4. You evaluated affinity of peginterferon to its receptor IFNAR2 as a characterization test but didn’t include this test in release and stability testing. Provide a scientific justification for your decision. Considering this assay may be more sensitive to detect potential changes in product quality and considering this assay may be less variable than the cell based CPE assay, we recommend that you consider including this assay in your release and stability testing.

IV. EXECUTIVE SUMMARY

A. Description of Product

Plegridy drug substance, peginterferon beta-1a is a pegylated form of recombinant human interferon beta-1a (IFNβ1a) expressed in Chinese Hamster Ovary (CHO) cells. The primary sequence of the recombinant interferon beta-1a is identical to the natural human IFNβ1. The (b) (4) IFNβ1a is pegylated with a single linear, 20kDa polyethylene glycol (PEG) molecule covalently conjugated to its amino terminal amino acid residue. The molecular weight of peginterferon is approximately (b) (4) kDa. (b) (4)

The glycans, together with the PEG chain, extend the circulation half-life of peginterferon beta-1a and affect clinical performance of Plegridy.

Plegridy Drug Product is supplied as a single-dose, preservative-free, prefilled syringe or pen containing 63, 94 or 125µg of the active ingredient, peginterferon, in 0.5ml solution. Plegridy syringes and pens are stored at 2° to 8°C (b) (4). The secondary container provides physical and light protection for Plegridy.

Biogen Idec, Inc. submitted a request for Categorical Exclusion from Environmental Assessment, which has been granted based on 21 CFR 25.31 (c).

Biogen also requests four- and twelve-year periods of exclusivity upon approval of Plegridy. Plegridy is structurally different from Biogen's previously approved product Avonex (IFNβ1a) because of the addition of the PEG moiety to the protein. Plegridy also differs from Avonex in pharmacokinetic and pharmacodynamic profiles, resulting in different administration schedule. We recommend that the requests for exclusivity be granted.

B. Clinical Trial Information

Plegridy was developed for treatment of patients with relapsing forms of multiple sclerosis (MS). Plegridy is provided in three dosage forms: 63, 94 and 125µg/dose and all three dosages forms are provided as prefilled syringes or pens. It is recommended that patients start treatment with the 63µg dose at dose 1, increasing to 94µg at dose 2 and reaching the full dose at dose 3 and continue with the 125µg dose.

The commercial formulation of Plegridy DP (peginterferon, Arginine, sodium acetate and polysorbate 20) was used in two phase I trials (105RI101 & 105HV103), the pivotal phase III clinical trial (105MS301) and its extension trial (105MS302). The manufacturing process for commercial Plegridy remains the same as the process used to manufacture the phase III clinical materials.

C. Stability

Accelerated and stressed stability studies identified two primary pathways of product degradation: [REDACTED] (b) (4)

However, as shown by RP-HPLC and SEC-HPLC testing results from stability samples, these degradation pathways were insignificant under the intended storage conditions. Photostability study results also suggest that the drug product is labile after exposure to intense light. However, the stability results of products stored in the secondary container clearly demonstrate that the drug product container closure packaging eliminates light-induced product degradation. The proposed storage condition of 2° to 8°C in a carton package is sufficient to minimize degradation of Plegridy DP within the requested expiry dating period as well as under in-use conditions as described by the label.

Plegridy Drug Substance ([REDACTED] (b) (4)) is stored in [REDACTED] (b) (4). Current stability testing results support a [REDACTED] (b) (4) expiry of Plegridy DS.

Plegridy Drug Product is supplied as a single-dose, preservative-free, prefilled syringe (PFS) or pen. Each PFS or pen contains 0.5ml solution with 63, 94 or 125µg of the active ingredient, peginterferon. The syringes and pens are stored at 2 - 8°C in the carton to protect from light. Current stability testing results supports a 36 month expiry of Plegridy DP. Temperature excursion stability study results also support the label claim that Plegridy PFS and pen can be left in room temperature (2 - 25°C) for up to 30 days.

