

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125499Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: May 05, 2014
To: Administrative File, STN 125499/0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Addendum to Biologic License Application (BLA) to address the drug product (b) (4) hold time qualification data with an additional conformance lot and endotoxin spiking and hold study to evaluate the potential for endotoxin masking over time in the drug product
Applicant: Biogen Idec Inc.
Mfg Facility: (b) (4) – Pre-filled syringe (PFS)
Biogen Idec Denmark Manufacturing ApS, Biogen Idec Allé 1, DK - 3400 Hillerød, Denmark (FEI # 3006339887) - Pre-filled pen (PFP)
Product: Plegridy® (peginterferon beta-1a)
Dosage: Sterile, liquid formulation in a pre-filled syringe or pre-filled pen for subcutaneous injection with three different dosage strengths of 63 µg, 94 µg and 125 µg at a nominal volume of 0.5 mL
Indication: For the treatment of relapsing forms of multiple sclerosis
Due Date: August 15, 2014

Recommendation for Approvability: The drug product section of this BLA, as amended, was reviewed from a product quality microbiology perspective and recommended for approval.

SUMMARY:

This addendum addresses sponsor’s responses for the following studies provided on March 31, 2014 (Sequence 0062) and on April 10, 2014 (Sequence 0064).

- Drug product (b) (4) hold time qualification data with an additional conformance lot.
- Data from endotoxin spiking study using containers of similar composition as those used for sampling and storage of drug product to evaluate the potential for endotoxin masking over time.
- Data demonstrating that the endotoxin sample storage conditions do not impact the recovery of endotoxin.

ASSESSMENTS:

(b) (4)

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/s/

LAKSHMI RANI NARASIMHAN
05/05/2014

PATRICIA F HUGHES TROOST
05/05/2014



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 4/11/2014
To: Administrative File, STN 125499/0
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Addendum to review memo for New Biologic License Applications (BLA) STN 125499/0 dated 1/8/2014
Applicant: Biogen Idec Inc.
US License: 1697
Facility: Biogen Idec Inc.
Cambridge, MA
FEI: 1220951
Product: Plegridy (peginterferon beta-1a)
Dosage: 63, 94, 125 micrograms, solution for subcutaneous injection
Indication: Multiple sclerosis
PDUFA date: August 15, 2014

Recommendation: The drug substance part of this BLA, as amended, is recommended for approval from product quality microbiology perspective.

This review amends the drug substance microbiology product quality review memo for Biogen's BLA STN125499/0 dated 1/8/2014 with new information and data submitted by the applicant [amendment dated 1/23/2014 (sequence 48), 1/31/2014 (Sequence 50), 2/13/2014 (Sequence 54), and 3/14/2014 (Sequence 61)] pertaining to:

-  (b) (4)
-
-

 (b) (4)

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/s/

BO CHI
05/01/2014

PATRICIA F HUGHES TROOST
05/02/2014



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: January 16, 2014
To: Administrative File, STN 125499/0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Biological License Application (BLA)
US License: # 1697
Applicant: Biogen Idec Inc.
Mfg Facility: [REDACTED] (b) (4)
Pre-filled syringe (PFS)
Biogen Idec Denmark Manufacturing ApS, Biogen Idec Allé 1, DK - 3400
Hillerød, Denmark (FEI # 3006339887) - Pre-filled pen (PFP)
Product: Plegridy® (peginterferon beta-1a)
Dosage: Sterile, liquid formulation in a pre-filled syringe or pre-filled pen for
subcutaneous injection with three different dosage strengths of 63 µg, 94 µg and
125 µg at a nominal volume of 0.5 mL.
Indication: For the treatment of relapsing forms of multiple sclerosis
Due Date: May 16, 2014.

Recommendation for Approvability: The drug product section of this BLA was reviewed from a product quality microbiology perspective. However, responses to information requests are pending and the sponsor has committed to provide the following information and data by March 31, 2014:

- Data from endotoxin spiking study using containers of similar composition as those used for sampling and storage of drug product to evaluate the potential for endotoxin masking over time.
- Data demonstrating that the endotoxin sample storage conditions do not impact the recovery of endotoxin.
- Drug product [REDACTED] (b) (4) hold time qualification data with an additional conformance lot.

The pending data will be reviewed and documented in an addendum to this review memo.

