

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125499Orig1s000

OTHER REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

To: Susan Kirshner, DTP, OBP, OPS, CDER

From: Ralph Bernstein, LI, DTP

Date: 12 August 2014

Re: PEGylated IFN-b1a Plegridy immunogenicity review

Product: PEGylated IFN-b1a Plegridy STN 125499.

Indication: RRMS, Relapsing-remitting multiple sclerosis.

Composition: Each (b) (4) mL of Plegridy PFS (intended chronic dosing level) contains 125 micrograms PEG-IFN β -1a, Water for Injection (b) (4) 15.8 mg, L-Arginine HCl, 0.25 mg, Glacial Acetic Acid, 0.79 mg, Sodium Acetate Trihydrate, and 0.025mg Polysorbate 20, pH 4.8

Manufacturer(s): DS: Biogen-IDEC, Cambridge MA.

DP: (b) (4)

DP: (b) (4)

Abbreviations:

DP: drug product.

DS: drug substance.

RRMS: Relapsing-remitting multiple sclerosis.

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

UC: Ulcerative Colitis.

CMC: chemistry manufacturing and controls, also known as Quality Review.

NC: negative control.

PC: positive control.

NHS: normal human serum.

CV: [coefficient of variance](#).

LOD: limit of detection.

Purpose:

The purpose of this review is to confirm the validation and appropriateness of the assays used to support the safety of treatment with Plegridy.

Recommendation:

The Plegridy immunogenicity assays are validated and acceptable for their intended purpose. The immunogenicity results from approximately 940 patients over a two year study are within the historic norm for IFN β products, and strongly suggest that Plegridy has an acceptable risk and safety profile regarding immunogenicity.

Immunogenicity Summary:

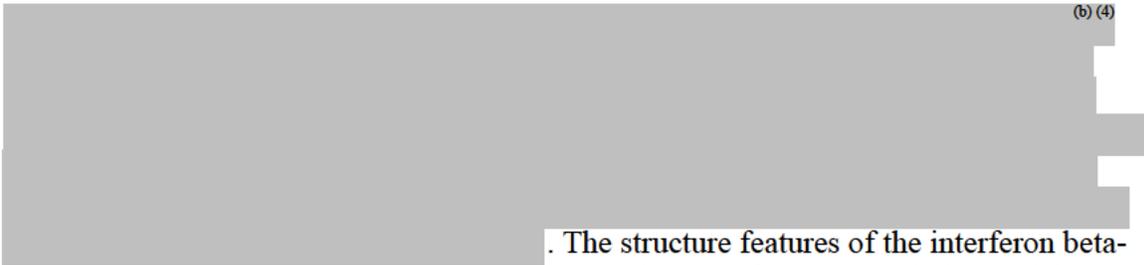
Plegridy is a recombinant PEGylated IFN β -1a intended to treat the symptoms of RRMS. The Sponsor, Biogen IDEC, submitted immunogenicity data for clinical studies treating patients with Plegridy and placebo. This submission includes antibody binding data for antibodies to IFN β -1a and antibodies to the PEG moiety. The Sponsor also submitted data for neutralizing antibodies. This package also includes the validation data for the two binding assays and the neutralizing assays. There were 465 patients enrolled in the every 4 week administration study and 471 patients in the every 2 weeks administration study. Patients treated for two years with Plegridy every 2 or every 4 weeks had binding antibodies to IFN β -1a at an incidence of 8 and 4%, respectively. Baseline positivity for anti-IFN β antibodies was 3% in placebo patients. Neutralizing antibodies were observed at less than 1%. The incidence of anti-PEG binding antibodies was 7% in patients treated every two weeks and 9% in patients treated every 4 weeks. Baseline positivity for anti-PEG antibodies was 8% in the placebo patients. Treatment with Plegridy every two weeks decreased the relapse rate by 39%. These immunogenicity rates are within or slightly below the historic norm for the IFN β -1a Avonex and are consistent with an acceptable risk and safety profile.

Description of Plegridy API:

(This section is slightly modified and taken from the CMC DS review of Plegridy 125499 DS, CMC reviewer Ennan Guan).

Peginterferon beta-1a is pegylated form of human interferon beta-1a in which a single, linear 20 kDa mPEG-O-2-methylpropionadehyde molecule is attached to the alpha-amino group of the N-terminal methionine residue. (b) (4)

(b) (4). The interferon beta-1a portion of DS is a 22.5 kDa recombinant glycoprotein. The molecular weight of peginterferon beta-1a is around (b) (4) kDa. The primary sequence of the interferon beta-1a portion of peginterforen beta-1 contains 166 amino acids (Figure 1) (b) (4)



. The structure features of the interferon beta-1a portion of molecule are consistent with those observed for commercially-available Avonex. See below for the AA sequence of Plegridy and the predicted 3D structure.

Figure 1: Amino Acid Sequence of the Interferon beta-1a Polypeptide Chain



Schematic of the peginterferon beta-1a structure

(b) (4)

Peginterferon beta-1a is indicated for treatment of relapsing-remitting multiple sclerosis (RRMS). Compared to Avonex, peginterferon beta-1a offers patients a less frequent dosing schedule due to its prolonged action. Type I interferons mediate a wide range of biological effects. Their actions on cells include induction of resistance to viral infections, inhibition of proliferation of normal and transformed cells, regulation of the differentiation state of immune system cells, and modulation of their functions.

Interferon-beta (IFN-beta) is a polypeptide, normally produced by fibroblasts, that has antiviral and antiproliferative effects. Binding of IFN-beta to its receptor induces a complex transcriptional response. In immune cells (the most likely target of IFN-beta's therapeutic effect in MS), IFN-beta reduces antigen presentation and T-cell proliferation, alters cytokine and matrix metalloproteinase (MMP) expression, and restores suppressor function. Biological potency of peginterferon beta-1a was assessed with an Antiviral activity by Cytopathic Effects (CPE) assay since activation of the type I IFN receptor is known to induce an antiviral state in cells. DS samples are tested (b) (4)

The biological potency of peginterferon beta-1a is approximately 50% of interferon beta-1a as measured by the CPE assay, while the binding to the extracellular portion of the human IFNAR2 receptor chain is comparable to that of interferon beta-1a.

Immunogenicity Assay Reviews:

All assays were developed by Biogen, then transferred to (b) (4) then validated all assays.

(b) (4)

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/s/

RALPH M BERNSTEIN
08/12/2014

SUSAN L KIRSHNER
08/13/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Memorandum:	June 16, 2014
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 125499
Product Name and Strength:	Plegridy (Peginterferon beta-1a) Injection Plegridy Pen (Peginterferon beta-1a) Injection 63 mcg/0.5 mL, 94 mcg/0.5 mL, 125 mcg/0.5 mL
Submission Date:	June 11, 2014
Applicant/Sponsor Name:	Biogen Idec
OSE RCM #:	2013-2791
DMEPA Primary Reviewer:	Justine Harris, RPh
DMEPA Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMO

Division of Neurology Products (DNP) requested that we review the revised Plegridy pre-filled syringe (PFS) and Plegridy Pen labels and labeling for the training devices (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

¹ Harris J. Label and Labeling Review for PLEGRIDY AND PLEGRIDY PEN (BLA 125499). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US);2014 May 14. 23 p. OSE RCM No.: 2014-95.

2 CONCLUSIONS

The revised training labels and labeling for Plegridy Pen and Plegridy PFS are acceptable from a medication error perspective.

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/s/

JUSTINE HARRIS
06/16/2014

TINGTING N GAO
06/16/2014

PMR/PMC Development Template for BLA 125499
Plegridy (peginterferon beta-1a)

PMR #1

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: A randomized, controlled, parallel group superiority trial in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of Plegridy (peginterferon beta-1a) compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2015</u>
	Study/Trial Completion:	<u>08/2018</u>
	Final Report Submission:	<u>11/2019</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is a PREA requirement. A waiver has been given for children under from birth to nine years of age because necessary studies are impossible or highly impracticable due to the small number of patients less than 10 years old with multiple sclerosis. A deferral has been given for those ages 10 up to 17; it is appropriate for a PMR because the drug is about to be approved and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to evaluate the safety and efficacy of peginterferon beta-1a in pediatric patients ages 10 to up to 17 compared to an appropriate control for treatment of relapsing forms of multiple sclerosis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, controlled, parallel group superiority trial in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of Plegridy (peginterferon beta-1a) compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
PREA pediatric clinical trial

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for BLA 125499
Plegridy (peginterferon beta-1a)

PMR #2

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Plegridy Pregnancy Registry

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2015</u>
	Study/Trial Completion:	<u>12/2023</u>
	Final Report Submission:	<u>5/2024</u>
	Other: <u>1st interim report</u>	<u>08/2015</u>
	2 nd interim report	08/2016
	3 rd interim report	08/2017
	4 th interim report	08/2019
	5 th interim report	08/2020
	6 th interim report	08/2021
	7 th interim report	08/2022
	8 th interim report	08/2023

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Pregnancy registries are conducted post-marketing to obtain safety data on drug use during pregnancy including maternal and infant outcomes. Historically, pregnancy registries are not conducted during the pre-marketing period, because except in unusual circumstances, it is ethically and medically important to demonstrate safety and efficacy in nonpregnant women before studying the drug in pregnant women.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is no adequate animal data regarding the effect of Plegridy on embryo-fetal development and there are no adequate and well-controlled studies in pregnant women. The goal of the pregnancy registry is to obtain data on Plegridy exposure during pregnancy including data on infant outcomes to inform prescribing for and counseling of women affected by multiple sclerosis that are pregnant and of childbearing potential.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective, observational exposure cohort study conducted in the United States that compares the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Plegridy (peginterferon beta-1a) during pregnancy to unexposed control populations (one with women with multiple sclerosis who have not been exposed to Plegridy in pregnancy and the other in women without multiple sclerosis). The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes will be assessed through at least the first year of life.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for BLA 125499
Plegridy (peginterferon beta-1a)

PMR # 3

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Re-evaluate the acceptance criteria for release and stability specifications for Plegridy drug substance and drug product

PMR/PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY
Study/Clinical trial Completion Date: MM/DD/YYYY
Final Report Submission Date: 09/2017
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is appropriate for a PMC because the acceptance criteria for release and stability specifications do not affect the safety of the product but will improve consistency of product quality.

Plegridy (peginterferon beta-1a)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Some of acceptance criteria for release and stability specifications for Plegridy drug substance and drug product are wider than the clinical experience and the currently available manufacturing experience. The Sponsor needs to reevaluate the following release and stability specifications after gathering adequate manufacturing experience :

For Plegridy drug product (DP):

Cytopathic effect potency (CPE) assay, (b) (4) high molecular weight impurities measured by SEC-HPLC, (b) (4), and purity measured by RP-HPLC.

For Plegridy drug substance:

Cytopathic effect potency (CPE) assay, (b) (4) high molecular impurities measured by SEC-HPLC, (b) (4)

The sponsor should justify the revised acceptance data using data collected from 30 lots of production scale Plegridy DS and DP in conjunction with clinical importance of these product quality attributes.

The goal of the study is to re-evaluate the release and stability acceptance criteria for Plegridy drug substance and drug product to ensure product consistency and to ensure the product conforms to its clinical experience throughout product lifecycle. The sponsor will revise these specifications using a dataset adequate for meaningful statistical analysis. Based on its production schedule, the sponsor projects that it should achieve the number of lots necessary for statistical analysis (approximately 30 lots) within 3 years. The completion of the PMC will provide better control of the product and ensure a higher level of consistency of Plegridy product.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Plegridy (peginterferon beta-1a)

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Re-evaluate the acceptance criteria release and stability specifications for Plegridy (peginterferon beta-1a) drug substance (DS) and reevaluate Plegridy (peginterferon beta-1a) drug product (DP) release and stability specifications' acceptance limits for: cytopathic effect potency (CPE) assay, (b)(4) high molecular weight impurities as measured by size exclusion chromatography, (b)(4) and purity as measured by reverse phase HPLC for drug product. Justify revised acceptance data using data collected from production scale Plegridy (peginterferon beta-1a) DS and DP manufactured using 30 distinct DS batches and knowledge about the clinical importance of product quality attributes. The re-evaluation will be submitted as a prior approval supplement after data is analyzed from the DP and DS batches or within three years, whichever is sooner.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other _____
-

5. Is the PMR/PMC clear, feasible, and appropriate?)Fill in Y for these

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Plegridy
PMC #4**

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Extend the Plegridy (peginterferon beta-1a) pre-filled syringe leachables study from 24 months to 36 months, the intended shelf life of the product.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>11/2014</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Plegridy drug product container closure system leachable study submitted to the BLA only includes results of leachables from drug product stored for up to 24 months. The intended shelf life of Plegridy drug product pre filled syringes is 36 months. The Sponsor will submit data that include up to 36 months to ensure that there are no potential additional leachables present at the end of the intended shelf life. This is appropriate for a PMC because the current 24 month study demonstrated that there are few leachables and including this as a PMC is an acceptable level of risk.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The Plegridy drug product leachable study submitted to the BLA only includes results of leachables from drug product stored for up to 24 months. The intended shelf life of Plegridy drug product pre filled syringes is 36 months. The extended leachable study will confirm the lack of leachables at the end of the intended 36 month shelf life of the Plegridy PFS.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Extend the Plegridy (peginterferon beta-1a) pre-filled syringe leachables study from 24 months to 36 months, the intended shelf life of the product.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?)Fill in Y for these

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Plegridy
PMC #5**

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Reevaluate the sub visible particulate level in Plegridy (peginterferon beta-1a) drug product pre-filled syringe by using an orthogonal method(s) to support the results submitted in the BLA.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>11/2014</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Sponsor submitted HIAC data to demonstrate that Plegridy drug product has low levels of sub visible (2-10 microns) particulates. Using HIAC method alone may bias the actual particulate counts. As the particulate counts appear low, the HIAC data is acceptable at this time. The Sponsor will submit particulate analyses using an orthogonal method(s) to confirm the low levels of sub visible particulates in Plegridy drug product reported in the BLA. This is acceptable as a PMC as the HIAC data appear to indicate acceptable levels of risk.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The Sponsor submitted HIAC data to demonstrate that Plegridy drug product has low levels of sub visible (2-10 microns) particulates. Using one method may bias the actual particulate counts. As the particulate counts appear low, the HIAC data is acceptable at this time. The Sponsor will submit particulate analyses using an orthogonal method(s) to confirm the low levels reported in the BLA. The goal of the study is to confirm the low levels of sub visible particulates reported in the BLA by an orthogonal method, thereby confirming the low levels of particulates.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reevaluate the sub visible particulate level in Plegridy (peginterferon beta-1a) drug product pre-filled syringe by using an orthogonal method(s) to support the results submitted in the BLA.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?)Fill in Y for these

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

SALLY U YASUDA
06/12/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 11, 2014
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 125499
Product Name and Strength:	Plegridy (Peginterferon beta-1a) Injection Plegridy Pen (Peginterferon beta-1a) Injection 63 mcg/0.5 mL, 94 mcg/0.5 mL, 125 mcg/0.5 mL
Submission Date:	May 15, 2014
Applicant/Sponsor Name:	Biogen Idec
OSE RCM #:	2013-2791
DMEPA Primary Reviewer:	Justine Harris, RPh
DMEPA Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMO

Division of Neurology Products (DNP) requested that we review the revised Instructions for Use (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised Instructions for Use is acceptable from a medication error perspective.

¹ Harris J. Label and Labeling Review for PLEGRIDY AND PLEGRIDY PEN (BLA 125499). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 APR 16. 34 p. OSE RCM No.: 2013-2791.

APPENDIX A. LABEL AND LABELING SUBMITTED ON MAY 15, 2014

We reviewed the revised Plegridy and Plegridy Pen Instruction for Use (no image) submitted on May 15, 2014.

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/s/

JUSTINE HARRIS
06/11/2014

TINGTING N GAO
06/11/2014

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA125499

Submission Date(s): 24April 2013

Applicant: Biogen Idec

Product: PEGylated interferon β -1a

Reviewer: Lawrence Rodichok MD

Date of Review: 14January 2014

Covered Clinical Study (Name and/or Number): 105MS301

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>1277</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>34</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>34</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The sponsor has provided adequate financial disclosure information. This financial data does not raise significant concern for the integrity of the data. The sites with disclosed financial interest randomized only 190 subjects the majority of which were in (b) (6) where the (b) (6) sites with investigators reporting a financial interest randomized 105 subjects. The United States accounts for 57% of the money reported but the US contributed only 3% of the subjects in the study. At FDA request the sponsor has provided an analysis of the primary endpoint by sites with and without a financial interest. The reduction in the Annualized Relapse Rate is numerically greater at the sites with a financial interest but the difference is not statistically significant. The disclosed financial interest of investigators in the study does not affect the approvability of the application.

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/s/

LAWRENCE D RODICHOK
05/20/2014

JOHN R MARLER
05/20/2014

LABEL, LABELING and USABILITY STUDY REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 16, 2014

Requesting Office or Division: Division of Neurology Products (DNP)

Application Type and Number: BLA 125499

Product Name and Strength: Plegridy (Peginterferon beta-1a) Injection
Plegridy Pen (Peginterferon beta-1a) Injection
63 mcg/0.5 mL, 94 mcg/0.5 mL, 125 mcg/0.5 mL

Product Type: Combination

Rx or OTC: Rx

Applicant/Sponsor Name: Biogen Idec

Submission Date: August 2, 2013

OSE RCM #: 2013-2791

DMEPA Primary Reviewer: Justine Harris, RPh

DMEPA Acting Team Leader: Julie Villanueva Neshiewat, PharmD, BCPS

1 REASON FOR REVIEW

This review responds to a request from the Division of Neurology Products (DNP) to evaluate the results of the validation usability studies and the proposed labels and labeling for Plegridy and Plegridy Pen (Peginterferon beta-1a) Injection from a medication error perspective. The Applicant is proposing to market both prefilled syringe and pen (injection device) packaging presentations.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA previously evaluated the results of validation usability studies and proposed labels and labeling for Plegridy and Plegridy Pen in OSE Review 2013-1291, 2013-1294 and 2013-1295 dated October 17, 2013. In the previous review, DMEPA concluded that the Applicant had not demonstrated usability of Plegridy and Plegridy Pen. DMEPA made recommendations to improve the Plegridy and Plegridy Pen IFUs and labels and labeling to minimize confusion and clarify instructions that were associated with failures and performance difficulty during the usability studies. The Applicant was requested to perform another small scale, simulated use,

validation study with the syringe and Pen configurations after addressing all device engineering issues, IFU, label, and labeling recommendations.

In this review, DMEPA evaluated the new Plegridy and Plegridy Pen validation usability study reports to determine if the changes to the IFU, labels and labeling, demonstrate that the changes are effective at reducing the use errors from the previous validation usability studies and do not introduce any new hazards. In addition, we compared the revised labels and labeling against our recommendations in OSE Review 2013-1291, 2013-1294 and 2013-1295 dated October 17, 2013, to assess whether the revised labels and labeling address our concerns from a medication error perspective. The Applicant submitted labels and labeling for training devices and packaging configurations that will be provided to patients at no charge, which were not previously reviewed.