D. Complexity

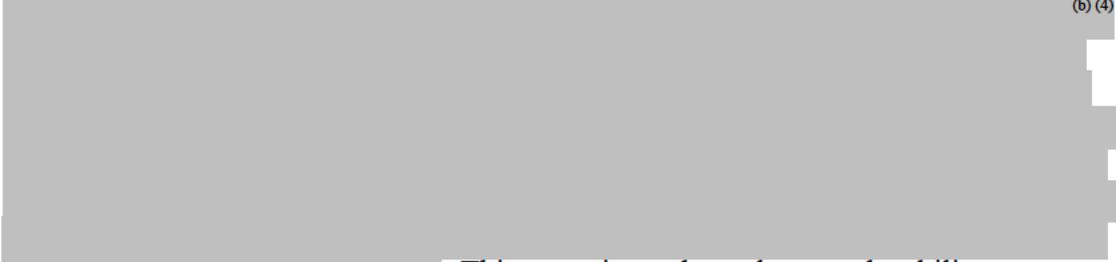
Critical Quality Attributes

The IFNβ1a moiety of peginterferon is expressed in CHO cells, which are frequently used for manufacture of biotech products. [REDACTED] (b) (4) IFNβ1a protein is pegylated with a 20kDa PEG. [REDACTED] (b) (4)

The glycans, together with the PEG chain, impact the circulation half-life of peginterferon beta-1a. Therefore the overall clinical efficacy of Plegridy is achieved by the combined effects from the biological activity of the IFNβ1a protein and modifications (pegylation and glycosylation) of the protein to prolong PK.

With regard to safety, the products from each of the two major product degradation pathways are assessed at release and on stability. The degradation products assessed are: [REDACTED] (b) (4)

The critical quality attributes and control methods are listed below:

-  (b) (4)

This assay is used as release and stability specifications to control for peginterferon biological activity during manufacturing and during storage throughout expiry. Available stability data do not indicate any trend towards loss of biological activity throughout the proposed expiry under the proposed storage conditions.

-  (b) (4)

-  (b) (4)

-  (b) (4)

E. Homology to Other Products

The amino acid sequence of the interferon moiety of Plegridy is identical to native human interferon beta and the approved Avonex. The glycosylation of Plegridy is comparable to native

human interferon and Avonex. The site-specific pegylation on the interferon protein molecule is unique to Plegridy.

F. Mechanism of Action

Plegridy is recombinant human interferon beta-1a with a 20kDa PEG molecule covalently attached to its amino terminal amino acid residue. The attachment of PEG extends the half-life of interferon, resulting in less frequent administration. The mechanism of action of IFNB1a for MS treatment is not well understood, but IFNB1a most likely functions by inducing anti-inflammatory activities to temper autoimmune inflammation events in central nervous system. The clinical efficacy is therefore a combined effect from the PEG and interferon moieties of the molecule.

The integrity of the molecule is assessed by RP-HPLC which can detect the appearance of ^{(b) (4)} with high sensitivity.

The biological function of interferon can be assessed by the following two assays:

1. Anti-viral CPE assay:

This assay is discussed in section D “Critical Quality Attributes”. It is used to assess potency at release and on stability for both DS and DP.

2. IFNAR2 binding:

IFNB1a mediates its biological activity by binding to the extracellular portions of IFN receptors. The association constant of peginterferon to INF receptors can be measured by an *in vitro* binding assay. The assay evaluates how well peginterferon binds to its receptors but doesn't evaluate peginterferon's ability to stimulate cellular activities. Compared to the cell-based anti-viral CPE assay, this type of assay can be very sensitive and the results can be much less variable. The sponsor used this assay in characterization study but didn't further develop it into release or stability specification. This will be discussed with the sponsor and may result in an additional PMC.

G. Manufacturing Process

Recombinant interferon is produced in CHO cells, purified and pegylated with 20kDa PEG through covalent attachment of mPEG to the amino terminal amino acid residue. ^{(b) (4)}

The control limits and in-process

test limits/specifications are acceptable with the exception of (b) (4).
 The review of (b) (4) will be provided as an addendum to the BLA review.

For the manufacture of DP, DS is (b) (4)
 (b) (4) to a final concentration of 63, 94 or 125µg/0.5ml, (b) (4)
 (b) (4)
 (b) (4) The finished DP is stored at 2 -
 8°C in a carton protecting it from light.