SUMMARY:

Biogen Idec Inc. submitted a new biologics license application, STN 125499 to license Plegridy® (peginterferon beta-1a) for the treatment of relapsing multiple sclerosis. Drug substance is manufactured by Biogen Idec, Cambridge, MA and drug product in pre-filled syringe is manufactured at [REDACTED] (b) (4) and pre-filled pen is manufactured at Biogen Idec Denmark Manufacturing ApS, Hillerød, Denmark.

Both PFS and PFP are available either a starter pack or an administration pack. The starter pack will include two syringes/pens, one containing 63 µg and the other containing 94 µg of

peginterferon beta-1a to enable dose titration at the initiation of therapy. The administration pack contains two syringes/pens, both containing 125 µg of peginterferon beta-1a.

The supplement was submitted in eCTD format and included Module 1.1.2-FDA form 356h, Module 1.2-Cover letter, and Module 2 and 3. Information request responses submitted in amendments on July 17, 2013 (sequence 004), July 24, 2013 (sequence 004), August 01, 2013 (Sequence 007), September 23, 2013 (Sequence 022), October 31, 2013 (Sequence 030), October 31, 2013 (Sequence 030), December 02, 2013 (Sequence 0035) and December 17, 2013 (Sequence 0038) and December 30, 2013 (Sequence 0040) were also reviewed. TYPE III DMF (b)(4) has been reviewed for the (b)(4).

ASSESSMENTS:

Peginterferon beta-1a is a pegylated form of interferon beta-1a used for the treatment of patients with relapsing multiple sclerosis. Interferon beta (IFN β) products are the first-line injectable multiple sclerosis (MS) therapies available for over 15 years with an established safety and efficacy profile.

The α-amino group of the N-terminal amino acid residue of the interferon has been modified with a single, linear molecule of 20 kDa mPEG-O-2- methylpropionaldehyde. (b)(4)

Peginterferon beta-1a is supplied as a sterile, clear to slightly opalescent liquid for subcutaneous injection in either a pre-filled syringe (PFS) or pre-filled pen (PFP).

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective. For the review of drug substance aspects of the application, please see review by Dr. Bo Chi.

DRUG SUBSTANCE

Interferon beta-1a is manufactured from Chinese Hamster Ovary (CHO) cell (b)(4). The manufacturing process is comprised of (b)(4) resulting in the peginterferon beta-1a drug substance.

3.2.P DRUG PRODUCT

Peginterferon beta-1a drug product-PFS

Peginterferon beta-1a drug product-PFS is manufactured for Biogen Idec by (b)(4) in the facility located at the (b)(4). The PFS is packaged into either a starter pack or an administration pack. The starter pack contains two syringes, one containing 63 µg and one containing 94 µg of peginterferon beta-1a. The administration pack contains two syringes, each containing 125 µg of peginterferon beta-1a.

3.2.P.1 Description and Composition of the Drug Product- Pre-Filled Syringe

The peginterferon beta-1a drug product is a sterile, clear to slightly opalescent liquid formulation in a pre-filled syringe at a nominal volume of 0.5 mL for subcutaneous injection. The intended dosage forms for the Pre-filled Syringe are the 63 and 94 µg strengths for initial dose titration and the 125 µg strength for the long term presentation. The quantitative composition, function, and

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/s/

LAKSHMI RANI NARASIMHAN
01/17/2014

PATRICIA F HUGHES TROOST
01/17/2014



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 1/8/2014
To: Administrative File, STN 125499/0
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Applications (BLA)
Applicant: Biogen Idec Inc.
US License: 1697
Facility: Biogen Idec Inc.
Cambridge, MA
FEI: 1220951
Product: Plegridy (peginterferon beta-1a)
Dosage: 63, 94, 125 micrograms, solution for subcutaneous injection
Indication: Multiple sclerosis
PDUFA date: May 16, 2014

Recommendation: The approval of the drug substance part of this BLA is pending until the following information and data have been submitted and reviewed:

-
-
-

(b) (4)

The sponsor is currently conducting the studies and has committed to provide the data by January 31, 2014. The pending data will be reviewed in an addendum to this review memo.

Review Summary

Biogen Idec has submitted this Biologics License Application (BLA) for peginterferon beta-1a for the treatment of relapsing multiple sclerosis. The drug substance (DS) is manufactured at the Biogen Idec facility at Cambridge, MA. The drug product (DP) is manufactured at (b) (4). The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of peginterferon beta-1a drug substance from microbiology perspective.