Based on the results of the usability study, we determined the changes to the IFU, labels and labeling helped decrease the use errors reported in the previous validation usability studies. However, we identified areas of reported confusion regarding the needle guard and difficulty during the checking pen and injection tasks. We discussed these issues with the Patient Labeling reviewer and provide recommendations to improve the IFU with language that may be easier for patients to understand. In addition, we provide recommendations to increase the readability and prominence of important information on the labels and labeling to promote the safe use of the product and mitigate any potential confusion. Since these changes are to clarify current information and we do not anticipate these changes would increase the risk for medication errors, another validation study is not needed at this time.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the labels and labeling to promote the safe use of the product and mitigate any potential confusion.

The Applicant has demonstrated usability of the Plegridy and Plegridy Pen based on the validation studies. Changes to the IFU for the Pen, as recommended in Section 4.2, may help address areas of reported confusion regarding the needle guard and difficulty during the checking pen and injection tasks.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the Review Division prior to the approval of this BLA:

A. Prescribing Information

1. In the Highlights of Prescribing Information, Dosage and Administration Section, we recommend relocating the statement "Plegridy dose should be titrated..."

to above the statement “Recommended dose: 125 micrograms...” since dose titration occurs prior to establishment of maintenance dose.

2. Under Section 2.1, relocate the “*Treatment initiation*” section above the statement “The recommended dosage of Plegridy is 125 mcg injected subcutaneously...” since dose titration occurs prior to establishment of a maintenance dose.
3. Under Section 2.2, *Important Administration Instructions*, we recommend adding “back of the” upper arm for consistency with the IFU.

4.2 RECOMMENDATIONS FOR THE APPLICANT

A. General Comments for Label and Labeling

1. We note that the strength of 63 mcg and 94 mcg for the syringe and pen Starter Pack carton labeling (commercial and no charge) appear in (b) (4) text making this hard to read. Previously submitted versions for these labeling had black text, which was easier to read. To improve readability, we recommend changing this text to black. (b) (4)
2. The Plegridy syringe carton labeling for the Starter Pack (commercial and no charge) do not contain a statement of usual dosage. 21 CFR 201.55 requires that labels for prescription drugs bear a statement of the recommended or usual dosage. Compliance with this requirement would be met by a statement such as, “Usual Dosage: See package insert.”
3. For consistency with the Prescribing Information, change “(b) (4)” to “single-dose” on the device labels, tray lid labeling, and carton labeling.

B. Instructions for Use (IFU) Plegridy Pen

1. Several participants in the Plegridy Pen validation study were confused (b) (4)

(b) (4)

consider revising to the term to “needle cover” in the figures and text. Revise the cautionary statement, to verbiage such as “Do not touch or push down on the needle cover, you could get a needle stick,” which may be more easily understood by patients.

2. Results reported in the Plegridy Pen validation study identified several participants who failed or had difficulty locating the injection status window. Consider revising Figure (b) (4) of Step 2 ‘ (b) (4) of the 125 mcg pen IFU and Figure (b) (4) Step 2 of the starter pack pen IFU to increase visibility and clarify position of the injection status window on the pen. Revise the figures to show the pen in its entirety with the injection status window clearly marked. (b) (4)

3. Several participants in the Plegridy Pen validation study did not press down with sufficient force to start the injection. We recommend revising Section 6 of the IFU by moving the adjective ‘firmly’ into the first sentence.

C. Training Kit Labels and Labeling

1. In the Plegridy Pen Training IFU, we recommend revising Figure (b) (4) of Step 2 ‘Check (b) (4) Training Pen’ to increase visibility and clarify position of the injection status window on the pen. See comment B.2. above.
2. Avoid use of the term (b) (4) in the Plegridy syringe Training IFU. We recommend using the wording “no active medication” or “does not contain active medication” as it may be easier for patients to understand.

3. The carton labeling for the training pen includes a statement (b) (4)

4. For the Plegridy syringe training kit carton labeling, we recommend revising (b) (4)

In addition, for the Plegridy syringe training IFU, we recommend revising [REDACTED] (b) (4) to “Training Unit for Plegridy Prefilled Syringe”.

5. For the Plegridy Pen training kit carton labeling we recommend revising

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

If you have further questions or need clarification, please contact Ermias Zericlassie, OSE Project Manager, at 301-796-0097.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Plegridy and Plegridy Pen that Biogen Idec submitted on January 23, 2014.

Relevant Product Information for Plegridy Pen and Prefilled Syringe																				
Active Ingredient	Peginterferon beta 1-a																			
Indication	Treatment of patients with relapsing forms of multiple sclerosis																			
Route of Administration	Subcutaneous																			
Dosage Form	Injection																			
Strength	(pen and syringe): 63 mcg/0.5 mL, 94 mcg/0.5 mL, and 125 mcg/0.5 mL																			
Dose and Frequency	<p>Peginterferon beta-1a is dosed every 14 days. It is generally recommended that patients titrate the dose as follows:</p> <table border="1"> <thead> <tr> <th>Dose</th> <th>Time*</th> <th>Amount (micrograms)</th> <th>Color of Pen or Syringe label</th> </tr> </thead> <tbody> <tr> <td>Dose 1</td> <td>On day 1</td> <td>63</td> <td>Orange</td> </tr> <tr> <td>Dose 2</td> <td>On day 15</td> <td>94</td> <td>Blue</td> </tr> <tr> <td>Dose 3</td> <td>On day 29 and every 14 days thereafter</td> <td>125 (full dose)</td> <td>Grey</td> </tr> </tbody> </table>				Dose	Time*	Amount (micrograms)	Color of Pen or Syringe label	Dose 1	On day 1	63	Orange	Dose 2	On day 15	94	Blue	Dose 3	On day 29 and every 14 days thereafter	125 (full dose)	Grey
Dose	Time*	Amount (micrograms)	Color of Pen or Syringe label																	
Dose 1	On day 1	63	Orange																	
Dose 2	On day 15	94	Blue																	
Dose 3	On day 29 and every 14 days thereafter	125 (full dose)	Grey																	
How Supplied	<p>PLEGRIDY PEN Single-Dose Prefilled Pen</p> <ul style="list-style-type: none"> •  (b) (4) • A carton containing two single-dose prefilled pens, each providing 125 micrograms of PLEGRIDY. • A Starter Pack carton containing two single-dose prefilled pens: dose 1 provides 63 micrograms of PLEGRIDY and dose 2 provides 94 micrograms of PLEGRIDY. 																			

	<p>PLEGRIDY Single-Dose Prefilled Syringe</p> <ul style="list-style-type: none"> • [REDACTED] (b) (4) • A carton containing two single-dose prefilled syringes, each providing 125 micrograms of PLEGRIDY. • A Starter Pack carton containing two single-dose prefilled syringes: dose 1 provides 63 micrograms of PLEGRIDY and dose 2 provides 94 micrograms of PLEGRIDY.
<p>Storage</p>	<p>Store in the closed original carton to protect from light until ready for injection.</p> <p>Store in a refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze. Once removed from the refrigerator, PLEGRIDY should be allowed to warm to room temperature (about 30 minutes) prior to injection. If refrigeration is unavailable, PLEGRIDY may be stored between 2°C to 25°C (36°F to 77°F) for a period up to 30 days, protected from light. PLEGRIDY can be removed from, and returned to, a refrigerator if necessary. The total combined time out of refrigeration, within a temperature range of 2°C to 25°C (36°F to 77°F), should not exceed 30 days.</p>
<p>Container Closure</p>	<ul style="list-style-type: none"> ○ Single-Use Prefilled Pen: Each unit of Plegridy is stored in a 1 mL glass syringe with a [REDACTED] (b) (4) rubber stopper and rigid needle shield. A 29 gauge, 0.5 inch, staked needle is pre-affixed to the syringe. The glass syringe is contained within a single-use, disposable, injection device (pre-filled pen). ○ Single-Use Prefilled Syringe: Each unit of Plegridy is stored in a 1 mL glass syringe with a [REDACTED] (b) (4) rubber stopper and rigid needle shield. A 29 gauge, 0.5 inch, staked needle is pre-fixed to the syringe.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive and AIMS on December 31, 2013 using the terms, 'Plegridy' to identify reviews previously performed by DMEPA.

C.2 Results

Proprietary name reviews were conducted in OSE Review # 2012-2154 and 2012-2155 for IND 100110 on March 8, 2013 and it was concluded that the proposed proprietary names Plegridy and Plegridy Pen were conditionally acceptable from both a promotional and safety perspective. The names Plegridy and Plegridy Pen were reviewed for BLA 125499, OSE # 2013-3277 and 3278 due to changes in product characteristics and DMEPA concluded that the names were acceptable.

A previous label, labeling and usability study review was conducted in OSE 2013-1291, 1294, and 1295 for BLA 125499 on October 17, 2013. Failures in critical tasks included (b) (4) for both Plegridy and Plegridy Pen. In both the validation usability study and the supplemental IFU study for the Plegridy Pen, participants reported being (b) (4) (b) (4) Participants also experienced (b) (4)

Based on this review, DMEPA made recommendations for changes to the Instructions for Use for both Plegridy and Plegridy Pen and recommendations to revise other labels and labeling. In addition, it was concluded that the Applicant had not demonstrated usability of Plegridy and Plegridy Pen. DMEPA recommended the Applicant conduct a new risk analysis and consider failures and performance difficulty observed, along with the subjective feedback collected, to make changes to the IFU. DMEPA also recommended the Applicant to validate the changes to the IFU prior to approval.

APPENDIX D. HUMAN FACTORS STUDY

D.1.a. Plegridy Prefilled Syringe (PFS)

The Applicant submitted results of the human factors validation study for the PFS on February 4, 2014.

Study Design

The study was a small scale, simulated use, validation study focusing on the final user interface including the commercial device, IFU, container, and carton labeling. The study was conducted using an in-depth interview (IDI) format for all participants (MS patients, lay caregivers) and was conducted as a cognitive walk through of the IFU where for each step, participants were asked to read the instruction aloud, perform the step, and provide feedback on the clarity of the instruction.

Following each step, the moderator asked questions to investigate the root cause(s) of any steps that were assessed as “Failed,” or reported difficulty understanding or performing the step.

Additionally, a confirmation step was added to the study design to ensure the participants read the IFU prior to initiating any simulated experiences with either the PFS or PFP. This is the only change from the previous Human Factors studies with respect to non –IFU related validation changes.

Study Population

- 17 patients and caregiver participants average 49 years (range: 27 to 63)
- Ten patients with confirmed diagnosis of MS and seven non-professional caregivers.
- Each study included at least 15 untrained participants representing the worst-case user experience.

D.1.b. Results (PFS)

IFU Step #	Task and Task Assessment Critical=C Essential=E Desirable= D	# of Participants Committing Task Failures	# of Participants Having Close Calls/ Operational Difficulty	Comments
(b) (4)	Place Supplies and wash hands (D)	0	0	
	Check Pack and Prefilled Syringe (D)	0	0	
	Choose the Injection Site (E)	1 (6%)	0	Participant intentionally chose an incorrect injection site based on prior injection experience.
	Firmly Remove Needle Cover (C)	0	1 (18%)	One participant removed the needle cap early and tried to recap the needle.
	Prepare Injection Site (D)	2 (12%)	0	One participant struggled to figure out how to pinch. She noted that the instructions said to pinch but not to hold the pinch. One participant let go of the pinch before inserting the needle.
	Inject Medication (C)	1 (6%)	0	Participant injected almost parallel to the injection pad rather than 90°. During her second trial, she injected at a 90° angle.
	Remove PFS from site (E)	2 (12%)	0	Two participants recapped the needle after completing this step. One stuck herself with the needle. She did this because of prior experience with another injection device. The other participant stated that she recaps the needle on her current system.
	Disposal (D)	1 (6%)	0	Participant put used needle back in the tray, put the tray back in the box, and threw the box into the garbage. She did not read to (b) (4) before disposing of the syringe.
N/A	Choose Dose (C)	0	0	

D.2. a. Plegridy Prefilled Pen (PFP)

The Applicant submitted results of the human factors validation study for the PFP on February 4, 2014.

Study Design

The study assessed end user interaction with the Plegridy Pen and the IFU. It was conducted as an in-depth interview, which consisted of a cognitive walk through of the IFU, and performance of the dose selection task using the Starter Kit IFU only. The IFU for the administration dose pack was used to assess the PFP use process. Following each step, the moderator asked questions to investigate the root cause(s) of any steps that were assessed as “Failed,” or reported difficulty understanding or performing the step. Participants were required to complete 9 tasks, 3 of which were deemed critical, Dose Selection, Remove Cap, and Inject Medication.

Study Population

- 18 Non-professional participants comprised of 10 patients with a confirmed diagnosis of MS and 8 caregivers average age of 45 years (range: 27 to 63)
- Each study included at least 15 untrained participants representing the worst-case user experience.

D.2. b. Results (PFP)

IFU Step #	Task and Task Assessment Critical=C Essential=E Desirable= D	# of Participants Committing Task Failures	# of Participants Having Close Calls/ Operational Difficulty	Comments
-	Preamble/Pre- Injection Information	0	5 (28%)	(b) (4)

				5 participants (28%) were confused by the wording or meaning of the warning
1	Place supplies and wash hands (D)	0	0	
2	Check Prefilled Pen (E)	4 (22%)	7 (39%)	4 participants failed to find the injection status window without moderator assistance. Other participants felt Figures (b) (4) did not clearly indicate window placement, thought it was located on a different position on the pen, or that holding the pen would obscure the window.
3	Choose injection site (E)	2 (11%)	0	One participant chose to inject on lateral hip area based on prior use of her current injector. One participant failed to use an alcohol wipe stating that he rarely uses alcohol wipes.
4	Remove cap (C)	0	0	
5	Position pen and check (D)	0	0	
6	Inject medication (C)	4 (22%)	0	3 participants pressed down to inject but not with sufficient force to start injection. 1 participant started to press down to inject but then re-positioned pen. During subsequent attempts, 3 participants succeeded on the second attempt and one succeeded on fifth attempt.
7	Remove pen from site (E)	0	0	
8	Verify dose delivery (E)	0	0	
9	Disposal (D)	1 (6%)	0	Participant believed the device was similar to her current device and that she must remove the needle.
-	Dose Selection (C)	0	0	

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Plegridy and Plegridy Pen commercial, no charge, and training kit labels and labeling submitted by Biogen Idec:

- Commercial Device Labels (Pen and Syringe) received January 23, 2014 (Appendix G 2.1)
- Commercial Tray Lid Labeling (Syringe) received January 23, 2014 (Appendix G 2.2)
- Commercial Carton Labeling (Pen and Syringe) received January 23, 2014 (Appendix G 2.3)
- No Charge Carton Labeling (Pen and Syringe) received January 27, 2014 (Appendix G 2.4)
- No Charge Device Labels (Pen and Syringe) received January 27, 2014 (Appendix G 2.5)
- No Charge Tray Lid Labeling (Syringe) received January 27, 2014 (Appendix G 2.6)
- Training Kit Carton Labeling (Pen and Syringe) received January 10, 2014 (Appendix G 2.7)
- Training Kit Tray Lid Labeling (Syringe) received January 10, 2014 (Appendix G 2.8)
- Training Kit Device Labels (Pen and Syringe) received January 10, 2014 (Appendix G 2.9)
- Instructions for Use (IFU) Training Kit (Pen, Syringe) received January 10, 2014 (no image)
- Instructions for Use (IFU) (Pen, Syringe) received January 17, 2014 (no image)
- Full Prescribing Information (PI) and Medication Guide (MG) received April 2, 2014 (no image)

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

JUSTINE HARRIS
04/16/2014

JULIE V NESHIEWAT
04/16/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

*** This document contains proprietary information that cannot be released to the public***

DATE: April 9, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Nicole Bradley, Regulator Project Manager, CDER/OND/ODEI/DNP

SUBJECT: **BLA 125499**
Applicant: Biogen Idec, Inc.
Drug: PEGylated interferon beta-1a
Device: Autoinjector and Prefilled Syringe
Intended Use: Treat Multiple Sclerosis
CTS Tracking: ICC1300286/ICC1400126

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Overview and Recommendation

The Division of Neurology Products, Office of New Drugs, Center for Drug Evaluation and Research, requested a Human Factors consultative review of two human factors validation study for Biogen Idec prefilled syringe and prefilled peninjector under BLA125499. These delivery devices are used to administer PEGylated interferon beta-1a to treat Multiple Sclerosis (MS).

Biogen Idec submitted two human factors validation study reports: one for the prefilled syringe, and one for the peninjector. In addition, Biogen Idec supplied supplemental study where they conducted a cognitive walkthrough of the revised IFU (modifications made after the validation study) via an information request response.

Review of the two study reports identified two major CDRH HF deficiencies that were transmitted via the Midcycle Review Letter 10/10/2013. These deficiencies can be found in Appendix 2 of this review memo. The Sponsor provided an interim response to these deficiencies on 11/27/2013, and requested a teleconference on 12/9/2013 to discuss the proposed response. The Sponsor plans to make IFU changes to address use-related problems seen in both the PFS and PEN HF study reports, and intends to revalidate those changes in additional human factors studies. However, the proposed changes and the study protocols have not been submitted for review. At this time, the original deficiencies remain outstanding. This consultant provided comments that have been consolidated with DMEPA to be included in the late cycle meeting background briefing package on 2/10/2014.

Prior to the late cycle meeting, Biogen Idec submitted two additional validation studies, one for the prefilled syringe, and one for the autoinjector. These studies included smaller number of representative users (18 and 17 patients and caregivers combined for the pen and prefilled configuration respectively) with the intent to demonstrate that the changes made to the Instructions for Use improve use performance. The performance was assessed based on whether the IFU was understood by representative users and whether it guided them to perform the user tasks correctly. The results of these studies demonstrated that the changes made to the IFU showed improvement of use performance in comparison to the original studies.

This consultant found the results of the two additional validation studies acceptable, and does not have any outstanding concerns on the human factors review component of the submission.

Consult Request

Request Dated May 17, 2013

Consult Review Completed October 8, 2013

Application Information

EDR link: \\cbsap58\m\ectd_submissions\stn125499\0000

Global Submit link: \\cbsap58\m\ectd_submissions\stn125499\125499.enx

BLA 125499

BIIB017 (PEGylated interferon beta-1a)

Proposed Proprietary Name: PLEGRIDY and PLEGRIDY PEN

Sponsor: Biogen Idec, Inc.

Product developed under IND 100110

Priority designation requested in cover letter: Final decision to be made at filing meeting

Key PDUFA Goal Dates

Submission Receipt date: May 16, 2013

Filing Meeting: July 2, 2013

Day 60 letter: July 15, 2013

Day 74: July 29, 2013

Primary reviews due: January 22, 2014

Action Goal date: May 16, 2014

Additional Regulatory History

Developed under the following IND: 100110

Pre-BLA meeting held

Primary Clinical Reviewer: John Marler, MD

Primary CMC Reviewer: Ralph Bernstein

Appendix 1: Summary of Human Factors Validation Study Reports (review performed on 4/9/2014)

Biogen Idec submitted two additional focused validation studies, one for the prefilled syringe, and one for the autoinjector (sequence 053 dated 2/7/2014). These studies included smaller number of representative users (18 and 17 patients and caregivers combined for the pen and prefilled configuration respectively) with the intent to demonstrate that the changes made to the Instructions for Use improve use performance. The studies were conducted via in-depth interview where the participants walked through the IFU, perform the step, and provide feedback on the clarity of the instruction. Instances of failures/use errors were followed up with test participants to identify possible root cause. Both the PEN and prefilled syringe study results showed use improvement across the majority of the user tasks with one exception. The PEN study results showed similar failures seen with the original validation study with the step of inspecting the injection status, which can impact the user's ability to recognize that the injection is complete. The possible causes associated with these failures include participants holding the pen by the base and therefore obscuring the injection status window with their fingers, or they did not realize that the window was on the other side. Review of the latest version of the IFU for the PEN configurations showed that specific instructions are provided to users as follows:



The consultant believes that the IFU as shown are acceptable and that additional changes may not be needed to further improve use performance.