H. Comparability

The process used to manufacture materials for part of the phase I and the phase III pivotal trails remains the same as the proposed commercial process. The only change for commercial production is that the sponsor proposed to include an alternative mPEG supplier for future commercial Plegridy production. The sponsor provided comparability study results to demonstrate that lots manufactured using mPEG from the two suppliers were physicochemically comparable and share comparable stability profiles. The sponsor implemented a rigorous program, including a use-test, to quality each mPEG lot for commercial Plegridy production. Because of this qualification program, the potential impact of different mPEG lots on Plegridy product quality is minimal.

I. Immunogenicity

The evaluation of anti-peginterferon beta-1a antibodies (ADAs) shows a low immunogenicity rate among all patients tested. Less than 1% (4/489) of the patients developed persistent neutralizing antibodies to interferon beta-1a. About ~2% of the patients developed persistent treatment-emergent antibodies to the PEG moiety of Plegridy. Current available clinical data indicated no discernible negative impact on primary or secondary endpoints of clinical efficacy associated with antibodies against either IFN β-1a or PEG in subjects receiving up to 2 years of treatment.

The review of module 3.2 is attached as a separate document.

V. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Amy Rosenberg, MD Director Division of Therapeutic Proteins	
Susan Kirshner, Ph.D. Review Chief Division of Therapeutic Proteins	
Juhong Liu, PhD	

SUMMARY BLA 125499 Plegridy

Division of Therapeutic Proteins	
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/s/

JUHONG LIU
01/30/2014

SUSAN L KIRSHNER
02/01/2014

AMY S ROSENBERG
02/03/2014

BLA STN 125499

Plegridy

Biogen Idec, Inc.

**Primary Reviewer:
Ralph M Bernstein
Ennan Guan
Serge Beaucage
Tracy Denison**

**CMC Team Lead:
Juhong Liu**

Division of Therapeutic Proteins

OBP CMC Review Data Sheet

1. **BLA#: STN 125499**

2. **REVIEW DATE: January 16, 2014**

3. **PRIMARY REVIEW TEAM:**

Medical Officer: Lawrence Rodichok
Pharm/Tox: Rick Houghtling
Product Quality Team: Serge Beaucage, Ralph Bernstein, Tracy Denison, Ennan Guan, Juhong Liu
BMT or Facilities: Bo Chi/ Lakshmi Narasimhan
Clinical Pharmacology: Ta-Chen Wu
Statistics: Tristan Massie
OBP Labeling:
RPM: Nicole Bradley

4. **MAJOR 21st Century Review DEADLINES**

Filing Meeting: July 2, 2013
Mid-Cycle Meeting: October 2, 2013
Wrap-Up Meeting: March 11, 2014
Primary Review Due: January 16, 2014
Secondary Review Due: January 23, 2014
CDTL Memo Due: April 4, 2014
PDUFA Action Date: May 16, 2014

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)

7. **DRUG PRODUCT NAME/CODE/TYPE:**

- a. Proprietary Name: Plegridy
- b. Trade Name: Plegridy
- c. Non-Proprietary/USAN: peginterferon beta-1a

- d. CAS name:
- e. Common name:
- f. INN Name:
- g. Compendial Name:
- h. OBP systematic name:
- i. Other Names: BIIB017

- 8. **PHARMACOLOGICAL CATEGORY:**
- 9. **DOSAGE FORM:**
- 10. **STRENGTH/POTENCY:**
- 11. **ROUTE OF ADMINISTRATION:**
- 12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)

- 13. **INSPECTIONAL ACTIVITIES**
- 14. **CONSULTS REQUESTED BY OBP**
- 15. **QUALITY BY DESIGN ELEMENTS**

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
	Design of Experiments
x	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

- 16. **PRECEDENTS**

17. ADMINISTRATIVE

A. Signature Block

Recorded in DARRTS

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA STN 125499 for Plegridy (peginterferon beta-1a) manufactured by Biogen Idec, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Plegridy (peginterferon beta-1a) is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

The sponsor will provide responses to our future information request. The review of these items will be an addendum to this review and based on the adequacy of the responses, the resulting issues may become additional PMCs.

II. List Of Deficiencies To Be Communicated

The review of the BLA did not identify CMC-deficiencies that would preclude the approval.