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/s/

BO CHI
01/14/2014

PATRICIA F HUGHES TROOST
01/14/2014

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

BLA/NDA Number: 125499 Applicant: Biogen Idec Inc. Stamp Date:

**Established/Proper Name: BLA/NDA Type: Standard
peginterferon 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	
Form 356h completed <input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y N	Not required
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: <input type="checkbox"/> PI –non-annotated <input type="checkbox"/> PI –annotated <input type="checkbox"/> PI (electronic) <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Insert <input type="checkbox"/> package and container <input type="checkbox"/> diluent <input type="checkbox"/> other components <input type="checkbox"/> established name (e.g. USAN) <input type="checkbox"/> proprietary name (for review)	Y Y N Y Y N Y Y N Y Y N Y Y	Defer to OBP and OND

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: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> compatible file formats <input type="checkbox"/> navigable hyper-links <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays <input type="checkbox"/> summary reports reference the location of individual data and records <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y Y Y Y Y Y Y	
Companion application received if a shared or divided manufacturing	Y N	NA

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

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	Not required
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	Defer to OBP
<input type="checkbox"/> Novel Excipients	Y N	Defer to OBP
<input type="checkbox"/> Executed Batch Records	Y N	Defer to OBP
<input type="checkbox"/> Method Validation Package	N	Provided in 3.2.S and 3.2.P.
<input type="checkbox"/> Comparability Protocols	N	

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

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> control of critical steps and intermediates <ul style="list-style-type: none"> ○ justification of specifications ○ stability 	Y	
<input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions)	Y	
<input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	Defer to OBP.
<input type="checkbox"/> characterization of drug substance	Y	
<input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ specifications <ul style="list-style-type: none"> ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses 	Y Y Y	
<input type="checkbox"/> reference standards	Y N	Defer to OBP.
<input type="checkbox"/> container closure system	Y	
<input type="checkbox"/> stability <ul style="list-style-type: none"> □ summary □ post-approval protocol and commitment □ pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	Y	
Drug Product [3.2.P] [Dosage Form]		
<input type="checkbox"/> description and composition	Y	
<input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity 	Y N	NA
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> batch formula	Y	Defer to OBP
<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)	Y	<div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> ^{(b)(4)} data for PFS is not provided. This information will be requested.
<input type="checkbox"/> controls of critical steps and	Y	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
intermediates		
<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 validation <input type="checkbox"/> Other needed validation data (hold times) 	Y	Additional information regarding (b) (4)  will be requested.
	NA	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	Defer to OBP
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
<input type="checkbox"/> reference standards or materials	Y N	Defer to OBP.
<input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs <input type="checkbox"/> administration device(s) 	Y	Container closure integrity for refilled Pen during assembly will be requested.
<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 <input type="checkbox"/> method validation 	Y	
Diluent (vials or filled syringes) [3.2P']		NA- No diluent included
<input type="checkbox"/> description and composition of diluent	Y N	
<input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <input type="checkbox"/> preservative effectiveness 	Y N Y N	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
○ container-closure integrity	Y N	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
<input type="checkbox"/> batch formula	Y N	
<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)	Y N	
<input type="checkbox"/> controls of critical steps and intermediates	Y N	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y N	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation	Y N	
○ Validation of aseptic processing (media simulations)		
○ Environmental Monitoring Program	Y N	
○ Lyophilizer sterilization validation		
○ Other needed validation data (hold times)		
<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	Y N	
<input type="checkbox"/> container closure system	Y N	
○ specifications (vial, elastomer, drawings)		
○ availability of DMF & LOAs		
<input type="checkbox"/> stability	Y N	
<input type="checkbox"/> summary		

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

Examples of Filing Issues	Yes?	If not, justification, action & status
substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)		
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Defer to OBP.
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to OBP.
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to OBP.
Certification that all facilities are ready for inspection	Y	
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.	Y	
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 Y N Y	Rabbit pyrogen test data will be requested. Defer to OBP
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	Y N	Defer to OBP
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

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

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? YES

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

NA

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

NA

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/s/

LAKSHMI RANI NARASIMHAN
07/17/2013

BO CHI
07/17/2013

ZHIIHAO PETER QIU
07/17/2013