Appendix 2: Summary of Human Factors Validation Study Reports (review performed on 1/21/2014)

Prefilled Syringe Validation Study Report (P1539-R-004 v1.0)

The human factors validation study included 45 participants: 15 patients diagnosed with MS, 15 caregivers who administer medications to patients with MS, and 15 healthcare providers who administer training or medication to patients with MS. The study was designed to evaluate use performance on all steps in the use sequence of the prefilled syringe, which included a total of 14 steps. Table 7 of the report outlined these steps, and the corresponding IFU steps, and the criterion type for each step i.e. critical, essential, and desirable. It was noted that a comprehensive risk analysis was not provided for review, and the consultant is unclear on the rationale on how the criterion type was determined for each step. In addition, of the 14 steps, several steps did not have a corresponding IFU steps, and therefore, the consultant is unclear i.e. whether the IFU do not include those steps, and if so, why they were being studied.

The following section provides a brief summary of study results focusing on the failures that were seen in the study that are of concern to the consultant. These results were reported using Biogen Idec's criterion type:

Critical step

- 2 participants (4%) experienced difficulty with the 'Critical' step of quickly inserting the needle: One participant inserted, removed, and then reinserted the needle. One participant did not insert the needle all the way, and when she pulled the needle back, a drop of medication was seen. The study report is not clear on the clinical significance of needle being inserted twice, or whether inserting the needle less than specified depth would have resulted in any clinical significance.

Essential steps

- 1 participants (2%) experienced failures choosing the correct PFS: The participant handed the moderator the administration dose instead of the starter dose. This would have resulted in an overdose delivery. The participant was reported to have realized the error when opening the starter pack. This consultant discussed this finding with the medical officer on the team. Overdosing of this drug product may increase flu-like symptoms that patient may experience but they do not represent safety concerns.
- 6 participants (13%) experienced difficulty choosing the correct PFS: One participant indicated that while the packaging contains the words [REDACTED] (b) (4) dose but neither specifically states "first dose." Another participant expressed confusion that administration pack was the first dose, and then the start dose could be used. Three participants indicated that they would require assistance in making the selection (call physician or customer support, or seek help from patient). These results indicated that the user need clear information on which pack is the first dose pack, the second dose pack, and the third dose pack. In addition, one participant self-corrected. However, the report was unclear on whether the device labeling or the device itself made the participant realized the error and self-corrected.

Desirable steps

A total of 43 participants (96%) experienced failures across 8 different essential steps:

- 19 participants (42%) experienced failures checking the expiration: subjective feedback from these participants indicated that they either do not typically check expiration date or they believe that this task belongs to the pharmacist or in the case of caregivers, they believe that the patient should check the expiration date. The report is not clear on whether administering an expired product has any clinical significance, or can result in patient harm.
- 25 participants (56%) experienced failures allowing the PFS to warm: subjective feedback from these participants indicated that they did not acknowledge the need to wait for 30 minutes. They indicated that in actual use, they do not typically let the medication warm up to room temperature up to 30 minutes. Some indicated that they are okay with injecting the medication cold. While this task was categorized as desirable, i.e. should be performed in accordance to good clinical practice, the report is not clear on whether administering the drug product that has not been warmed up to room temperature has any clinical significance, or can result in patient harm.
- 7 participants (16%) experienced failures checking the medication: subjective feedback from these participants indicated that they do not normally check the medication. Some indicated that they did not because of the study setting. One participant indicated that she notices the color when mixing, and one indicated he did not know how to check the medication. The report is not clear on whether administering the drug product that do not appear to have the correct color has any clinical significance, or can result in patient harm.
- 11 participants (24%) experienced failures holding the PFS at 90 degrees: subjective feedback from these participants indicated that some injected at less than 90 degrees because of leverage, difficulty for injecting at 90 degrees to the arm, or because of the injection pad set up. The report is not clear on whether these participants were able to administer the prescribed doses despite failures to inject at the specified angle.
- 17 participants (38%) experienced failures waiting [REDACTED]^{(b)(4)}: subjective feedback from these participants indicated that some participants did not read the instructions, not aware of or not used to wait for [REDACTED]^{(b)(4)}, and expect the drug representative to instruct to wait for [REDACTED]^{(b)(4)}. The report is not clear on whether these premature removals of the prefilled syringe resulted in any wet injection which would have result in potential underdose.

Prefilled Peninjector Validation Study Report (P1539-R-003 v2.0)

The human factors validation study included 45 participants: 15 patients diagnosed with MS, 15 caregivers who administers medications to patients with MS, and 15 healthcare providers who administer training or medication to patients with MS. The study was designed to evaluate use performance on all steps in the use sequence of the prefilled syringe, which included a total of 15 steps. Table 7 of the report outlined these steps, and the corresponding IFU steps, and the criterion type for each steps i.e. critical, essential, and desirable. Similar to the prefilled syringe report, it was noted that a comprehensive risk analysis was not provided for review, and the consultant is unclear on the rationale on how the criterion type was determined for each step. In addition, of the 15 steps, several steps did not have a corresponding IFU steps, and therefore, the consultant is unclear i.e. whether the IFU do not include those steps, and if so, why they were being studied.

The following section provides a brief summary of study results focusing on the failures that were seen in the study that are of concern to the consultant. These results were reported using Biogen Idec's criterion type:

Critical step

- 5 participants (11%) inclusive of 2 patients, 2 caregivers and 1 nurse, experienced failures on the critical step of pressing the PEN into the site and hold until the clicking stops and the green checkmark appears. Subjective feedback from these participants indicated that two participants lifted the PEN prematurely after hearing the clicking sound. One participant indicated that they did not hear the clicking sound. One participant noticed the medication dripping from the PEN. One participant indicated that they saw the green checkmark.

Essential steps

- 3 participants (7%) experienced failures choosing the correct PEN: subjective feedback from these participants indicated that two participants did not read the IFU but stated that they would be able to select the correct PEN afterwards during IFU assessment. However, we do not have the data to demonstrate that these participants would be able to select the correct PEN in actual use. (b) (4)
- Biogen Idec indicated that these errors would have resulted in overdosing. This consultant discussed this finding with the medical officer on the team. Overdosing of this drug product may increase flu-like symptoms that patient may experience but they do not represent safety concerns. These results indicated that the user need clear information on which pack is the first dose pack, the second dose pack, and the third dose pack.
- 1 participants (2%) experienced failures and 3 participants (7%) experienced difficulty in checking the injection status by looking for the green strips: subjective feedback from these participants indicated that participants had difficulty in finding the green strips, and it was not obvious from the IFU. One participant indicated that they did not read the instructions.
- 5 participants (11%) experienced failures checking for completion: subjective feedback indicated that three study participants lifted the PEN prematurely, and did not check the PEN. One participant did not look for the checkmark, and one participant indicated that they heard the clicking sound and believed that the medication was delivered. Biogen Idec believes that relying on the clicking and checkmark are acceptable alternatives to checking for injection completion.
- 7 participants (16%) experienced difficulty removing the cap: subjective feedback indicated that four participants experienced difficulty due to force required, and two due to getting a grip on the device.

Desirable steps

- 16 participants (36%) experienced failures checking the expiration: subjective feedback indicated most participants assumed that the medication received from pharmacy is not expired.
- 18 participants (40%) experienced failures allowing the PEN to warm: subjective feedback from these participants indicated that they did not think they need to warm the product to room temperature because of the study setup. Some did not wait because they did not read that part of the IFU, and one indicated that the instruction did not stand out.
- 7 participants (16%) experienced failures checking the medication for color and clarity: subjective feedback indicated that one participant suggested that the checking window should be wider. Several participants either did not pay attention to that step or did not think that was necessary or did not read the IFU.
- 16 participants (36%) experienced failures verifying dose delivery: subjective feedback from these participants indicated that they did not read the IFU. Several others indicated

that they heard the clicking sound, and saw the checkmark so that did not check for the yellow plunger rod.

The consultant is unclear on the clinical significance associated with the failures in essential and desirable steps.

Prefilled Peninjector Supplemental IFU Validation Study Report (P1539-R-005 v0.9)

This supplemental study included 16 participants (11 MS patients, and 5 caregivers). The study was designed to validate the revised IFU by having participants read the instructions aloud, perform the step, and provide feedback. The following sections provide a summary of the study results, particularly the use errors and reported difficulties:

- 3 participants associated their difficulty in choosing the correct PEN with the clarity of the IFU. 2 of these participants had difficulty in identifying the PEN for use after Day 28.
- 14 participants experienced difficulty in understanding the word (b) (4) in the IFU
- 7 participants experienced difficulty in checking the injection status and suggested that the green stripes should be in a more prominent location, and two indicated that they experienced difficulty finding the green strips.
- 2 participants tried to pull the needle guards from the PEN after they had removed the cap. These use errors were unexpected.
- 2 participants experienced use error and difficulty with pressing and holding the PEN to the injection sites.

Review Comments

Both the PFS and PEN human factors validation studies included 45 participants. The study was designed to evaluate use performance on all steps in the use sequence of the prefilled syringe. Table 7 of the reports outlined these steps, and the corresponding IFU steps, and the criterion type for each steps i.e. critical, essential, and desirable. It was noted that a comprehensive risk analysis was not provided for review, and the consultant is unclear on the rationale on how the criterion type was determined for each step. In addition, of the steps identified, several steps did not have a corresponding IFU steps, and therefore, the consultant is unclear i.e. whether the IFU do not include those steps, and if so, why they were being studied.

Review of the validation study results for the prefilled syringe and PEN identified similar patterns of use errors. The consultant was unclear if the use errors were seen across all user groups or they were unique to a particular user group.

- The most concerning use errors seen with the PFS were users not selecting the correct PFS, not injecting the needle at the specified depth, , not checking expiration date, not waiting for the drug to warm up to room temperature, not checking the medication color, not holding the device at a 90 degrees angle, and not waiting (b) (4). The consultant is concerned that some of these use errors can result in misdosing (overdosing, or underdosing) when the user selects the wrong PFS. The report does not include a comprehensive evaluation of use-related risks, and therefore, the consultant is unclear on whether patient harm can result from the remaining use errors. And in the case of premature removal of the prefilled syringe, the consultant is unclear whether the study participants did indeed administer a complete dose or whether they result in under dosing.

- The most concerning use errors seen with the PEN were users premature lifting of the PEN, not checking for completion, and not verifying dose delivery (i.e. users not pressing the PEN into the site and hold until the clicking stops and the green checkmark appears). Some users reported difficulty in finding the green strips. In addition, the report showed users errors where users not choosing the correct PEN, not checking the expiration, not allowing the PEN to warm, not checking the medication for color and clarity. The consultant is also concerned about the users reporting difficulty in removing the caps in particular because the intended user population has multiple sclerosis. And similarly, the report does not include a comprehensive evaluation of use-related risks, and therefore, the consultant is unclear on whether patient harm can result from the remaining use errors. And in the case of premature removal of the PEN, the consultant is unclear whether the study participants did indeed administer a complete dose or whether they result in under dosing.

Review of the supplemental IFU validation study for the PEN showed that the revised IFU continued to show use errors and difficulties that were previously reported. For example, users experienced difficulty choosing the correct PEN and associated their difficulty with the clarity of the IFU. Users expressed difficulty in understanding the word (b) (4) in the IFU. Users experienced difficulty in checking the injection status and suggested that the green stripes should be in a more prominent location, and two indicated that they experienced difficulty finding the green strips. Users experienced use error and difficulty with pressing and holding the PEN to the injection sites. In addition, users tried to pull the needle guards from the PEN after they had removed the cap, which were unexpected use errors.

Based on the result of the supplemental IFU validation study, this consultant believes that the use errors and difficulties seen in the validation study for the PEN have not been effectively minimized i.e. recurrence of the same use errors and reported difficulty. In addition, Biogen Idec did not provide a rationale for why they believe the IFU changes and the proposed supplemental study will be adequate in addressing use-related issues identified in the prior study. With regards to the PFS, the consult does not believe that the PFS is optimized for safe and effective use given the use errors and reported difficulties seen in the validation study.

Review of the two study reports identified two major CDRH HF deficiencies that were transmitted via the Midcycle Review Letter 10/10/2013. These deficiencies can be found in Appendix 2 of this review memo. The Sponsor provided an interim response to these deficiencies on 11/27/2013, and requested a teleconference on 12/9/2013 to discuss the proposed response. The Sponsor plans to make IFU changes to address use-related problems seen in both the PFS and PEN HF study reports, and intends to revalidate those changes in additional human factors studies. However, the proposed changes and the study protocols have not been submitted for review. At this time, the original deficiencies remain outstanding. This consultant provided the following comments that have been consolidated with DMEPA to be included in the late cycle meeting background briefing.

Human Factors (DMEPA/CDRH HF consolidated)

1. [Plegridy Prefilled Syringe: As indicated in the October 10, 2013 Mid-cycle Communication and the November 8, 2013 Information Request, you have not demonstrated safe and effective use of the prefilled syringe \(PFS\) with representative users. Prior to approval of the PFS, you need to address our concerns described in](#)

previous communications. You will be required to validate changes to the IFU that are designed to address task failures, use errors, and reported difficulties that have been determined critical to the safe use of your PFS and submit the results of this validation study for review. We ask that you provide a table that outlines all of the IFU changes, and links them with the task failures, use errors, and reported difficulties that were reported in the study. In addition, all label and labeling recommendations should be addressed prior to conducting your IFU validation study.

2. Plegridy Pen: As indicated in the October 10, 2013 Mid-cycle Communication and the November 8, 2013 Information Request, you have not demonstrated safe and effective use of the Pen with representative users. Prior to approval of the Pen, you need to address our concerns described in previous communications. Any proposed changes that are designed to address task failures, use errors, and reported difficulties that have been determined critical to the safe use of your Pen device should be validated in another usability study with the intended-to-market commercial presentation of the product and its associated labels and labeling. We note that that your supplemental validation study incorporating IFU changes that were made after the first study, continued to show similar task failures, use errors, and reported difficulties. This indicated that you have not effectively addressed the task failures, use errors, and reported difficulties with those IFU changes. Note that if you intend to make additional changes to only the IFU, please provide a rationale for why you believe that these IFU changes alone would adequately address these outstanding concerns, and that other aspects of the device user interface have been optimized. In addition, the engineering aspects of your Pen device and all label and labeling recommendations should be addressed prior to conducting any additional human factors evaluation/study.

Appendix 2: Deficiencies to be Transmitted to the Sponsor

Review of the validation study results for the prefilled syringe and PEN identified similar patterns of use errors. We request that you address the following:

1. Prefilled syringe

- a. You reported that the human factors validation was designed to evaluate use performance on all steps in the use sequence of the prefilled syringe, which included a total of 14 steps. Table 7 of the report outlined these steps, and the corresponding IFU steps, and the criterion type for each steps i.e. critical, essential, and desirable. However, it was noted that a comprehensive risk analysis was not provided for review, and we are unclear on the rationale on how the criterion type was determined for each step. In addition, of the 14 steps, several steps did not have a corresponding IFU steps, and therefore, we are unclear i.e. whether the IFU do not include those steps, and if so, why they were being studied. Please provide clarification.
- b. We have summarized the study results according to your three task criteria that are focused on the failures that were seen in the study that are of concern to us in that there are multiple participants failed to perform the tasks.

Critical step: 2 participants (4%) experienced difficulty with the ‘Critical’ step of quickly inserting the needle. The study report is not clear on the clinical significance of needle being inserted twice, or whether inserting the needle less than specified depth would have resulted in any clinical significance.

Essential steps:

- 1 participants (2%) experienced failures choosing the correct PFS. You reported that this would have resulted in an overdose delivery. Please clarify if overdosing can result in patient harm or clinical significance.
- 6 participants (13%) experienced difficulty choosing the correct PFS: We are concerned that these results indicated that the user do not appear to have clear information on which pack is the first dose pack, and the subsequent dose packs, and this failure can result in misdosing. We believe that the device user interface could be further optimized to communicate clear information on how users safely differentiate the first dose pack and subsequent dose packs.

Desirable steps: A total of 43 participants (96%) experienced failures across 8 different essential steps:

- 19 participants (42%) experienced failures checking the product expiration.
- 25 participants (56%) experienced failures allowing the PFS to warm.
- 7 participants (16%) experienced failures checking the medication.
- 11 participants (24%) experienced failures holding the PFS at 90 degrees.
- 17 participants (38%) experienced failures waiting (b) (4)

We believe that the number of failures seen in this study indicated that the product user interface has not been adequately optimized or that it does not adequately call out the importance for performing those steps. If failure on performing any of these steps (critical, essential, and desirable) can result in patient harm, we ask that you discuss whether modifications are required, and whether additional validation study is necessary.

- c. Also, please clarify if the failures were seen across all user groups or they were unique to a particular user group.

2. Prefilled Pen

- a. The human factors validation study for the peninjector was designed to evaluate use performance on all steps in the use sequence of the prefilled syringe, which included a total of 15 steps. Table 7 of the report outlined these steps, and the corresponding IFU steps, and the criterion type for each step i.e. critical, essential, and desirable. Similar to the prefilled syringe report, it was noted that a comprehensive risk analysis was not provided for review, and we are unclear on the rationale on how the criterion type was determined for each step. In addition, of the 15 steps, several steps did not have a corresponding IFU steps, and therefore, we are unclear i.e. whether the IFU do not include those steps, and if so, why they were being studied. Please clarify.
- b. Subsequently, you performed a supplemental study. Review of the supplemental IFU validation study for the PEN showed that the revised IFU continued to show use errors and difficulties that were previously reported.
- c. You did not provide a rationale for why you believe only the IFU changes would address the failures and use errors seen in the previous study. Please provide this clarification.
- d. Based on the result of the supplemental IFU validation study, we believe that the use errors and difficulties seen in the first validation study for the PEN have not been effectively minimized i.e. recurrence of the same use errors and reported difficulties. In addition, the risk to health resulting from the use difficulties and errors are not clearly described such that we can conclude that the benefits of use outweigh the risks. If the errors represent instances where the patient could be harmed, then we believe that the data demonstrate that there are serious design problems with your device. Please provide a risk assessment of the errors and implications for actual users concluding that the use errors identified in the studies will not result in patient harm. If your assessment is unable to make this conclusion based on the facts available, then you should implement additional mitigations to the device and provide additional studies to demonstrate the effectiveness of the mitigations.

Appendix 3: Device Information

Prefilled Syringe

The BIIB017 prefilled syringe (PFS) is a single use, disposable injection device. This device is designed to deliver an injection of 0.5 mL of BIIB017 to a multiple sclerosis (MS) patient. The BIIB017 PFS is intended to be used for (b) (4) bi-weekly (b) (4) injections.