III. List Of Post-Marketing Commitments:

1. To reevaluate release and stability specifications for CPE Potency, (b) (4) for drug substances (DS) manufactured using the commercial process. The evaluation will be provided in a PAS after thirty (30) batches are manufactured or within three (3) years, whichever is sooner.
2. To reevaluate release and stability specifications for CPE Potency, (b) (4) HMW impurities, (b) (4) and purity for drug product (DP) manufactured from Peginterferon beta-1a DP commercial process. The evaluation will be provided in a PAS after thirty (30) batches or within three (3) years, whichever is sooner.
3. To evaluate levels of leachables for the components detected in the extractable studies for samples at the end of expiry.
4. To conduct subvisible (2-10 microns) particulate testing of Plegridy PFS using orthogonal methods.

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/s/

RALPH M BERNSTEIN
01/16/2014

SERGE BEAUCAGE
01/16/2014

MARIA T GUTIERREZ LUGO on behalf of TRACY A DENISON
01/16/2014

ENNAN GUAN
01/16/2014

JUHONG LIU
01/16/2014

PRODUCT QUALITY (Biotechnology)

FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number: 125499

Applicant: Biogen IDEC

Stamp Date: 16 May 2013

Established/Proper Name: **BLA/NDA Type: Original**
Plegridy / pegylated interferon
beta -1a

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed	Y N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y N	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Labeling:	Y N	
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
<input type="checkbox"/> legible	Y N	
<input type="checkbox"/> English (or translated into English)	Y N	
<input type="checkbox"/> compatible file formats	Y N	
<input type="checkbox"/> navigable hyper-links	Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a	Y N	Not applicable

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
shared or divided manufacturing arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Quality overall summary [2.3]	Y N	N/A-the excipients are all standard
<input type="checkbox"/> Drug Substance	Y N	
<input type="checkbox"/> Drug Product	Y N	
<input type="checkbox"/> Facilities and Equipment	Y N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	
<input type="checkbox"/> Novel Excipients	Y N	
<input type="checkbox"/> Executed Batch Records	Y N	
<input type="checkbox"/> Method Validation Package	Y N	
<input type="checkbox"/> Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y N	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
<input type="checkbox"/> description of manufacturing process and process control	Y N	
o batch numbering and pooling scheme	Y N	
o cell culture and harvest	Y	
o purification		
o filling, storage and shipping	Y	
<input type="checkbox"/> control of materials		
o raw materials and reagents	Y N	
o biological source and starting materials		
o cell substrate: source, history, and generation		
o cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y N	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> ○ justification of specifications ○ stability □ process validation (prospective plan, results, analysis, and conclusions) □ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) Y N □ characterization of drug substance Y N □ control of drug substance <ul style="list-style-type: none"> ○ specifications ○ justification of specs. ○ analytical procedures ○ analytical method validation Y N ○ batch analyses Y N □ reference standards □ container closure system □ stability <ul style="list-style-type: none"> □ summary Y N □ post-approval protocol and commitment Y N □ pre-approval Y N <ul style="list-style-type: none"> ○ protocol ○ results Y N ○ method validation 		
<p>Drug Product [3.2.P] [Dosage Form]</p> <ul style="list-style-type: none"> □ description and composition Y N □ pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness Y N ○ container-closure integrity □ manufacturers (names, locations, and responsibilities of all sites involved) Y N □ batch formula Y N □ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <ul style="list-style-type: none"> Y N Y N □ controls of critical steps and intermediates Y □ process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> ○ Filter validation Y N ○ Component, container, closure depyrogenation and sterilization validation Y N 		<p>N/A there is no preservative. Defer to OMPQ/BMAB</p> <p>Defer to OMPQ/BMAB Defer to OMPQ/BMAB Defer to OMPQ/BMAB</p>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times) <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin) <input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities) <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s) <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	<p align="center">Y</p> <p align="center">Y N</p> <p align="center">Y N</p> <p align="center">Y</p> <p align="center">Y N</p> <p align="center">Y N</p> <p align="center">Y</p> <p align="center">Y N</p>	<p>Defer to OMPQ/BMAB</p> <p>Defer to OMPQ/BMAB</p> <p>Both DTP and BMAB</p> <p>Defer to OMPQ/BMAB</p>
<p>Diluent (vials or filled syringes) [3.2P']</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <input type="checkbox"/> controls of critical steps and intermediates 	<p align="center">Y N</p>	<p>N/A, there is no diluent, this is a PFS</p>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation <input type="checkbox"/> Validation of aseptic processing (media simulations) <input type="checkbox"/> Environmental Monitoring Program <input type="checkbox"/> Lyophilizer sterilization validation <input type="checkbox"/> Other needed validation data (hold times) 	Y N Y N Y N Y N Y N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
<input type="checkbox"/> reference standards		
<input type="checkbox"/> container closure system <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs 	Y N Y N	
<input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results 	 Y N	
Other components to be marketed (full description and supporting data, as listed above): <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit) 	Y N Y N	There are no other devices or marketed chemicals associated with this application.
Appendices for Biotech Products [3.2.A] <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas 	 Y N	Defer to OMPQ/BMAB