As part of the dosing ramp-up for newly prescribed patients, the manufacturer will provide a starter pack for the PFS. The BIIB017 starter pack is a self-contained package, which consists of:

- One 63 mcg dose BIIB017 prefilled syringe contained within primary packaging
- One 94 mcg dose BIIB017 prefilled syringe contained within primary packaging
- One set of Instructions for Use (IFU)
- Prefilled syringe and packaging labeling



Peninjector

The BIIB017 PEN is a single use, disposable, (b) (4) injection device. This device is designed to deliver an injection of 0.5 mL of BIIB017 from a staked needle prefilled syringe to a multiple sclerosis (MS) patient. The BIIB017 PEN is intended to be used for (b) (4) bi-monthly (b) (4) injections.

As part of the dosing ramp-up for newly prescribed patients, the manufacturer will provide a starter pack for the PEN. The BIIB017 starter pack is a self-contained package, which consists of:

- One 63 mcg dose BIIB017 PEN contained within primary packaging
- One 94 mcg dose BIIB017 PEN contained within primary packaging
- One set of Instructions for Use (IFU)
- PEN and packaging labeling



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

/s/

NICOLE L BRADLEY

04/15/2014

Checking into DARRTS for Quynh Nhu Nguyen

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 5, 2014

To: Eric Bastings, M.D.
Acting Director
Division of Neurology Products (DNP)

Nicole Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products (DNP)

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 125499
OPDP Package Insert (PI) and Carton and Container labeling comments for PLEGRIDY™ (peginterferon beta-1a) injection, for subcutaneous injection.

On July 23, 2013, DNP consulted OPDP to review the proposed package insert (PI), Medication Guide, and carton and container labeling for the original BLA submission for PLEGRIDY™ (peginterferon beta-1a) injection, for subcutaneous injection.

Product Label (PI)

Comments on the proposed PI are based on the version received via email from DNP (Nicole Bradley) on February 19, 2014, entitled, "B_125499_FDA_workingversion_PI_2014_0219_SCPI_Clean.docx."

Please note that OPDP's comments on the proposed PI are provided directly on the marked version below.

Carton and Container Labeling

OPDP has reviewed the proposed version of the carton and container labeling accessed at the links below and does not have comments at this time.

\\Cdsesub1\bla\CTD Submissions\STN125499\0047\m1\us

\\Cdsesub1\bla\CTD Submissions\STN125499\0056\m1\us

\\Cdsesub1\bla\CTD Submissions\STN125499\0036\m1\us

\\Cdsesub1\bla\CTD Submissions\STN125499\0041\m1\us

\\Cdsesub1\bla\CTD Submissions\STN125499\0049\m1\us

Medication Guide

A combined OPDP and DMPP patient labeling review was conducted, and comments on the Medication Guide were sent under separate cover by DMPP on February 28, 2014.

If you have any questions, please contact Aline Moukhtara at 301-796-2841 or Aline.Moukhtara@fda.hhs.gov.

Thank you for the opportunity to comment.

Enclosure: Proposed Carton and Container Labeling and Marked up PI with OPDP Comments.

59 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ALINE M MOUKHTARA
03/05/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: February 21, 2014
From: Ryan McGowan
Biomedical Engineer, General Hospital Devices Branch
CDRH/ODE/DAGRID/GHDB
To: Nicole Bradley
CDER/OND/ODEI/DNP
Subject: Supplementary Memo: BLA125499, Inter-center Consult ICC1300191

I. Purpose

CDER has requested review of device design-relevant aspects of an auto-injector product intended to support BLA 125499 Plegridy (peginterferon beta-1a) for Multiple Sclerosis. This memorandum serves to provide a final review of outstanding non-human factors device design-related content and follows from the high-level overview of all non-human factors device-relevant review content for BLA 125499 provided to CDER/OND/ODEI/DNP on January 21, 2014.

II. Updates to January 21, 2014 Memorandum

A single outstanding issue was identified within the non-human factors device-relevant review memo content for BLA 125499 provided to CDER/OND/ODEI/DNP on January 21, 2014. This issue was described to the firm within the late cycle review letter sent on January 28th 2014. The original question is provided below:

1. Within your January 15th information response to the Agency, contained within Serial No.: 0045, you have provided information to support ISO 11608-1:2012 testing, specifically free fall testing completed by independent testing laboratory and Notified Body, (b) (4) concluded within Report 89203092.03 that the batch tested did not pass criteria of ISO 11608-1:2012. The Agency has reviewed your firm's position that the failure which caused (b) (4) to conclude the batch did not pass testing requirements constitutes an obvious failure and does not agree with your position. However, the Agency requests responses to the following questions in order to understand the purpose and importance of ISO 11608-1:2012 free-fall/drop testing as it relates to the subject submission:
 - a. State what design requirements/specifications are in place for your device relevant to freedom from breakage/malfunction after a fall or drop.
 - b. Contrast the design requirements and specifications outlined in your response to a, above with methods used to verify these requirements and specifications
 - c. If your firm considers the results of the (b) (4) Report 89203092.03 to adequately verify product requirements and specifications as outlined within your response to a, above, provide rationale for this determination
 - d. Provide an analysis of risks to the user if they encounter a delivery such as the one experienced within (b) (4) Report 89203092.03 device sample number F13 and provide a

listing of current or proposed mitigations your firm has established (if any) to reduce the risk to the patient in such a scenario.

During the late-cycle meeting held with the sponsor on 2/14/14, the sponsor outlined a proposed response plan for answering the Agency's remaining questions concerning freedom from breakage or malfunction after a fall or drop. The Agency concurred with the items tentatively contained within the plan, including clarifications on how ISO 11608-1:2012 is used to verify device requirements, but stated that acceptability of supporting information could only be asserted after evaluation of formal response materials. On February 14th, 2014, the sponsor provided a response to Agency questions regarding freedom from damage after drop testing.

The sponsor cited the following information to support device requirements related to exposure to a drop or fall:

- Design input requirement 9.3 is present to ensure freedom from breakage or malfunction after a fall or drop of the device. The test methods used to verify this requirement are in accordance with ISO 11608-1:2012, which includes a free-fall test, and are executed by (b) (4) in their testing facilities.
- The device passed the ISO 11608-1 requirements for free-fall testing and therefore fulfilled the DIR Section No 9.3 tests associated with freedom from breakage after a fall.

The sponsor cited the following information to support improper drop test conclusions from vendor

(b) (4)

- In the response sent to FDA on 15 January 2014, regarding (b) (4) Report 89203092.03, Biogen Idec acknowledged that syringe breakage may have been the probable cause of failure reported for device sample number F13. However, in this particular case breakage was not visually present on inspection of the device as noted in the (b) (4) Report 89203092.03. Therefore, after Biogen Idec retrieved the device sample number F13, inspection via X-ray was performed to further understand the failure modes that would cause the device to expel contents outside of the device and needle. Based on the results, it is clear that the syringe has no glass breakage post-drop testing and no other fluid paths are visible for the device to expel its contents outside the device or needle path. Biogen Idec has also confirmed that the needle did not dislodge from the syringe.
- Based on this supporting evidence, Biogen Idec has concluded that (b) (4) Device Sample Number F13 was a functioning device. Probable root cause of the liquid not dispensing into the collection container was the test fixture to perform testing, which does not adequately simulate actual use. (b) (4)

(b) (4) This is the observation which contributed to (b) (4) conclusion that Device Sample Number F13 had a nonvisible post-drop testing device failure for dose accuracy.

The sponsor cited the following information to support safe use of the device and explanation of risks and need for no further mitigations related to falls or drops:

- Biogen Idec investigation has determined that even if (b) (4) Device Sample Number F13 had not functioned properly and the failure was not obvious to the user, as determined by (b) (4) the clinical impact on the user would only be a partial or no dose. This implies that no other user

risks could be present since there was no glass breakage and the device was intact in the user hands.

- In the event of either a No Dose or Partial Dose, the risks have been classified as “Acceptable” because the rate of occurrence is very low. Further, the following has been concluded in regards to an isolated “No dose”:
 - Plegridy is a chronic therapy for the treatment of relapsing forms of multiple sclerosis with the prophylactic goal of reducing the frequency of clinical exacerbations and slowing the accumulation of physical disability. These effects associated with Plegridy have been observed in a trial of 2 years in duration.
 - Plegridy has no demonstrated role as a rescue treatment for acute worsening of MS and is not intended as an acute treatment of MS symptoms. Given the chronic prophylactic use and length of time needed to manifest the benefits of Plegridy, Biogen Idec believes that an isolated, inadvertent use of a lower-than intended dose, or isolated, inadvertent missed dose caused by user error would have a negligible impact on the efficacy anticipated over the following years of treatment with the full dose (125mcg).

Based on the information concerning the root-cause evaluation of test failures, a redundant passing dose accuracy test submitted in January 2014 by the sponsor, as well an evaluation of expected risks to users in the event of a missed or partial dose, the consultant concurs with the sponsor’s determination that the device risks have been adequately mitigated in terms of breakage/malfunction after a fall.

III. Review Determination

After receipt of the sponsors February 14th, 2014 response to outstanding device engineering and design questions, the consultant has not additional questions or concerns to be relayed to the sponsor. This memorandum, along with the January 21st, 2014 memorandum provided to CDER/OND/ODEI/DNP concludes that review of non-human factors device design is considered complete and acceptable.

IV. Concurrence

Ryan McGowan Biomedical Engineer General Hospital Devices Branch CDRH/ODE/DAGRID/GHDB	
Richard Chapman Chief General Hospital Devices Branch CDRH/ODE/DAGRID/GHDB	

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/s/

NICOLE L BRADLEY

02/27/2014

Checked into DARRTS for Ryan McGowan

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 27, 2014

To: Eric Bastings, MD
Director (acting)
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)
Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Aline Moukhtara, RN, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): PLEGRIDY (peginterferon beta-1a)

Dosage Form and Route: Injection for subcutaneous use

Application Type/Number: BLA 125499

Applicant: Biogen Idec, Inc.

1 INTRODUCTION

On May 15, 2013, Biogen Idec, Inc., submitted for the Agency's review an original Biologics Licensing Application (BLA 125499) for PLEGRIDY (peginterferon beta-1a) injection for subcutaneous use, indicated for the treatment of relapsing forms of Multiple Sclerosis (MS).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on May 17, 2013, and July 23, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for PLEGRIDY (peginterferon beta-1a) injection for subcutaneous use.

2 MATERIAL REVIEWED

- Draft PLEGRIDY (peginterferon beta-1a) MG received on May 15, 2013 and received by DMPP on February 19, 2014.
- Draft PLEGRIDY (peginterferon beta-1a) MG received on May 15, 2013 and received by OPDP on February 19, 2014.
- Draft PLEGRIDY (peginterferon beta-1a) Prescribing Information (PI) received on May 15, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 19, 2014.
- Draft PLEGRIDY (peginterferon beta-1a) Prescribing Information (PI) received on May 15, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on February 19, 2014.
- Approved AVONEX (interferon beta-1a) comparator labeling dated February 27, 2013.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
02/28/2014

ALINE M MOUKHTARA
02/28/2014

MELISSA I HULETT
02/28/2014

LASHAWN M GRIFFITHS
02/28/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Filing Memo

DATE: June 28, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Nicole Bradley, Regulatory Project Manager, CDER/OND/ODEI/DNP

SUBJECT: Original BLA 125499
Company: Biogen Idec, Inc.
Drug: BIIB017 (PEGylated Interferon beta-1a)
Device: Prefilled Syringe and Peninjector
Intended Use: Treatment of Multiple Sclerosis
CDRH CTS Tracking: ICC1300286/CON1311787

The Division of Neurology Products, Office of Drug Evaluation I, Office of New Drugs, Center for Drug Evaluation and Research requested a Human Factors consultative review of the original BLA 125499 submitted by Biogen Idec for their BIIB017 PEN and prefilled syringe and peninjector.

The BIIB017 PEN is a single use, disposable, (b) (4) injection device. This device is designed to deliver an injection of 0.5 mL of BIIB017 from a staked needle prefilled syringe to a multiple sclerosis (MS) patient. The BIIB017 prefilled syringe (PFS) is a single use, disposable injection device. This device is designed to deliver an injection of 0.5 mL of BIIB017 to a multiple sclerosis (MS) patient. Both the BIIB017 PEN and PFS are intended to be used for (b) (4) bi-monthly (b) (4) injections.

As part of the dosing ramp-up for newly prescribed patients, the manufacturer will provide a starter pack for the PEN/PFS. The BIIB017 starter pack is a self-contained package, which consists of:

- One 63 mcg dose BIIB017 PEN contained within primary packaging
- One 94 mcg dose BIIB017 PEN contained within primary packaging
- One set of Instructions for Use (IFU)
- PEN/PFS and packaging labeling

(b) (4)

(b) (4)

. An IFU was developed for the BIIB017 medication presentation using the output from the BIIB017 PEN

Baseline IFU per P1539-RD-004.

(b) (4)

Review Recommendation:

The BLA contains the necessary information to perform a human factors review i.e. validation study report for both the PEN and the PFS. Therefore, CDRH HF recommends the submission be “filed” so we can proceed with the review.

-

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Molly Story, Human Factors and Accessible Medical Technology Specialist for
Ron Kaye, Human Factors and Device Use-Safety Team Leader

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/s/

NICOLE L BRADLEY

02/10/2014

Checking into DARRTS for Quynh Nhu Nguyen



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: January 21, 2014
From: Ryan McGowan
Biomedical Engineer, General Hospital Devices Branch
CDRH, ODE, DAGRID, GHDB
To: Nicole Bradley
CDER/OND/ODEI/DNP
Subject: BLA125499, Inter-center Consult ICC1300191

I. Purpose

CDER has requested review device relevant aspects to support BLA 125499 Plegridy (peginterferon beta-1a) for Multiple Sclerosis. Multiple requests for information and firm responses have been received for this BLA across two lead reviewers.

This memorandum serves to provide a high-level overview of all device-relevant review content for BLA 125499 which is considered to be outside the scope of human factors and usability. This memorandum will also serve to present any outstanding review issues as of January 21, 2014.

Device content related to human factors and usability is deferred to Quynh Nhu Nguyen, Human Factors Reviewer within CDRH.

II. Review History, Lead-Device Review Transition, and Outstanding Issues at Time of Transition

From June 2013-November 2013, Jason To, Biomedical Engineer within CDRH served as lead device reviewer for BLA125499, Inter-center Consult ICC1300191. During his time as lead review, he performed ongoing reviews of device material. He created two memoranda to document questions requested of the sponsor, these memoranda are: a September 17, 2013 memo titled "CDRH Consult, ICC1300191, BLA125499" as well as an October 7, 2013 memo titled "BLA 125499 – Engineering Performance Issues (CR) to be Communicated to Sponsor 10-10-13"

Since November 2013, the role of lead device reviewer has been assigned to Ryan McGowan, Biomedical Engineer within CDRH/ODE/DAGRID/GHDB. Within Jason To's September 17th memorandum, 14 issues had been identified and additional information was requested of the sponsor. On September 27th 2013, the sponsor provided a response to these issue. Mr. To reviewed the responses, and composed the October 10th memorandum to provide a listing of outstanding topics to be discussed at the "mid-cycle meeting" on October 10, 2013. At the time of transition, the following outstanding issues had been identified by lead reviewer Jason To, as interpreted though Mid-cycle Meeting Minutes.

- 1) Needle Shield Function Claim and Sharps Injury Prevention
- 2) (b) (4) Failures of the Device
- 3) Device (b) (4) Failures
- 4) Vibration Pre-Conditioning Testing

On December 9, 2013 CDRH held a teleconference with the sponsor to discuss items 1 through 3. This discussion resulted in the issuance of additional questions posed to the firm on December 30,

2013. These responses were reviewed as part of a January 17th memorandum from Ryan McGowan and all concerns were considered resolved relevant to items 1-3 Jason To identified.

Since the time of the teleconference, the sponsor submitted a formal response to the October 10th Mid-cycle meeting discussion, responses to a November 8th information request, as well as a follow up to a single outstanding issue from the initial response to the September 17th information request.

All review issues currently considering outstanding as of January 21st are presented within the table below. This assessment was completed by examination of CDRH questions and firm responses presented within a series of email messages with Nicole Bradley on 1-21-14.

Outstanding Device Review Issue	Location of Firm Response
Vibration Pre-Conditioning Testing	January 13 Response, Serial 042
Outstanding Response for Free Fall Testing	January 16 Response, Serial 045
Biocompatibility Sample Prep and Rationale	January 13 Response, Serial 042

This memorandum will serve as a review of the outstanding elements listed within the table above. All other items are considered to be resolved at this time.

III. Review of Outstanding Review Issues as of 1-21-2014

Vibrational Pre-Conditioning Testing

Within Jason To's October 7th memorandum and subsequent Mid-cycle review minutes, the following additional inquiry regarding device vibrational testing was posed:

"Please verify that you have performed vibration pre-conditioning testing on the final finished device with the drug product containing syringes in accordance with ISO 11608-1:2012. Please provide the test reports and results for review if you have performed this testing."

In response, the firm provided the following information within their January 13 Response, Serial 042:

"Biogen Idec has completed vibration pre-conditioning testing on the final finished prefilled pens assembled with prefilled syringes containing peginterferon beta-1a drug product in accordance with ISO 11608-1:2012. Testing was performed by an independent testing laboratory, (b) (4), which was contracted for ISO 11608-1:2012 testing on the final prefilled pen."

In addition, the firm provided the original test reports and excerpted relevant sections showing the pens were representative of final finished products.

The firm's response to this outstanding review issue is considered acceptable.

Outstanding Response for Free Fall Testing
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Within Jason To's September 17th questions, the following issue was raised:

Following free fall preconditioning, visual inspection showed that sample #30 for drop orientation 3 had (b) (4) no further functional testing were conducted. You state that ISO 11608-1:2012 allows for a 3 failed device threshold, and thus, the test article was replaced with a device within the same batch and testing was repeated. However, FDA is still concerned about the effects of the observed failure. Please provide a detailed description of the functionality of the device following this failure mode and explain the effects it may have on the system. In addition, please describe your mitigation strategy in which you address all safety concerns associated with this observed failure mode and why they are adequate in mitigating all risks. Note that based on your response, additional information regarding this matter may be required.

In response, the firm provided information regarding the performance of the device and found that one of the test reports relating to device function after drop could not be verified, therefore they committed to supplying this test report by January 15, 2014. The root cause of the unverified findings were attributed to mis-interpretation of information and inadequate handling of devices prior to testing

On January 16th, the firm provided a response sequence relating to the updated findings. The firm implemented a corrective action to address this anomalous result was for (b) (4) to perform free fall testing using PFPs that were assembled with the same PFS batch, under controlled shipment and storage conditions, with an approved protocol containing controls for recording raw data.

The firm tested 30 devices, and dropped them from 3 orientations as specified within ISO11608-1. Of these 30, one was found to have obvious damage, noted when the cap was removed and the syringe body separated and spilled and 6 were noted to have minor damage that did not result in a failure to deliver. In total, 23 devices showed no visible damage, of these, 21 were chosen for dose accuracy testing, results summarized form within the table below:

Table 3: ISO11608-1:2012 10.5d Freefall Test (System D1)

Number of Pens Tested	Mean Results	(b) (4)	Test Result
20	0.497mL	(b) (4)	Pass

The test company (b) (4) considers the batch to have not passed, as one of the 21 devices which showed no obvious visual damage (b) (4). The firm considers this to be a delivery failure that is not obvious and not compliant with ISO11608-1.

The sponsor, Biogen, contends that this failure should not constitute a batch failure per ISO11608-1 as the failure was obvious to the user during injection; therefore the firm believes the company should be able to consider this a "replaceable device" per ISO11608-1.

CDRH evaluation of the test report does show a non-compliant delivery with one of the devices which represents a non-obvious failure and does not meet the ISO11608-1 standard. However, adherence to this particular standard is not necessarily required by the Agency. The acceptability of the device performance should be based on the firm's requirements and Agency approval should be based on the acceptability of a missed dose with the subject drug. Therefore the following questions will be posed to the sponsor:

1. Within your January 15th information response to the Agency, contained within Serial No.: 0045, you have provided information to support ISO 11608-1:2012 testing, specifically free fall testing completed by independent testing laboratory and Notified Body, (b) (4) concluded within Report 89203092.03 that the batch tested did not pass criteria of ISO 11608-1:2012. The Agency has reviewed your firm's position that the failure which caused (b) (4) to conclude the batch did not pass testing requirements constitutes an obvious failure and does not agree with your position. However, the Agency requests responses to the following questions in order to understand the purpose and importance of ISO 11608-1:2012 free-fall/drop testing as it relates to the subject submission:
 - a. State what design requirements/specifications are in place for your device relevant to freedom from breakage/malfunction after a fall or drop.
 - b. Contrast the design requirements and specifications outlined in your response to a, above with methods used to verify these requirements and specifications
 - c. If your firm considers the results of the (b) (4) Report 89203092.03 to adequately verify product requirements and specifications as outlined within your response to a, above, provide rationale for this determination
 - d. Provide an analysis of risks to the user if they encounter a delivery such as the one experienced within (b) (4) Report 89203092.03 device sample number F13 and provide a listing of current or proposed mitigations your firm has established (if any) to reduce the risk to the patient in such a scenario.

Outstanding Biocompatibility Information
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Within Jason To's October 7th memorandum and subsequent Mid-cycle review minutes, the firm was requested to provide follow-up information to biocompatibility information requested previously in the form of two questions. Each question is listed separately below with the firm's responses, and current CDRH assessment.

Composite Sample Preparation

The firm was presented with the following question relevant to biocompatibility sample prep: "Please provide a detailed description describing your composite sampling methodology and discuss the methodology used to ensure all skin contacting components of your subject device are represented proportionally in this sample."

In response, the firm stated that composite sampling (pooling the device components for extraction) method for biocompatibility testing was based on ISO 10993-12:2012, Biological Evaluation of Medical Devices, Part 12: Sample Preparation and Reference Materials.

The firm also stated that the methodology for this composite sampling was to identify the components of the device that will come into contact with the patient's skin, based on the design of the device and its intended use.

For the composition, only external components identified as "skin contact components" were used for the study. For each test extraction, one set of 9 components was used. The 9 components were:

(b) (4)

The firm claims that proportions of the sampling were based on the laboratory testing method requirements (Surface Area) for each test, as specified in the testing protocols which are based on the

ISO 10993 Biocompatibility Testing Guidelines and references full test reports and protocols submitted to the Agency within August of 2013.

Based on the adherence to accepted biocompatibility standards and completion of the study within a GLP certified lab, as well as prior review by biocompatibility consultants under the lead review of Jason To, **this response is considered acceptable.**

Sample Extraction

The firm was presented with the following question relevant to biocompatibility sample extraction – “Please clarify whether an extraction study was performed at the worst case conditions for your subject device to mimic the change in the physical and chemical properties that the varying conditions can cause during your subject device’s (final finished device) use life/ shelf life. If so, please provide the results from this study. If not, please provide and perform an extraction study at the worst case conditions to mimic the change in the physical and chemical properties in your subject device’s use life/shelf life. Please note we expect a full analytical and safety assessment analysis of all extracts from this study.”

In response, the firm states that the [REDACTED] (b) (4)

[REDACTED] The firm states that the syringe is the primary container closure device and that extraction studies have been performed with acceptable results on components of the prefilled syringe that do come into direct contact with the drug product, which have been previously submitted in the original BLA submission.

The submission materials were referenced to find the original question nominated by the biocompatibility reviewer. Within Jason To’s September memorandum, it was found that the initial question was “Please clarify whether an extraction study was performed at the worst case conditions to mimic the change in the physical and chemical properties that the varying conditions can cause during your subject device’s use life.” Based on this statement, the reviewer believes this question should have been directed at the master file holder related to MAF [REDACTED] (b) (4) not the BLA sponsor. After review of the MAF, it appears the extractions were completed at a temperature of [REDACTED] (b) (4) degrees Celcius. The sponsor states that they consider [REDACTED] (b) (4) degrees celcius to be indicative of an “exaggerated, worst case scenario for patient use” as the Instructions for Use indicate the product is required to be kept under refrigeration (2-8°C) and be brought to room temperature (22-25°C) before injection.

The firm also states that the portions of the device that come into contact with the skin during use have been assessed for cytotoxicity, irritation, and sensitivity in accordance with ISO 10993-5. They state that extraction time and temperature for the components used for the biocompatibility tests were selected as they represent an exaggerated, worst case scenario for patient use.

Based on the response from the sponsor, and re-review of submission materials the response is considered acceptable.

IV. Final CDRH Device Concerns to be Expressed to the Sponsor in Advance or as part of the End-Cycle Meeting

1. Within your January 15th information response to the Agency, contained within Serial No.: 0045, you have provided information to support ISO 11608-1:2012 testing, specifically free fall testing completed by independent testing laboratory and Notified Body, [REDACTED] (b) (4) [REDACTED] concluded within Report 89203092.03 that the batch tested did not pass criteria of ISO 11608-1:2012. The Agency has reviewed your firm’s position that the failure which caused [REDACTED] (b) (4) to conclude the batch did not pass testing requirements constitutes

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Ryan McGowan
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/s/

NICOLE L BRADLEY

02/06/2014

Checking into DARRTS for Ryan McGowan



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: January 17, 2014
From: Ryan McGowan
Biomedical Engineer, General Hospital Devices Branch
CDRH, ODE, DAGRID, GHDB
To: Nicole Bradley
CDER/OND/ODEI/DNP
Subject: ICC1300191/S008 – 12/9/13 Teleconference Request

I. Background

CDER has requested review of responses to questions sent to the sponsor (Biogen) related to meeting information provided by the sponsor to support BLA 125499 Plegridy (peginterferon beta-1a) for Multiple Sclerosis. The questions were outlined within a 12/16/13 memorandum from CDRH. The responses to the questions posed were received 1/12/14.

This memorandum is a continuation of the version provided by the CDRH consultant on 12-19-14.

II. Review Documents

“MID-CYCLE COMMUNICATION Final”
“PFP 30 December 2013 IR Response”
“Plegridy Pen_FDA Responses_PFS_PFP 08 November 2013 IR”
“(b) (4) Vibration Testing Report”

III. Background and Device Description

For detailed background on the subject submission and device, please consult CDRH mid-cycle review information. The CDER consult repository location is unknown at this time, however ICC1300191 serves as the CDRH document repository for these files.

IV. Review

The consultant finds that the previous performance reviewer requested multiple deficiencies from the combination product sponsor. The sponsor desires to hold follow up discussions concerning some of the deficiencies requested. Each discussion topic discussed within the 12/9/13 teleconference is included below along with additional comments and questions provided to the firm from the 12-19-13 CDRH memorandum.

SHARPS INJURY PREVENTION

In the Mid-cycle Communication, dated October 10, 2013, FDA stated the following: “The claims that you are making appear to be contradictory.” (b) (4)

In response the firm states the following”

- Reference to ISO11608:2012 Needle-based injection systems for medical use – Requirements and test methods, to clarify the definition of “needle hiding” v. sharps prevention.
- The needle shield feature of the PFP is intended for needle hiding, (b) (4)
- (b) (4) However, Biogen Idec understands FDA’s concern that the labeling should be clarified with respect to how end-users are instructed to operate the PFP under normal use conditions and has revised the labeling accordingly.

Additionally, Annotated PFP IFU – 125 mcg, the revised IFU, was inspected to examine the new disposal instructions. These were found to be appropriate.

Based on the sponsor’s statements regarding needle hiding (b) (4) the reviewer generally believes that the claims are appropriate (b) (4) However:

1. Further clarification on the point the sponsor has made concerning ISO11608:2012 to clarify the definition of “needle hiding.”

During the 12/9/13 teleconference with the firm, they referenced section 3.10-3.12 of 11608-5. Definition of needle hiding per that standard is below:

Needle hiding

Function which obscures the needle from the user’s sight either before, during or after the injection cycle

NOTE: The needle hiding function only has a visual requirement designed to reduce patient trauma in case of needle phobia. It is not subject to any physical or dimensional requirements intended to restrict access to the needle. It does not imply any increased level of safety from needle stick injuries.

2. The firm should provide additional detail on how labeling was clarified revised “with respect to how end-users are instructed to operate the PFP under normal use conditions”

12-19-13 Memo Review

During the 12/9/13 teleconference with the firm, they stated that the device instructions had been modified with respect to disposition and disposal of the device. FDA initially recommended placing a warning to state that the device is not capable of sharps protection. Firm asked for FDA to propose language. FDA determined that they would consider this issue and respond to the firm.

CDRH re-reviewed the injector information to determine the extent to which the device had been designed or equipped to prevent inadvertent needle sticks. (b) (4)

(b) (4)

A comparison of the subject injector to existing injectors for similar indications for extent of sharps protection revealed the Avonex pen, approved for use in the injection of AVONEX® (Interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

The Avonex pen does not appear to lend any needle shielding or guarding to the user after the injection process is complete, instead the user is instructed to place the pen back in the needle cover after injection.

STEP 17: Do not hold the AVONEX PEN cover with your hands. Place the AVONEX PEN cover on a flat work surface. Line up the exposed needle with the hole of the AVONEX PEN cover, and insert directly into the opening (See Figure V).



(Figure V)

When the existing requirements and comparable pens are examined, it appears the protections present on the current pen are adequate to mitigate needle sticks; however the firm will be requested to provide the Agency with confirmation of the (b) (4) feature of the needle shield and the most up to date risk analysis documentation containing a listing of mitigations to the risk of inadvertent needle sticks to users.

In response to 12-9-13 teleconference agenda item 1, Clarification of the sharps injury prevention requirements on the pen:

Please confirm that the system requirement “ (b) (4) described within *Pre-filled Pen Performance Expectations* of submission section 3.2.P.2 *Pharmaceutical Development* is intended to communicate that the device, (b) (4)

Please perform a review of existing risk management documentation for the subject injector device relevant to the risk of inadvertent needle sticks or sharps injury. After review, provide the Agency with the most up to date risk analysis documentation containing a listing of mitigations to the risk of inadvertent needle sticks to users and specifically state any modifications which have been made as part of the risk documentation review process.

Please provide a description of how existing device usability validation protocols are sensitive to a possible failure of the (b) (4) design feature on the device as well as any subsequent sharps injury or close-call sharps injury. If the existing protocols do not specifically monitor for these occurrences please alter the protocols and provide relevant draft sections for Agency review.

1-17-14 Memo Review

The below review contains the original question posed to the firm from the 12-19-13 memo and an evaluation of the firm's response.

1. Please confirm that the system requirement “ (b) (4) described within Pre-filled Pen Performance Expectations of submission section 3.2.P.2 Pharmaceutical Development is intended to communicate that the device, (b) (4)

Based on the above information, the firm states “Biogen Idec can therefore confirm that the design intent of the system requirement “ (b) (4)

Based on the firm's certifications and prior review of the product, the consultant does not have any additional concerns of the device design's intention of the needle shield (b) (4)

2. Please perform a review of existing risk management documentation for the subject injector device relevant to the risk of inadvertent needle sticks or sharps injury. After review, provide the Agency with the most up to date risk analysis documentation containing a listing of mitigations to the risk of inadvertent needle sticks to users and specifically state any modifications which have been made as part of the risk documentation review process.

In response the firm stated:

In the instance that an end-user injures themselves on their previously used needle, the resulting harm is classified as a “minor injury,” as according to the Risk Management Plan. However, if a third party suffers from an accidental needle stick via a needle that has been previously used, the resulting harm to that third party is classified as “major infection.” Because this has not been observed in any setting, the occurrence was rated as a 1-Very Low. In accordance with the Risk Management Plan, the risk acceptability for an accidental needle stick to a third party was classified as As Low As Reasonably Practicable (ALARP). However, upon cross-functional team assessment of this failure within the User FMEA (see lines U81 and U88), it was determined that information provided within the Instructions for Use (IFU) was adequate in raising end-user awareness to this issue.

Biogen Idec has implemented mitigations within the Instructions for Use (IFU) to further mitigate the potential for accidental needle stick caused by an observation of device (b) (4) and to raise end-user awareness of both needle guard function and device function:

(b) (4)

Based on the above information, the consultant does not have any additional concerns with the risk of inadvertent needle sticks in terms of design or risk analysis. The final validation of all labeling will be completed within usability testing.

3. Please provide a description of how existing device usability validation protocols are sensitive to a possible failure of the (b) (4) design feature on the device as well as any subsequent sharps injury or close-call sharps injury. If the existing protocols do not specifically monitor for these occurrences please alter the protocols and provide relevant draft sections for Agency review.

The firm provided the below response:

... to ensure that the PFP performs as intended during this IFU validation study, a new protocol is being generated with special consideration being given to a possible failure of the (b) (4) design feature on the device, as well as the potential for any subsequent sharps injury, through moderator intervention.

The moderator of the study session will give special consideration to any non-typical behaviour that is expressed during the study, such as manipulation of the needle shield prior to injection. In the event that the study moderator feels the participant is at risk of an accidental sharps injury, they will quickly intervene and ask the participant to cease the behaviour in question, while appropriately recording the circumstances.

Based on the above information, the consultant does not have any additional concerns with the risk of inadvertent needle sticks in terms of design or risk analysis. The final validation of all labeling will be completed within usability testing.

(b) (4) FAILURES OF THE DEVICE

In the Mid-cycle Communication, dated October 10, 2013, FDA stated the following regarding observed mechanical failure of the (b) (4) feature, "During the Design Verification testing performed by the component manufacturer (b) (4) therefore, the above failure rate is unacceptable."

The firm responded by stating that the failure information presented within the early assessments was due to inexperience manufacturing the device. The firm states that since that time, significant additional manufacturing experience has been obtained and additional data have been generated from multiple sources such as: release testing performed by the component manufacturer, as well as final assembly manufacturing and release testing performed by Biogen Idec. These data include a significant decrease in the rate of (b) (4) observations in comparison to the initial design verification lot data provided to the FDA within the DVTR, which occurred shortly after validation of the subcomponent assembly manufacturing process. Given the data and outputs of the revised risk assessments, Biogen Idec does not plan to make any further design changes at this time. The table below was included as reference:

Data Source	Stage and Description	(b) (4)
Component Manufacturer's DVT (n=1 lot)	Design Verification Lot	
Rate		
Component Manufacturer's Supply Release Testing (n=8 lots)	Subsequent Commercial Lots	
Biogen Idec Data on Assembled PFP (n=3 lots)		
Total – Subsequent Commercial Lots		
Rate		

Based on the sponsor's statements regarding decrease in the rate of failure of the (b) (4) feature, the reviewer generally believes that the information supported is sufficient. However:

1. Further clarification on the sampling criteria used to generate the above table is needed
2. Full test reports which support both "subsequent commercial lots are needed
3. Further explanation of the statement that "additional manufacturing experience" has been obtained
4. Confirmation that no special manufacturing techniques were applied to the component manufacturer's supply release or assembled PFP release that will not be part of final commercial lot manufacturing were applied to the manufacturing runs
5. Description of any mitigations which may be added to the manufacturing process to reduce the risk of a non-compliant (b) (4) mechanism from exiting the facility

During the 12/9/13 teleconference with the firm, they provided generalized information concerning the above questions. Each of the above should be provided to the firm in writing.

In response to 12-9-13 teleconference agenda item 2, (b) (4) failure rates, please provide:

- a. Further clarification on the sampling criteria used to generate the above table is needed
- b. Full test reports which support both “subsequent commercial lots are needed
- c. Further explanation of the statement that “additional manufacturing experience” has been obtained
- d. Confirmation that no special manufacturing techniques were applied to the component manufacturer’s supply release or assembled PFP release that will not be part of final commercial lot manufacturing were applied to the manufacturing runs
- e. Description of any mitigations which may be added to the manufacturing process to reduce the risk of a non-compliant (b) (4) mechanism from exiting the facility

In response to 12-9-13 teleconference agenda item 2 (b) (4) failure rates, please provide:

- a. Further clarification on the sampling criteria used to generate the above table is needed

The firm provided sampling rationale which was found to be acceptable

- b. Full test reports which support both “subsequent commercial lots are needed

The firm states that all data from the component manufacturer is included as part of the Certificates of Analysis and Certificates of Compliance; because of this, there are no formal reports available for submission with this request

- c. Further explanation of the statement that “additional manufacturing experience” has been obtained

The firm provided the following information regarding manufacturing strategies to reduce the occurrence of (b) (4) failure:



- (b) (4)
- d. Confirmation that no special manufacturing techniques were applied to the component manufacturer's supply release or assembled PFP release that will not be part of final commercial lot manufacturing were applied to the manufacturing runs

Biogen Idec can confirm that there were no special manufacturing techniques applied to the component manufacturer's supply release or assembled PFP release that will not be part of final commercial lot manufacturing.

- e. Description of any mitigations which may be added to the manufacturing process to reduce the risk of a non-compliant (b) (4) mechanism from exiting the facility

(b) (4)

Based on the firm's responses, the reviewer is confident that the mechanisms put in place to reduce the occurrence of (b) (4) failures is adequate.

(b) (4) FAILURES OF THE DEVICE

The firm provided additional assessment of the risk of (b) (4), which was part of earlier discussions with FDA reviewers. (b) (4) however additional detail as to the cause was not made available.

In addition to observations of (b) (4) FDA also expressed concerns about the PFP rate of (b) (4). This observation was also evaluated via risk assessments to determine the acceptability of the residual risk relating to this issue. If an end-user were to experience an occurrence of (b) (4) the ultimate effect to that user may be a "no dose," as reported within the PFP uFMEA (Attachment 2); there is no safety impact to the end-user due to (b) (4) given that this therapy is chronic, and an inadvertent delay in a dose due to (b) (4) would have a negligible impact on the efficacy anticipated over the following years of treatment. Given the combined assessment of the effect of this observation on the end-user and the total reported occurrence rate, this risk was determined to be acceptable.

Assessment of this information will be deferred to the CDER review representatives present during the telecom (b) (4) failure rate is not alarming to the CDRH reviewer, however no root cause information was presented to the reviewer, and risk of a missed dose cannot be evaluated by CDRH.

IFU, LABELING, AND SECONDARY PACKAGING

Evaluation of the content presented to support this section will be the responsibility of the CDRH Human Factors reviewer.

Additional Discussion During the 12-9-13 Teleconference

The sponsor was advised that usability studies should not be started until the device is found to be within its final finished form. The firm stated that they believed that after resolution of the teleconference agenda items, the device design concerns would be considered closed. The Agency informed them that they have not evaluated all responses to existing device-related questions from the mid-cycle meeting and so they could not be certain that all device-related concerns had been addressed. The firm should be provided with the following statement.

Before your firm begins usability analysis, you are encouraged to assure that all outstanding concerns with physical device design as communicated by the Agency have been resolved. Please provide a descriptive listing contain each outstanding device question along with how your firm believes they have adequately addressed each concern, as well as the location of the communication with the Agency which contained the proposed resolution content. Examples of device-related issues the Agency does not believe have been resolved include the biocompatibility and storage qualification items listed within the Mid-cycle meeting minutes document.