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection	Y N	Defer to BMAB/OMPQ
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	<input checked="" type="checkbox"/> Y N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y N <input type="checkbox"/> Y N <input checked="" type="checkbox"/> Y N <input type="checkbox"/> Y N	Defer to OMPQ/BMAB Defer to OMPQ/BMAB Defer to OMPQ/BMAB
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	<input checked="" type="checkbox"/> Y N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	Defer to OMPQ/BMAB
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	Defer to OMPQ/BMAB

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)
IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes No

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Product Quality Reviewer(s)	Date
Branch Chief/Team Leader/Supervisor	Date
Division Director	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RALPH M BERNSTEIN
07/02/2013

ENNAN GUAN
07/08/2013

SERGE BEAUCAGE
07/09/2013

SUSAN L KIRSHNER
07/09/2013

AMY S ROSENBERG
07/09/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

Instructions:

The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS “Communication Group” is “BLA Administrative Form” and the “Communication Name” is “FRM-BLAADMIN-61 – Establishment Evaluation Request Form.”

TB-EERs should be submitted:

- 1) within 10 business days of the application filing date (initial TB-EER)
- 2) 15-30 days prior to the planned action date (final TB-EER)

When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes. For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: May 14, 2014

Applicant Name: Biogen Idec Inc.
U.S. License #: 1697
STN(s): STN 125499/0
Product(s): Plegridy® (peginterferon beta-1a)
Summary: New BLA

FACILITY INFORMATION

Firm Name: Biogen Idec Inc.
Address: 14 Cambridge Center
Cambridge, MA 02142
FEI: 1220951
Short summary of manufacturing activities performed: Manufacture and storage of master and working cell banks; (b) (4)
Drug Substance Manufacture; Drug Substance QC testing (Bioburden and Endotoxin)

[This site was inspected by NWE-DO on March 4 – 15, 2013 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance](#)

manufacturing operations. The TRP profile was updated and is acceptable. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.**

Firm Name: Biogen Idec Inc.
 Address: 5000 Davis Drive
 Research Triangle Park, NC 27709-4627
 FEI: 3000719749
 Short summary of manufacturing activities performed: Storage of master and working cell banks; (b) (4) Drug Substance and drug product QC testing (Pre-filled Syringe); Drug product Stability Testing (Pre-filled Syringe); Stability Testing (Functionality Testing) of pre-filled pen

This site was inspected on September 19 – 30, 2011 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance manufacturing and testing operations. The CTX and TRP profiles were updated and are acceptable.

CDRH should be consulted to determine whether this site (or any other sites submitted in this BLA) requires device inspectional coverage prior to the approval of this BLA. Once this has been determined, NDMAB or GDMAB will enter a FACTS assignment request for any required device inspections.

Firm Name: Biogen Idec Denmark Manufacturing ApS
 Address: Biogen Idec Allé 1
 DK-3400
 Hillerød, Denmark
 FEI: 3006339887
 Short summary of manufacturing activities performed: Drug Substance and drug product QC testing (Pre-filled Syringe); Drug product Stability Testing (Pre-filled Syringe); Assembly of the pre-filled pen components with the pre-filled syringe; Release Testing (Functionality Testing) and EU QP Release of the pre-filled pen; Secondary packaging of pre-filled syringe and pre-filled pen; Stability Testing of pre-filled syringe; Stability Testing (Functionality Testing) of pre-filled pen

This site was inspected by CDER on May 6 – 13, 2013 and initially classified VAI. Although this inspection was primarily conducted as a PLI for new biotech drug substance manufacturing, this inspection provided in-depth systems-based coverage, including extensive review of the firm's Quality System. The site was also inspected by IOG May 23-27, 2011, providing coverage of the testing and packaging responsibilities. This site is acceptable for the purposes of this BLA from a drug CGMP compliance perspective.