V. 12-19-13 CDRH Questions

In response to 12-9-13 teleconference agenda item 1, Clarification of the sharps injury prevention requirements on the pen:

1. Please confirm that the system requirement “ (b) (4) ” described within Pre-filled Pen Performance Expectations of submission section 3.2.P.2 Pharmaceutical Development is intended to communicate that the device, (b) (4)
2. Please perform a review of existing risk management documentation for the subject injector device relevant to the risk of inadvertent needle sticks or sharps injury. After review, provide the Agency with the most up to date risk analysis documentation containing a listing of mitigations to the risk of inadvertent needle sticks to users and specifically state any modifications which have been made as part of the risk documentation review process.
3. Please provide a description of how existing device usability validation protocols are sensitive to a possible failure of the (b) (4) design feature on the device as well as any subsequent sharps injury or close-call sharps injury. If the existing protocols do not specifically monitor for these occurrences please alter the protocols and provide relevant draft sections for Agency review.

In response to 12-9-13 teleconference agenda item 2, (b) (4) failure rates, please provide:

1. Further clarification on the sampling criteria used to generate table 1 within your response to the mid-cycle review meeting minutes
2. Full test reports which support both of the “subsequent commercial” lots as described within table 1 of your response to the mid-cycle review meeting minutes
3. Further explanation of the statement that “additional manufacturing experience” has been obtained relative to production of subsequent commercial lots. Specifically, please describe the types of manufacturing experiences which your firm believes led to the observations included within 1 of your response to the mid-cycle review meeting minutes.
4. Confirmation that no special manufacturing techniques were applied to the component manufacturer’s supply release or assembled PFP release that will not be part of final commercial lot manufacturing were applied to the manufacturing runs which produced results within table 1 of your response to the mid-cycle review meeting minutes
5. A description of any mitigations which may be added to the manufacturing process to reduce the risk of a non-compliant (b) (4) mechanism from exiting the facility

Related to 12-9-13 teleconference discussions concerning outstanding device development activities:

1. Before your firm begins usability analysis, you are encouraged to assure that all outstanding concerns with physical device design as communicated by the Agency have been resolved. Please provide a descriptive listing contain each outstanding device question along with how your firm believes they have adequately addressed each concern, as well as the location of the communication with the Agency which contained the proposed resolution content. Examples of device-related issues the Agency does not believe have been resolved include the biocompatibility and storage qualification items listed within the Mid-cycle meeting minutes document.

VI. 12-19-13 CDRH Questions

The consultant has reviewed the sponsor’s responses to the questions sent on 12-19-2013 from CDRH and considers the responses acceptable. Final validation of the user labeling will be conducted through validation testing and human factors evaluation.

Ryan McGowan
Biomedical Engineer
General Hospital Devices Branch
Division of Anesthesiology, General Hospital, Respiratory
Infection Control, & Dental Devices
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration

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/s/

NICOLE L BRADLEY

01/25/2014

Checking into DARRTS for Ryan Mcgowan



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: July 17, 2013

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/GHDB

To: Nicole Bradley
CDER/Division of Neurology Products

Subject: CDRH Consult, ICC1300191, BLA125499

Biogen Idec Inc.
133 Boston Post Road
Weston, MA 02493

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding BLA125499. The device constituent of this combination product is a single-use, disposable, [REDACTED] (b) (4) pre-filled pen, which consists of a pre-filled syringe containing a nominal fill volume of 0.5 mL of sterile peginterferon beta-1a drug product liquid formulation.

2. Device Description

Drug Product

The pre-filled pen was co-developed and designed by a component manufacturer and Biogen Idec. The component manufacturer has provided design, verification, and manufacturing records in MAF (b) (4). In addition, Biogen Idec has performed design verification and design validation to test the prefilled pen's functionality.

The proposed commercial pre-filled pens are presented in three different dose configurations: 63, 94, and 125 µg of peginterferon beta 1-a. The pre-filled syringe is then assembled into the pre-filled pen and is uniquely identified by the colors orange, blue, and gray, representing the 63, 94, and 125 µg doses respectively. (b) (4)

The pre-filled pen was designed to encapsulate the pre-filled syringe to provide end-users with an alternative convenient means to inject a single dose of medication from a pre-filled syringe.



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/s/

NICOLE L BRADLEY

01/25/2014

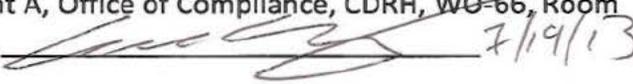
Checking into DARRTS for Jason To

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: July 18, 2013

TO: Nicole Bradley, Office of Biotechnology Products, Center for Drug Evaluation and Research, WO-21, Room 1521

Cc: Office of combination products at combination@fda.gov

THRU: Carl Fischer, PhD., Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, ~~WO-66~~, Room 3526
 7/19/13

FROM: Felicia L. Brayboy, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3574

Firm: Biogen Idec Inc.
133 Boston Post Road
Weston, MA 02493

Application # BLA 125499

Product Name: BIIB017 (PEGylated interferon beta-1a)

Consult Instructions: Attendance at the internal filing meeting for BLA 125499 scheduled July 2, 2013

The Office of Compliance at CDRH received a consult request from CDER regarding BIIB017 (PEGylated interferon beta-1a), BLA 125499. Attendance at the internal filing meeting for BLA 125499 was requested.

Product Description

The peginterferon beta-1a drug product is a sterile, liquid formulation in a pre-filled syringe containing a nominal fill volume of 0.5 mL. In addition to the pre-filled syringe, a single-use, disposable, (b) (4) pre-filled pen will also be available for patients. The pre-filled pen is designed to assist Multiple Sclerosis (MS) patients with the injection of the pre-filled syringe. The intent of the pre-filled pen is to

provide the end user with a convenient alternative to performing manual injections and to address patients that have injection anxieties or needle phobia during the injection process.

Consult Evaluation

CDRH Office of Compliance has reviewed the information provided and determined that the submission does not include medical device GMP information needed for a comprehensive review. If the applicant declares it is following 21 CFR 210 and 211, the following 21 CFR 820 regulations apply:

- a. 820.20 Management Responsibility
- b. 820.30 Design Controls
- c. 820.50 Purchase Controls
- d. 820.100 Corrective And Preventative Actions (CAPA)

We are not requesting that procedures for Management Responsibility be provided for a desk review; however the applicant should be ready to show compliance if asked or during an inspection.

Design Controls appear to be incomplete. There is some information for Design Inputs, Design Outputs, Design Verification, and Design Validation. Information about the applicant’s Purchase Controls and CAPA procedures could not be found.

Manufacturers of the Pre-Filled syringe

Location	Activities	FEI #
(b) (4)	Drug Product Manufacturing and Primary Packaging Drug Product Visual Inspection and Bulk Packaging Drug Product Release Testing (Sterility)	(b) (4)

Manufacturers of Pre-Filled Pen

Name and Location	Activities	FEI #
Biogen Idec Denmark Manufacturing ApS Biogen Idec Allé 1 DK - 3400 Hillerød	Assembly of the pre-filled pen components with the pre-filled syringe Release Testing (Functionality Testing) and EU QP Release Secondary packaging Stability Testing (Functionality Testing) Drug Product Release Testing (Sterility)	3006339887

[REDACTED] (b) (4)
[REDACTED]

The last inspection for [REDACTED] (b) (4),
[REDACTED] was [REDACTED] (b) (4)

[REDACTED] This inspection covered the Quality, Production, Facilities & Equipment, Materials, Laboratories, and Labeling & Packaging Systems. Compliance programs covered included C.P. 7356.002 for drug manufacturing inspections, C.P. 7356.002A for sterile drug process inspections, C.P. 7356.002M for sterile drug biotech facility process inspections, and C.P. 45848C for vaccines. This inspection resulted in issuance of a 19-item FDA 483, Inspectional Observations form, at the close of the inspection. This inspection was classified Official Action Indicated (OAI) but then down classified to Voluntary Action Indicated (VAI). This facility has not had a Medical Device inspection.

The firm was inspected [REDACTED] (b) (4), the inspection covered aspects of the quality, production, facilities and equipment, materials, and laboratory systems as well as corrections to the previous inspection. At the conclusion of the inspection, a 5-item FDA 483 was issued. This inspection was classified VAI. The firm was also inspected [REDACTED] (b) (4). At the conclusion of the inspection a 9-item FDA 483 was issued; the inspection was classified VAI.

The last inspection for Biogen Idec Denmark Manufacturing was November 29, 2011, to December 2, 2011. This was a premarket inspection under the Medical Device Regulation of a combination product. The systems evaluated during the inspection included Design Controls; Purchasing Controls; Production and Process Control; Process Validation; Acceptance Activities; and Corrective and Preventive Actions and Complaint Files. The inspection report was evaluated by CDRH/OC and the inspection was classified No Action Indicated (NAI).

CDRH Recommendation

Upon review of the documentation provided, CDRH/OC is requesting additional information from the applicant in order to complete the review of the application to ascertain compliance with the applicable 21 CFR part 820 regulations.

The applicant must provide enough information to show compliance with the following regulations:

- (21 CFR 820.30) Design Controls for the final combination product. If the applicant feels that the information has been provided, they should explicitly point out what portions of the application specifically address the design control

requirements (Design Inputs, Design Outputs, Design Review, Design Verification, Design Validation, Design Transfer, Design Changes, and Design History File) for the final combination product. Information from the device constituent manufacturers may be used to satisfy part of these requirements.

- (21 CFR 820.50) Purchase Controls
- (21 CFR 820.100) CAPA

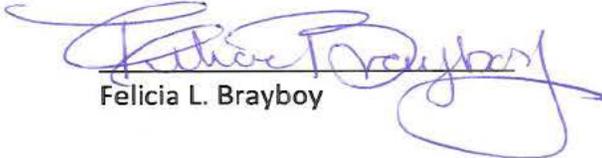
The applicant can use the guide listed below to determine what type of documents they should provide with the application.

'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003)
(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>)

The requested information should be provided in the Module 3.2.P.3 manufacturing section of the NDA.

CDRH recommends inspections under the applicable Medical Device Regulations of

(b) (4)
[REDACTED] The focus of this inspections should be Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), and Design Controls (21 CFR 820.30) for the PLEGRIDY (BLA 125499). Additionally, evaluate the manufacturing activities associated with the finished combination product, including in-process and final acceptance activities. An inspectional guidance will be provided upon request.


Felicia L. Brayboy

Prepared/typed: FBrayboy: July 12, 2013

Reviewed/approved: ITejero: July 18, 2013

Reviewed/approved: Carl Fischer: *[Signature]* 7/19/13

cc:

WO66-3515 (DOE-A Firm File)

WO66-3515 (Division Chron File)

WO66-3453 (FBrayboy, Reviewer)

CTS No.: ICC1300191

INSPECTIONAL GUIDANCE

SUBJECT: Inter-Center consult (CTS No.: ICC1300191) requested by CDER/ Division of Neurology Products. This is a pre-market consult for BIIB017 (PEGylated interferon beta-1a), BLA 125499

ASSIGNMENT

Manufacturers of the Pre-Filled syringe

Location	Activities	Facility Establishment Identifier
(b) (4)	Drug Product Manufacturing and Primary Packaging Drug Product Visual Inspection and Bulk Packaging Drug Product Release Testing	(b) (4)

Please conduct an inspection of the firm in order to assess compliance with the Quality System regulation (21 CFR Part 820). This inspection should specifically focus on Design Controls, Purchasing Controls, Acceptance Activities, Complaint Handling, and Corrective and Preventive Actions. The site/building where finished drug product (drug and device) is manufactured should be inspected.

Recommendations:

CDRH recommends the following:

1. The inspection of this firm should be conducted as a coordinated inspection.
2. The Office of Regulatory Affairs (ORA) should be consulted regarding the participation of a Medical Device and Drug Expert to assist with the inspection.
3. The CDRH inspectional guidance will serve as an attachment to the inspection assignment written and routed by CDER's Office of Compliance.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Felicia L. Brayboy
Consumer Safety Officer,
General Hospital Devices Branch
Division of Enforcement A
Office of Compliance, WO66 RM 3453
Phone: 301-796-8086

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Carl Fischer, PhD.
Consumer Safety Officer,
Chief, General Hospital Devices Branch
Division of Enforcement A
Office of Compliance, WO66 RM 3526
Phone: 301-796- 5770

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM
DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL
INFORMATION**

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/s/

NICOLE L BRADLEY

01/25/2014

Checking in DARRTS for Felicia Brayboy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing and Quality
Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

DATE: January 16, 2014

TO: Nicole Bradley, Office of Biotechnology Products, Center for Drug Evaluation and Research, WO-21, Room 1521
Nicole.Bradley@fda.hhs.gov
Office of combination products at combination@fda.gov

Through: Carl Fischer, PhD., Chief, Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch, Division of Manufacturing and Quality, Office of Compliance, CDRH, WO-66, Room 3526
Carl A. Fischer -5
2014.01.16 10:22:47 -05'00'

From: Felicia L. Brayboy, Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch, Division of Manufacturing and Quality, Office of Compliance, CDRH, WO-66, Room 3574

Applicant: Biogen Idec Inc.
133 Boston Post Road
Weston, MA 02493

Application # BLA 125499

Product Name: BLIB017 (PEGylated interferon beta-1a)

Consult Review of requested additional manufacturing information

Instructions:

The Office of Compliance at CDRH received a consult request from CDER regarding BIIB017 (PEGylated interferon beta-1a), BLA 125499, to review the additional manufacturing information provided in response to our memo dated July 18, 2013.

The device constituent of this combination product is a single-use, disposable, (b) (4) pre-filled pen, which consists of a pre-filled syringe containing a nominal fill volume of 0.5 mL of sterile peginterferon beta-1a drug product liquid formulation.

The pre-filled pen is designed to assist Multiple Sclerosis (MS) patients with the injection of the pre-filled syringe. The intent of the pre-filled pen is to provide the end user with a convenient alternative to performing manual injections and to address patients that have injection anxieties or needle phobia during the injection process.

Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following sections of the application were evaluated:

- 3.2.P.3. Manufacture [peginterferon beta-1a, 63, 94 and 125 µg Pre-filled Pen]
- 3.2.P.3.3 Description of Manufacturing Process and Process Controls
- 3.2.P.7 Container Closure System [peginterferon beta-1a, 63, 94 and 125 µg Pre-filled Syringe]
- 3.2.P.2.3 Manufacturing Process Development
- MAF (b) (4)
- MAF (b) (4)

The above listed sections of the application contained documents related to Design Controls (820.30), Purchase Controls (820.50), and Corrective And Preventative Actions [(CAPA) 820.100]

Design Controls: Standard Operating Procedures (SOPs) or other documentation was provided and addressed all aspects of 21 CFR 820.30. The documentation appeared to be adequate. Below is a list of documents reviewed (this list is not all-inclusive).

- Medical Devices/Combination Product Global Practice (Biogen Idec reference no. GLBL-25612)
- Design Control Procedure (Biogen Idec reference no. PRCD-26136)
- Risk Management Global Practice (Biogen Idec reference no. GLBL-24131)
- Risk Management Procedure (Biogen Idec reference no. PRCD-5662)
- Option, License, and Development Agreement (June 11, 2009)
- Quality Agreement (Biogen Idec reference no. PRCD-14674)

- Component Manufacturer Design and Development Plan ((b) (4) reference no. 0156-000-DD-0001)
- Product Development Plan (Biogen Idec reference no. PDP-83-10-02)
- Design Input Requirements ((b) (4) reference no. 0156-000-IR-0001)
- Component Manufacturer Bill of Materials ((b) (4) reference no. 0156-000-BE-0001 and 0156-000-BE-0002)
- Component Manufacturer Assembly Drawings ((b) (4) reference no. 0156-000-DA-1101 (S-1), 0156-000-DA-1102 (S-1), 0156-000-DA-1103 (S-1), 0156-000-DA-1104 (S-1))
- Component Manufacturer master file includes a high level overview of the device dimensions and functional specifications
- Combination Product Specifications (Biogen Idec reference no. SPEC-28666, SPEC-28667, and SPEC-28794)
- Design Review I ((b) (4) reference ((b) (4) date ((b) (4))
- Design Review II ((b) (4) reference ((b) (4) date ((b) (4))
- Technology Transfer (Biogen Idec reference number GLBL-19225)
- DMR Index (Biogen Idec reference no. RECD-39421)
- Change Management (Biogen Idec reference number GLBL-100800)
- Design History File (Component Manufacturer reference no. ((b) (4) 0156-000)
- Global Change Control Operations (Biogen Idec reference number PRCD-29819)

Purchase Controls: SOPs or other documentation was provided and addressed 21 CFR 820.50. The documentation appeared to be adequate. Per the firm, supplier selection and evaluation, and material receipt and control are managed using the following documents:

- Supplier Management (GLBL-24239)
- Materials Management (GLBL-24425)
- Specifications (GLBL-3908)
- Quality Control Laboratory Management (GLBL-24541)

Corrective And Preventative Actions: Standard Operating Procedures SOPs or other documentation was provided and addressed 21 CFR 820.100. The documentation appeared to be adequate. Per the firm, the identification and implementation of corrective and preventative actions resulting from investigations of complaints, product rejections, deviations, recalls, audits, regulatory inspections and findings, annual product review, and trends from process performance and product quality monitoring are managed using the following document:

- Corrective Action and Preventative Action (GLBL-24504)

Per the firm, corrective actions are taken to eliminate the cause of nonconformities in order to prevent recurrence. Preventative actions are identified and implemented to eliminate the causes of potential nonconformities to prevent occurrence. Records of all such actions are generated and maintained. Related CAPAs and deviations received from the Component Manufacturer are tracked and monitored as outlined in Article 9 of their Quality Agreements.

Deficiencies to be conveyed to the applicant

There are no deficiencies to be relayed to the applicant.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application BLA 125499 and has the following recommendations:

Application BLA 125499 approvability under the Medical Device Regulations should be delayed until the inspection of [REDACTED] ^{(b) (4)} has been completed, the FDA 483 and EIR have been reviewed, and the site is deemed acceptable. The desk review of the application for compliance with the Medical Device Regulations showed no apparent deficiencies.

Felicia L. Brayboy

Felicia L. Brayboy

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

/s/

NICOLE L BRADLEY

01/25/2014

Checking into DARRTS for Felicia Brayboy

Memorandum for the Record:

DNP consulted PMHS 5/17/2013 asking for review of this BLA and to assist with PeRC and any pediatric issues that may arise during the review of this BLA (BLA 125499).

PMHS reviewed the synopsis of the intended pediatric plan and participated in the filing meeting (July 2, 2013) and the mid-cycle meeting (October 2, 2013) for this BLA. DNP stated that the plan to waive pediatric studies in children younger than 10 years, and defer studies in children ages 10 to 17 years is consistent with the development plan for other recently approved drugs for this indication (treatment of multiple sclerosis). At the mid-cycle meeting the DNP project manager and clinical reviewer stated that PMHS participation in PeRC preparation would not be required. Per responses to the PMHS emails sent to the division on September 5 and 10, 2013, and per DNP's response at the mid-cycle meeting, no additional review or action is requested from PMHS at this time and DNP will notify PMHS if additional PMHS assistance with this BLA is required.

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

/s/

DENISE J PICA-BRANCO
10/18/2013

ETHAN D HAUSMAN
10/18/2013

ROSEMARY M ADDY
10/24/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, Packaging, and Usability Study Review

Date: October 17, 2013

Reviewer: Sue (Liu) Liu, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Plegridy (Peginterferon beta-1a) Injection
Plegridy Pen (Peginterferon beta-1a) Injection
63 mcg/0.5 mL, 94 mcg/0.5 mL, 125 mcg/0.5 mL

Application Type/Number: BLA 125499

Applicant/sponsor: Biogen Idec

OSE RCM #: 2013-1291, 2013-1294, 2013-1295

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review responds to a request from the Division of Neurology Products (DNP) to evaluate, from a medication error perspective, the results from the validation usability studies and the proposed labels and labeling for Plegridy (Peginterferon beta-1a) Injection and Plegridy Pen (Peginterferon beta-1a) Injection. If approved, this product will be the first pegylated formulation of interferon beta-1a available on the market. The Applicant is proposing to market both prefilled syringe and injection device (pen) packaging presentations.

1.1 PRODUCT INFORMATION

The following product information is provided in the draft labeling received on August 2, 2013.

- Active Ingredient: Peginterferon beta-1a
- Indication of Use: Treatment of patients with relapsing forms of multiple sclerosis
- Route of Administration: Subcutaneous
- Dosage Form: Injection
- Strength (pen and syringe): 63 mcg/0.5 mL, 94 mcg/0.5 mL, and 125 mcg/0.5 mL
- Dose and Frequency: Peginterferon beta-1a is dosed every 2 weeks. It is generally recommended that patients titrate the dose as follows:

Dose	Time*	Dose (micrograms)	Color Differentiation of Strength
Dose 1	Day 1	63	Orange
Dose 2	Week 2	94	Blue
Dose 3	Week 4 and every 2 weeks thereafter	125 (full dose)	Grey

*Dosed every 2 weeks

- How Supplied:
 - Plegridy Pen (Single-Use Prefilled Pen) and Plegridy (Single-Use Prefilled Syringe)
 -  (b) (4)
 - Carton containing two single-use prefilled pens or syringes, each providing 125 mcg (administration dose pack)
 - Starter Pack containing two single-use prefilled pens or syringes: dose 1 provides 63 mcg and dose 2 provides 94 mcg

- Storage:
 - Store in the closed original carton to protect from light until ready for injection. Store in a refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze. Discard if frozen. (b) (4) Once removed from the refrigerator, Plegridy should be allowed to warm to room temperature (about 30 minutes) prior to injection. Do not use external heat sources such as hot water to warm Plegridy.
 - Should refrigeration be unavailable, Plegridy may be stored between 2°C to 25°C (36°F to 77°F) for a period up to 30 days, protected from light. Plegridy can be removed from and returned to the refrigerator if necessary. The total combined time out of refrigeration, within a temperature range of 2°C to 25°C (36°F to 77°F), should not exceed 30 days.
- Container and Closure Systems:
 - Single-Use Prefilled Pen: Each unit of Plegridy is stored in a 1 mL glass syringe with a (b) (4) rubber stopper and rigid needle shield. A 29 gauge, 0.5 inch, staked needle is pre-affixed to the syringe. The glass syringe is contained within a single-use, disposable, injection device (pre-filled pen).
 - Single-Use Prefilled Syringe: Each unit of Plegridy is stored in a 1 mL glass syringe with a (b) (4) rubber stopper and rigid needle shield. A 29 gauge, 0.5 inch, staked needle is pre-fixed to the syringe.

2 METHODS AND MATERIALS REVIEWED

DMEPA evaluated the results from the validation usability studies and the proposed labels, labeling, and packaging design for Plegridy (Peginterferon beta-1a) Injection and Plegridy Pen (Peginterferon beta-1a) Injection.

2.1 VALIDATION HUMAN FACTORS STUDIES

We evaluated the study reports that provide the results from two validation usability studies, one conducted for the prefilled syringe and one conducted for the pen device, submitted by the Applicant on May 16, 2013. Additionally, we evaluated the supplemental IFU study results. The supplemental IFU study was conducted due to changes made to the IFU after completion of the validation usability study.

2.2 LABELS AND LABELING

Using the principles of Human Factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Device Labels (Pen and Syringe) received 5/16/13 (Appendices A & B)
- Carton Labeling (Pen and Syringe) received 5/16/13 (Appendices C to H)
- Tray Labeling (Syringe) received 5/16/13 (Appendices I & J)
- Instructions for Use (IFU) (Pen and Syringe) received 5/16/13 (No image)
- Medication Guide (MG) received 5/16/13 (No image)
- Package Insert (PI) received 8/2/13 (No image)
- Information Request (IR) responses received June 17, 2013, August 20, 2013, August 23, 2013, and September 4, 2013 (No image)

3 VALIDATION STUDY DESIGN AND RESULTS

The following section describes the design of the validation usability studies conducted by the Applicant and the results reported.

3.1 VALIDATION USABILITY STUDIES FOR PLEGRIDY PREFILLED SYRINGE (PFS) AND PLEGRIDY PEN

3.1.1 Study Design

The purpose of the validation usability studies was to 1) assess the ability of intended users to safely and effectively use the prefilled syringe in both starter and administration dose pack presentations and 2) assess the ability of intended users to select the correct dose for administration.

There were 45 participants in each validation usability study:

- 15 patients (P) with confirmed MS diagnosis
- 15 caregivers (C) that currently administer medications to MS patients
- 15 healthcare providers (N, all nurses) that currently administer training, medication to MS patients

Participants did not receive training prior to the use assessment and were not required to read the IFU prior to performing the use assessment. During the study participants were allowed to refer to the IFU at any time but were not required to do so.

For the first task, each participant was provided both a Starter Pack and Administration Dose Pack and asked to hand the moderator the syringe needed to inject the first dose, the dose on day 14, and the dose on day 28 of treatment. Each participant was then asked to prepare and perform a simulated injection of the administration dose into an injection pad through a series of subsequent tasks. Following completion of the tasks, the moderator asked questions to investigate root cause(s) of any steps “performed with difficulty” or “failed.” The moderator also asked questions regarding the ease of understanding each step in the IFU.

3.1.2 Validation Study Results for Plegridy PFS

Participants were required to complete 14 tasks, 2 of which were deemed critical: quickly insert the needle and slowly push the plunger (see Table 1 in Appendix K). The Applicant reported that all participants were able to successfully use the prefilled syringe

without failure on any critical tasks; however, two participants experienced difficulty with accomplishing the critical task of quickly inserting the needle.

Additionally, there were failures identified with essential and desirable tasks. See Appendix K for a table that shows the failures and observed difficulties, separated by task, that were seen in this validation usability study. After completion of tasks, subjective feedback was given by participants. Appendix K also summarizes the subjective feedback reported in the study results. Since the completion of the validation usability study for the prefilled syringe, the Applicant has made additional changes to the IFU. These changes are described in Appendix K.**3.1.3 Validation Study Results for Plegridy Pen**

Participants were required to complete 15 tasks, 1 of which was deemed critical: Press into site and hold until clicking stops and green checkmark appears (see Table 4 in Appendix L). The Applicant reported that 40 out of 45 participants (89%) were able to successfully use the pen without failure on the critical task. However, 2 participants experienced difficulty with the critical step.

Additionally, there were failures identified with essential and desirable tasks. See Appendix L for a table that shows the failures and observed difficulties, separated by task, that were seen in this validation usability study. After completion of tasks, subjective feedback was given by participants. Appendix L also summarizes the subjective feedback reported in the study results.

Since the completion of the validation usability study for the prefilled syringe, the Applicant has made additional changes to the IFU. These changes are described in Appendix L.

3.2 SUPPLEMENTAL IFU STUDY (PLEGRIDY PEN)

3.3.1 Study Design

The purpose of this validation study was to assess whether the revised IFU adequately mitigates the failures seen in the Plegridy Pen validation usability study and will allow for safe and effective use of the pen starter and administration dose packs.

The study included 16 participants:

- 11 patients (P) with MS diagnosis
- 5 caregivers (C) that currently administer medications to MS patients

For all of the tasks in the study, participants were asked to read the instruction aloud, perform the step, and then provide feedback on the clarity of the instruction. For the first task, each participant was provided both a Starter Pack and Administration Dose Pack and asked to hand the moderator the pen needed to inject the first dose, the dose on day 14, and the dose on day 28 of treatment. Each participant was then asked to prepare and perform a simulated injection of the administration dose into an injection pad through a series of subsequent tasks.

3.3.2 Study Results

Participants were required to complete 15 tasks, 1 of which was deemed critical: Press into site and hold until clicking stops and green checkmark appears. See Appendix M for

a table that shows the observed failures, observed difficulties, and IFU feedback, separated by tasks, which were reported. See Table 4 in Appendix L for a full list of all 15 tasks that participants were required to complete.

In addition to the feedback noted in Appendix M, one participant indicated that she thought the disposal step was misplaced and should be moved before the “Care for Injection Site” step. Another participant indicated he would expect the “Verify Dose Delivery” step to occur before the “Care for Injection Site” step.

4 RISK ANALYSIS

The following sections describe our analysis of safety concerns identified during this review.

4.1 USABILITY OF PREFILLED SYRINGE

Our review of the results of the validation usability study for the prefilled syringe (PFS) has determined that the Applicant has not achieved their first objective of demonstrating the safe and correct use of the PFS. Although no failure associated with a critical task identified by the Applicant was observed, multiple failures were observed with essential and desired tasks during the study. The study report indicates that 80% of participants did not record the date and location of their injection, 56% of participants did not allow the PFS to sit for 30 minutes to allow the medication to warm to room temperature, and 42% of participants did not check the expiration date prior to injection. We do not consider these critical tasks; however, the large number of participants that committed errors with these tasks is concerning and suggests that additional improvements can be made. We note that there was a 38% failure rate with the task of waiting 5 seconds before removing the needle, but we expect the full dose of medication to be injected prior to this task based on the sequence of tasks laid out in the IFU. In the occasional event that the needle is pulled away prior to full depression of the plunger, resulting in an underdose, we do not expect a clinically meaningful risk to the patient. It is unlikely that further design changes to the syringe can mitigate the risk for these failures. Therefore, changes can be made to the IFU to bring prominence and clarify instructions that were associated with failures and performance difficulty during the usability study.

The Applicant also did not achieve their second objective of demonstrating users can select the correct dose for administration for the PFS. The Applicant did not consider this a critical task; however, wrong dose selection can result in overdoses or underdoses, and we consider this a critical task. We are especially concerned with overdoses since the intent of the Starter Pack and titration is to minimize the adverse events that can occur at the beginning of therapy. We believe these failures can be addressed through improved strength differentiation within the product line and the addition of label and labeling statements for clarity. During subjective feedback some participants expressed confusion over the labeling (b) (4)

One participant indicated that the label contains a lot of information; making it difficult to identify the name, dose, and expiration of the product (it’s unclear from the report if this participant was referring to the syringe label or other labeling). We also note that the Applicant has (b) (4)

in the IFU and insert labeling. We believe this adds to the confusion regarding when injections should be administered. Therefore, we recommend the applicant refer to

the injection schedule by days only (i.e. Day 1, Day 14, Day 28, and every 14 days thereafter) for clarity. We will provide recommendations for the IFU to address these failures.

Overall, we will not require the applicant to perform another validation usability study for the PFS since we do not believe additional changes to the PFS can mitigate the failures and performance difficulty seen in the usability study; however, any revisions made to the IFU will require validation.

4.2 USABILITY OF PEN

Our review of the results of the validation usability study for the pen and the supplemental IFU study has determined that the Applicant did not achieve their first objective of demonstrating the safe and correct use of the pen. After the validation usability study was conducted, the Applicant made additional changes to the IFU based on failures they identified in the study. The Applicant then conducted a supplemental IFU study to validate the changes to the IFU.

In the original validation usability study for the pen, 5 participants (11%) experienced failures with the critical task of pressing the pen into the injection site and holding until the injection was completed. In both the validation usability study and the supplemental IFU study, participants reported being scared by the clicking sound or confused into believing that something had been done wrong. The Applicant attempted to address these failures by (b) (4). However, we do not believe this intervention fully addresses all root causes of the failures since the same failure occurred with a participant in the supplemental IFU validation study who indicated that she did not expect such a loud clicking noise. We recognize that an audible cue may be useful for patients that have visual impairments; however, it appears that additional improvements can be made to the IFU to warn patients of the clicking noise and minimize the risk of patients being startled by an unexpected sound. Additionally, the Applicant should consider whether the noise may be excessive and whether decreasing the sound will still allow for an auditory cue without eliciting the startled reaction from users.

In addition to the failures observed with pressing the pen into the injection site and holding until the injection was completed, participants also experienced difficulty when they did not fully depress and locked out their pens. Two participants in the validation usability study (both patients) and 2 participants in the supplemental IFU study (1 patient, 1 caregiver) experienced (b) (4). Of the 2 participants in the supplemental IFU study, 1 participant (caregiver) noted (b) (4).

(b) (4) The ability of the pens to (b) (4) is concerning and may represent a design flaw that should be further investigated by CDRH and the Applicant. (b) (4)

(b) (4) Our concerns were communicated to the CDRH device engineering reviewer for further investigation.

Additionally, we observed failures in removing the cap. During both the validation study and the supplemental IFU study, participants experienced performance difficulty when removing the cap (16% and 3% of participants respectively). In the validation study, 6 participants (4 patients, 1 caregiver, 1 nurse) had difficulty with either the force required for removal or gripping the device, and 1 participant (nurse) thought the cap was “twist off” even though the IFU states to “pull the cap off.” We question whether the force that is necessary to pull off the cap may be excessive given the intended patient population. Furthermore, during the supplemental IFU study for the pen, one participant expressed physical difficulty removing the cap, and two participants experienced performance difficulties after the cap was removed that required moderator intervention due to potential safety risks. In both cases, the participants tried to manipulate the needle guard. One participant tried to remove the needle guard thinking it was part of the cap. The other participant tried to push down on the needle guard to see the needle. It unclear what led to these behaviors; however, we are concerned with these unanticipated behaviors since they may result in needle-stick injury and may also lead to sterility problems. The Applicant will need to further investigate this issue and determine if changes to the device and/or labeling will be required.

In the validation usability study for the pen, there were also failures observed with essential and desired tasks during the study similar to those seen with the PFS validation study. We note that 36% of participants did not verify the dose delivery by checking the yellow plunger rod, and 13% of participants experienced performance difficulty when checking the yellow plunger rod. However, there is an audible cue along with a separate visual cue with this product that offers a measure of reassurance that users can determine when their injection is complete through other means. Additionally, 25% of participants experienced performance difficulty with checking the injection status by looking for green stripes before injection. Some participants indicated it was difficult to find the stripes on the pen because the IFU is unclear. The Applicant will need to consider what actions can be taken with the labels and labeling to mitigate the risk for failures observed with essential and desired tasks.

Like the PFS validation usability study, the Applicant did not achieve their second objective of demonstrating users can select the correct dose for administration for the pen injector. We consider this a critical task. Several participants indicated the blue and gray colors currently utilized to differentiate the 94 mcg and 125 mcg doses were too similar, which we agree with. Additionally, during subjective feedback some participants expressed confusion over the labeling of days vs. weeks or felt the doses should be designated as dose 1, dose 2, etc. We will provide recommendations for the labels and labeling to address these failures.

4.3 LABELS, LABELING, AND PACKAGING

(b) (4)

[REDACTED] We do not agree with this approach. [REDACTED]

[REDACTED] We recommend the Applicant creates a separate IFU for each pack that does not include information regarding doses that are not packaged in the pack.

Our review of the labels and labeling determined there is inadequate strength differentiation within the product line. In the validation human factors studies, some participants indicated that the blue and gray colors are very similar, and we agree. We recommend the Applicant revise the color differentiation scheme of either the 94 mcg or 125 mcg pen and prefilled syringe. This change in color differentiation scheme should be carried throughout all the labels and labeling for this product.

Additionally, our risk assessment of the proposed labels, labeling, and packaging identified areas of concern which can be improved for clarity, to increase the readability and prominence of important information on the labels, and to promote the safe use of the product. We provide recommendations in Section 5 below.

5 CONCLUSIONS

The Applicant has not demonstrated usability of the prefilled syringe. For the prefilled syringe, it is unlikely that further design changes to the syringe can mitigate the failures and performance difficulties observed in the validation study. Instead, we will provide recommendations for the IFU to bring prominence to and clarify instructions that were associated with failures and performance difficulty during the usability study. We would like the Applicant to validate the changes to the IFU based on our recommendations prior to approval of the prefilled syringe.

The Applicant has not demonstrated usability of the pen. Some failures and unintended behaviors identified in the studies will require the Applicant to conduct another risk analysis and consider what further modifications to the pen device and the user interface, including labels and labeling, are required to eliminate or reduce the failures and performance difficulties seen in the validation study and the supplemental IFU study. Any changes made should be validated in another usability study with the intended-to-market commercial presentation of the product and associated labels and labeling.

Additionally, we conclude that the proposed labels, labeling, and packaging can be improved to minimize confusion and increase the readability and prominence of important information in order to promote the safe use of the product and clarify information. We provide recommendations in Section 6 below that should be conveyed to the Applicant.

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

6 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA supplement:

A. Comments to the Division

1. Insert Labeling, *Full Prescribing Information (FPI), Section 2*

- a. Relocate the “Treatment initiation” section above the statement “The recommended dosage of Plegridy is 125 mcg injected subcutaneously...” since dose titration occurs prior to establishment of a maintenance dose.

- b. (b) (4)

We recommend revising Table 1 in Section 2 *Dosage and Administration* as follows:

Dose	Time*	Amount (micrograms)
Dose 1	Day 1	63
Dose 2	Day 14	94
Dose 3 and Maintenance Dose	Day 28 and every 14 days thereafter	125 (maintenance dose)

*Dosed every 14 days

- c. Under Section 2.2 *Important Administration Instructions*, we recommend clarifying whether injections into the upper arm are in the back or front of the upper arm.
- d. Under Section 2.3 *Premedication for Flu-like Symptoms*, if there are specific analgesics or antipyretics that were studied with Plegridy, we recommend including that information.

2. Insert Labeling, *Highlights of Prescribing Information (HPI)*

- a. We recommend relocating the statement “Plegridy may be titrated...” to above the statement “Recommended dose: 125 micrograms...” since dose titration occurs prior to establishment of maintenance dose.
- b. Under the Dosage and Administration section, revise the dose schedule based on recommendation A1b above.

3. Medication Guide

- a. We recommend including information on the appropriate sites of injection in the *How Should I use Plegridy* section before the statement “Change (rotate) the injection site....”.

B. Comments to the Applicant

1. Usability of Plegridy Prefilled Syringe

- a. You have not demonstrated usability of the Plegridy Prefilled Syringe. You did not achieve your second objective of demonstrating users can select the correct dose for administration for the PFS. While you do not consider this a critical task, wrong dose selection can result in overdoses or underdoses, and we consider this a critical task. Additionally, there were multiple failures that occurred with essential and desired tasks. For the prefilled syringe, it is unlikely that further design changes to the syringe can mitigate the failures and performance difficulties observed in the validation study. We provide recommendations below for the IFU to minimize confusion and bring prominence to and clarify instructions that were associated with failures and performance difficulty during the usability study (see B4 below). You will be required to validate the changes to the IFU prior to approval of the prefilled syringe. Submit the results from your IFU validation study for review.