CDRH should be consulted to determine whether this site (or any other sites submitted in this BLA) requires device inspectional coverage prior to the approval of this BLA. Once

this has been determined, NDMAB or GDMAB will enter a FACTS assignment request for any required device inspections.

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: Drug Substance QC testing
(b) (4)

This site was inspected by (b) (4) on (b) (4) and classified NAI. This was a routine GMP surveillance inspection covering drug product testing operations. The CTL profile was updated and is acceptable; however, because this site's compliance status is out-of-date, an inspection will be required prior to the approval of this BLA. A FACTS Assignment request will be created.

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: (b) (4)

This site was inspected by (b) (4) on (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering biotech testing operations. The CTL profile was updated and is acceptable.

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: (b) (4)

This site was inspected by IOG on (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance testing operations. The CTX profile was updated and is acceptable.

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)

Short summary of manufacturing activities performed: Drug Product Manufacturing and Primary Packaging of Pre-filled Syringe; Visual Inspection and Bulk Packaging of Pre-filled Syringe; Drug Product Release Testing (Sterility) of Pre-filled Syringe

This site was inspected by IOG on [REDACTED] (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering [REDACTED] (b) (4) drug product manufacturing operations. The BTP and [REDACTED] (b) (4) profiles were updated and are acceptable.

CDRH should be consulted to determine whether this site (or any other sites submitted in this BLA) requires device inspectional coverage prior to the approval of this BLA. Once this has been determined, NDMAB or GDMAB will enter a FACTS assignment request for any required device inspections.

Firm Name:

Address:

FEI:

Short summary of manufacturing activities performed: Drug Product Visual Inspection and Bulk Packaging and Secondary Packaging of Pre-filled Syringe; Drug Product Release Testing (Sterility) of Pre-filled Syringe; Secondary Packaging of Pre-filled Syringe

This site was inspected by IOG on [REDACTED] (b) (4) and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product packaging and testing operations. The [REDACTED] (b) (4) profile was updated and is acceptable.

CDRH should be consulted to determine whether this site (or any other sites submitted in this BLA) requires device inspectional coverage prior to the approval of this BLA. Once this has been determined, NDMAB or GDMAB will enter a FACTS assignment request for any required device inspections.

Firm Name:

Address:

FEI:

Short summary of manufacturing activities performed: Drug Product Visual Inspection and Bulk Packaging of Pre-filled Syringe; Drug Product Release Testing (Sterility) of Pre-filled Syringe

This site was inspected by IOG on [REDACTED] (b) (4) and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing and testing operations. The [REDACTED] (b) (4) profile was updated and is acceptable.

CDRH should be consulted to determine whether this site (or any other sites submitted in this BLA) requires device inspectional coverage prior to the approval of this BLA. Once this has been determined, NDMAB or GDMAB will enter a FACTS assignment request for any required device inspections.

Firm Name:

Address:

FEI:

Short summary of manufacturing activities performed: Drug Product Visual Inspection and Bulk Packaging of Pre-filled Syringe

This site was inspected by IOG on (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing and testing operations. The BTP and (b) (4) profiles were updated and are acceptable.

CDRH should be consulted to determine whether this site (or any other sites submitted in this BLA) requires device inspectional coverage prior to the approval of this BLA. Once this has been determined, NDMAB or GDMAB will enter a FACTS assignment request for any required device inspections.

Firm Name:

Address:

FEI:

Short summary of manufacturing activities performed: Drug Product Visual Inspection and Bulk Packaging of Pre-filled Syringe

This site was inspected by IOG on (b) (4) and classified NAI. This was a routine GMP surveillance inspection covering visual inspection activities.

CDRH should be consulted to determine whether this site (or any other sites submitted in this BLA) requires device inspectional coverage prior to the approval of this BLA. Once this has been determined, NDMAB or GDMAB will enter a FACTS assignment request for any required device inspections.

Firm Name:

Address:

FEI:

Short summary of manufacturing activities performed: Stability Testing (Container Closure Integrity) of Pre-filled Syringe

This site was inspected by (b) (4) on (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering drug testing operations. The CTB and CTL profiles were updated and are acceptable.

OVERALL RECOMMENDATION

Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIMOTHY J POHLHAUS
07/03/2013