2. Usability of Plegridy Pen

- a. You have not demonstrated usability of the Plegridy Pen. Based on the failures and unintended behaviors observed in your validation studies, you will need to conduct another risk analysis and consider what further modifications to the pen device and the user interface, including labels and labeling, are required to eliminate or reduce the failures and performance difficulties seen in the validation study and the supplemental IFU study. Any changes made should be validated in another usability study with the intended-to-market commercial presentation of the product and associated labels and labeling.
- b. In both the validation usability study and the supplemental IFU study, participants reported being scared by the clicking sound or confused into believing that something had been done wrong. You attempted to address these failures by (b) (4).
However, we do not believe this intervention fully addresses all root causes of the failures since the same failure occurred with a participant in the supplemental IFU study who indicated that she did not expect such a loud clicking noise. We recognize that an audible cue may be useful for patients that have visual impairments; however, it appears that additional improvements can be made to the IFU to warn patients of the clicking noise and minimize the risk of patients being startled by an unexpected sound. Additionally, you should consider whether the noise may be excessive and whether decreasing the sound will still allow for an auditory cue without eliciting a startled reaction from users.
- c. Two participants in the validation usability study (both patients) and two participants in the supplemental IFU study experienced pen (b) (4). Based on your study results, we request you re-evaluate (b) (4).
The ability

pack that does not include information regarding doses that are not packaged in the pack.

- b. In your validation usability study, failures were observed with essential and desired tasks during the study (e.g. 80% of participants did not record the date and location of their injection, 56% of participants did not allow the PFS to sit for 30 minutes to allow the medication to warm to room temperature, and 42% of participants did not check the expiration date prior to injection). These failures suggest the contents and design of your proposed IFU have not been optimized. We recommend you conduct a new risk analysis and consider the failures and performance difficulty observed, along with the subjective feedback collected, to make changes to your IFU. You will be required to validate the changes to the IFU prior to approval of the prefilled syringe. Submit the results from your IFU validation study for review.
- c. Per the Division of Medical Policy Programs' (DMPP) Patient Labeling Team, IFUs are generally organized as follows:
 - 1) Standard header
 - 2) Bulleted list of all the supplies needed to complete the task, including an illustration of all supplies needed.
 - 3) Patient instructions that are not sequential should be bulleted.
 - 4) Patient instructions that are sequential should be labeled as "Step 1, Step 2" etc.
 - 5) Figures should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related text. The figures should be labeled as "Figure A, Figure B" etc.
 - 6) Within the figures there should be detailed labeling for each part of any device that the patient expected to become familiar with.
 - 7) Refer to each figure at the end of each numbered step. For example, at the end of Step 1, say (See Figure A).
 - 8) Storage information as stated in the Prescribing Information (PI) should appear at the end of the IFU if the IFU will be a separate document. If the Patient Information and IFU are combined, the storage information should appear in the Patient Information only.
 - 9) Disposal information. If needles, syringes or injectable Pens are used to prepare or deliver the drug, disposal language should be consistent with the FDA "Safe Sharps Disposal" website language.
 - 10) Other pertinent miscellaneous instructions to the patient
 - 11) Manufacturer name and address
 - 12) If the IFU is a stand-alone document, add the statement "These Instructions for Use have been approved by the U.S. Food and Drug Administration."

13) If the IFU is attached to the Medication Guide, add the statement, “This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.”

14) “Approved” Month/Year

- d. Per the Division of Medical Policy Programs’ (DMPP) Patient Labeling Team, patient labeling materials should meet the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006).
 - e. Per the Division of Medical Policy Programs’ (DMPP) Patient Labeling Team, patient labeling materials should utilize simple wording and clear concepts where possible and should be consistent with the Prescribing Information. Do not use complex medical terminology.
 - f. Per the Division of Medical Policy Programs’ (DMPP) Patient Labeling Team, to enhance comprehension and readability, patient labeling materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. The grade level of your proposed prefilled syringe Instructions for Use (IFU) is 7.2 and the reading ease is 63.1%.
 - g. Per the Division of Medical Policy Programs’ (DMPP) Patient Labeling Team, patient labeling materials should be in fonts such as Verdana or Arial at font size 11 or greater to make medical information more accessible for patients with vision loss. We recommend Verdana 11, point font.
 - h. Per the Division of Medical Policy Programs’ (DMPP) Patient Labeling Team, do not use underlining, italics, all capital letters or text boxes in patient labeling as it is difficult to read for patients with vision loss. Consider using bolded text instead to highlight important information.
 - i. Per the Division of Medical Policy Programs’ (DMPP) Patient Labeling Team, use bolding for headers and to highlight important text only. Overuse of bolding minimizes the importance of certain important information for the patient.
 - j. Under “Choose the Injection Site”, it is unclear whether the third image represents the back or front of arms; therefore, revise the image to include the text “back of upper arms” if the intended site of administration is back of arms.
5. Instructions for Use (IFU): Prefilled Pen
- a. See recommendation 2b, 4a, and 4c through 4j above.
 - b. To enhance comprehension and readability, patient labeling materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. The grade level of your proposed prefilled pen IFU is 8.0 and 58.8%.

- c. In your validation usability study, failures were observed with essential and desired tasks during the study (e.g. 80% of participants did not record the date and location of their injection, 56% of participants did not allow the PFS to sit for 30 minutes to allow the medication to warm to room temperature, and 42% of participants did not check the expiration date prior to injection). These failures suggest the contents and design of your proposed IFU have not been optimized. We recommend you conduct a new risk analysis and consider the failures and performance difficulty observed, along with the subjective feedback collected, to make changes to your IFU. For example, consider whether relocating the subsection (b) (4)
- The results of your usability testing suggest users overlook this information in the last panel. You will be required to validate the changes to the IFU prior to approval of the pen.
- d. (b) (4) We recommend improving the contrast between the green check mark and the background.
- e. Ensure any image of the pen is an accurate depiction of what users will see in real life.
6. Pen Device Label (all strengths)
- a. (b) (4)
- b. Revise the route of administration statement to “For subcutaneous use only” and move it directly beneath the statement of strength.
7. Pen Carton Labeling (all configurations)
- a. (b) (4)
- b. (b) (4)
- c. Ensure the proprietary name, proper name, dosage form, strength, and route of administration are the most important information conveyed on the PDP.
- d. Ensure that the presentation of the entire proprietary name is in the same font style and size. As currently presented (b) (4)
- e. Ensure that the proper name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

- f. Revise the presentation of the proprietary name [REDACTED] (b) (4) to title case “Plegridy Pen”.
 - g. Increase the font size of the strength statement and utilize the appropriate color for strength differentiation for boxing or highlighting the statement of strength to improve strength differentiation in the product line.
 - h. Relocate the manufacturer’s name logo to the bottom of the Principal Display Panel (PDP) or the side panel.
 - i. Revise the statement “[REDACTED] (b) (4)” to “Usual Dosage: See package insert” and move this statement to the back panel.
 - j. See recommendation 6b above.
8. [REDACTED] (b) (4)
- a. [REDACTED] (b) (4).
 - b. [REDACTED] (b) (4).
 - c. [REDACTED] (b) (4).
 - d. [REDACTED] (b) (4).
 - e. [REDACTED] (b) (4).
9. Pen Carton Labeling, (2 autoinjectors, 125 mcg)
- a. See comments 6b, 8b, 8c, and 8e above.
 - b. [REDACTED] (b) (4)
10. Pen Carton Labeling, Starter Pack
- a. See comment 6b above.
 - b. The statement of strength is missing. Both 63 mcg/0.5 mL and 94 mcg/0.5 mL should be added underneath the dosage form.
 - c. [REDACTED] (b) (4)
- [REDACTED] We recommend the use of

a completely different color that does not overlap with the colors chosen for strength differentiation within the product line. Additionally, ensure the “Starter Pack” statements are not more prominent than the proprietary name, proper name, dosage form, and strength statements.

- d. Under “Contents” on the PDP, revise to include the dose number similar to the following:

Dose 1: 1 single-use 63 mcg/0.5 mL prefilled autoinjector

Dose 2: 1 single-use 94 mcg/0.5 mL prefilled autoinjector

- e. [REDACTED] (b) (4).

11. Prefilled Syringe Label (all strengths)

- a. Revise the presentation of the proprietary name, proper name, dosage form, strength, and route of administration as follows:

Plegridy

(peginterferon beta-1a)

Injection

X mcg/Y mL single-use prefilled syringe

For subcutaneous use only

[REDACTED] (b) (4)

12. Syringe Tray Labeling, all strengths

- a. See recommendations 6b, 7c, 7g, and 11a above.

- b. [REDACTED] (b) (4)

13. Syringe Carton Labeling (all configurations)

- a. Remove [REDACTED] (b) (4).

- b. See recommendations 6b, 7b, 7c, 7e, 7f, 7g, 7h, and 7i above.

14. [REDACTED] (b) (4)

- a. See comments 6b, 8b, and 8d above.

- b. Remove [REDACTED] (b) (4).

- c. Remove [REDACTED] (b) (4).

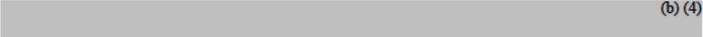
15. Syringe Carton Labeling, (2 syringes, 125 mcg)

a. See comments 6b, 8b, 14b, and 14c above.

b.  (b) (4)

16. Syringe Carton Labeling, Starter Pack

a. See recommendation 6b, 10b, 10c, and 10d above.

b.  (b) (4)

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

IRENE Z CHAN
10/17/2013

CAROL A HOLQUIST
10/17/2013



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 10, 2013

To: Eric Bastings, MD, Acting Director
Division of Neurology Products (DNP)

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Lori A. Love, M.D., Ph.D., Senior Medical Officer
Controlled Substance Staff

Subject: BIIB017 (PEGylated interferon beta-1a) BLA 125,499
Indication: Relapsing multiple sclerosis (MS)
Dosages: 125 µg Q2W as a Single-Dose subcutaneous injection -prefilled syringe and pen
Sponsor: Biogen Idec

Materials reviewed: Biogen's response to the FDA Filing letter dated 07/15/13 [Seq 0008]

1 Background

In the Filing letter dated 07/15/13 to the Sponsor on BLA 125,499 for BIIB017 (PEGylated interferon beta-1a or PEG INFβ-1a), CSS noted that the abuse potential materials submitted in the BLA did not include an in vitro abuse related receptor binding panel as discussed at the pre-BLA meeting. Biogen responded in Seq 0008, forwarded in an email from Nicole Bradley on August 2, 2013 [See below].

We provided an interim response on 08/15/2013. From our further review of the Sponsor's rationale for not conducting specific abuse potential studies, information in the BLA and the scientific literature, we provide the following recommendation and conclusions.

2 Recommendation and Conclusions:

CSS does not recommend further abuse potential characterization, including the conduct of a receptor binding study on INFβ-1a (and thus PEG INFβ-1a), based on the following properties of the substance, INFβ-1a:

1. We have found no evidence of abuse of INFβ-1a, following more than 16 years of marketing.

2. INFβ-1a and PEG INFβ-1a do not have opioid, cannabinoid, nicotinic, hallucinogen, stimulant, or depressant properties.
3. INFβ-1a and thus PEG INFβ-1a is not a prodrug of a drug of abuse.
4. INFβ-1a and PEG INFβ-1a are not chemically or pharmacologically related to a drug of abuse.
5. INFβ-1a and PEG INFβ-1a do not have active metabolites that are drugs of abuse.
6. INFβ-1a has a very long Tmax. Furthermore, pegylation of INFβ-1a increases the Tmax.
7. INFβ-1a and PEG INFβ-1a cannot be taken orally.

3 Discussion

Properties of the active drug substance, interferon beta-1a [INFβ-1a]

The active drug substance in PEGylated interferon beta-1a, has been marketed in the US since 1996 [BLA 103628 Avonex] for the treatment of relapsing remitting MS, an orphan disease designation. There is no postmarketing evidence of abuse and misuse; the safety data base comprises more than 400,000 patients and 1.6 million person-years of exposure to Avonex. **INFβ-1a** is currently registered in more than 80 countries.

INFβ-1a belongs to the well characterized class of beta interferons that are immunomodulators that bind to the type I interferon receptor on the surface of cells, which results in the regulation of interferon-responsive gene expression. These genes and their gene products are believed to mediate the efficacy of BIIB017 in MS.

Although a specific mechanism of action in MS has not been identified, it is thought to work by balancing pro-and anti-inflammatory agents in the brain and by preventing efflux of immune cells across the blood brain barrier.

INFβ-1a is a large protein molecule ~20KDa that must be injected to prevent digestion in the GI tract.

PEGylated interferon beta-1a

PEG INFβ-1a [BIIB017] is a glycosylated recombinant interferon beta-1a that is pegylated with a single 20kDa methoxypoly (ethyleneglycol)-O-2 methylpropionaldehyde (mPEG) moiety at the N-terminus of the protein.

Pegylation alters the formulation to enhance patient compliance by permitting less frequent injection [once every 2 weeks, instead of every week] and altering the administration route from intramuscular to subcutaneous.

The Cmax for PEG INFβ-1a [BIIB017] is reached between 1 to 1.5 days post-dosing (Tmax) (compared to Avonex Tmax: 15 hrs)]. The T½ is approximately 2 -3 days in MS patients (compared to Avonex's T½ life: 19 hours).

FDA Filing letter: Reference ID: 3341086 07/15/2013

Controlled Substance Staff

4. The abuse potential materials that were submitted in the BLA did not include an *in vitro* abuse-related receptor binding panel. We ask that you specify whether or not you intend to submit these data during the review cycle. Alternatively, if you believe that these data would not provide relevant information, you may provide scientific justification (with supportive data) for not conducting this study.

Biogen response: Seq 0008 Response to Filing Letter Requests Received 15-Jul-2013

RESPONSE 4

As discussed in Section 2.4.8 of the original BLA submission, abuse liability studies are not necessary for BIIB017 as BIIB017 belongs to the class of beta interferons which has a very well characterized safety profile and are not characterized as being drugs of potential abuse. None of the class members are currently controlled substances or subject to special instructions for use, handling, or disposal [Avonex® Prescribing Information 2013, Betaseron® Prescribing Information 2013, Rebif® Prescribing Information 2013]. While a definitive mechanism of action of BIIB017 in MS is not known, the potential mechanism is not consistent with CNS effects that could be associated with the potential for abuse. BIIB017 binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. These genes, and their gene products, are believed to mediate the efficacy of BIIB017 in multiple sclerosis. Furthermore, the preclinical safety studies that included daily detailed clinical observations and a histopathological analysis of the brain and CNS did not show any specific CNS related adverse events or behavioral changes.

From clinical trial data, the safety profile of BIIB017 is primarily associated with injection site reactions (e.g. erythema, pain, pruritus) and flu like symptoms (e.g. headache, pyrexia, myalgia, chills, and pain). The safety profile does not show the presence of any type of rewarding effects or other abuse-related behaviors related to drug abuse (e.g., mood elevation, euphoria, hallucination, sedation, somnolence, insomnia, cognitive disorder, anxiety). The majority of these events were rare (<1%), and no imbalances were observed between the placebo- and BIIB017-treated subjects for any of the terms. No cases of intentional overdose or drug abuse or rebound withdrawal effects have been reported in clinical studies with BIIB017 (2.7.4 Summary of Clinical Safety, Section 5). Thus, BIIB017 has a low potential for abuse and should not be considered a controlled substance.

If after the review of the nonclinical and clinical data, the Agency requires an abuse-related receptor binding panel study for BIIB017 then, consistent with the minutes from the Sponsor's pre-BLA Meeting (March 12, 2013), the study will be conducted as part of a post-marketing requirement for subsequent evaluation.

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

/s/

LORI A LOVE
10/10/2013

SILVIA N CALDERON
10/10/2013

MICHAEL KLEIN
10/10/2013



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 16, 2013

To: Eric Bastings, MD, Acting Director
Division of Neurology Products (DNP)

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Lori A. Love, M.D., Ph.D., Senior Medical Officer
Controlled Substance Staff

Subject: BIIB017 BLA 125,499
Indication: Relapsing multiple sclerosis
Dosages: 125 µg Q2W as a Single-Dose subcutaneous injection -prefilled syringe and pen
Sponsor: Biogen Idec

Materials reviewed: Biogen's response to the FDA Filing letter dated 07/15/13 [Seq 0008] and FDA Filing letter: Reference ID: 3341086 07/15/2013

1 Background

In the Filing letter dated 07/15/13 to the Sponsor, CSS noted that the abuse potential materials submitted in the BLA did not include an in vitro abuse related receptor binding panel as discussed at the pre-BLA meeting. Biogen responded in Seq 0008, forwarded in as an email from Nicole Bradley on August 2, 2013 [See attachment below].

2 Recommendation and Conclusions:

1. We acknowledge Biogen's response. We will continue our review of all available data so as to evaluate the adequacy of the abuse potential assessment for BIIB017 (PEGylated interferon beta-1a), including the need for an in vitro abuse related receptor binding panel.
2. Any requirement for an in vitro abuse related receptor binding receptor panel would not preclude approval and marketing (if approved).

Attachement:

Biogen response: Seq 0008 Response to Filing Letter Requests Received 15-Jul-2013

Controlled Substance Staff

4. The abuse potential materials that were submitted in the BLA did not include an *in vitro* abuse-related receptor binding panel. We ask that you specify whether or not you intend to submit these data during the review cycle. Alternatively, if you believe that these data would not provide relevant information, you may provide scientific justification (with supportive data) for not conducting this study.

RESPONSE 4

As discussed in Section 2.4.8 of the original BLA submission, abuse liability studies are not necessary for BIIB017 as BIIB017 belongs to the class of beta interferons which has a very well characterized safety profile and are not characterized as being drugs of potential abuse. None of the class members are controlled substances or subject to special instructions for use, handling, or disposal [Avonex® Prescribing Information 2013, Betaseron® Prescribing Information 2013, Rebif® Prescribing Information 2013]. While a definitive mechanism of action of BIIB017 in multiple sclerosis is not known, the potential mechanism is not consistent with CNS effects that could be associated with the potential for abuse. BIIB017 binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. These genes, and their gene products, are believed to mediate the efficacy of BIIB017 in multiple sclerosis. Furthermore, the preclinical safety studies that included daily detailed clinical observations and a histopathological analysis of the brain and CNS did not show any specific CNS related adverse events or behavioral changes.

From clinical trial data, the safety profile of BIIB017 is primarily associated with injection site reactions (e.g. erythema, pain, pruritus) and flu like symptoms (e.g. headache, pyrexia, myalgia, chills, and pain). The safety profile does not show the presence of any type of rewarding effects or other abuse-related behaviors related to drug abuse (e.g., mood elevation, euphoria, hallucination, sedation, somnolence, insomnia, cognitive disorder, anxiety). The majority of these events were rare (<1%), and no imbalances were observed between the placebo- and BIIB017-treated subjects for any of the terms. No cases of intentional overdose or drug abuse or rebound withdrawal effects have been reported in clinical studies with BIIB017 (2.7.4 Summary of Clinical Safety, Section 5). Thus, BIIB017 has a low potential for abuse and should not be considered a controlled substance.

If after the review of the nonclinical and clinical data, the Agency requires an abuse-related receptor binding panel study for BIIB017 then, consistent with the minutes from the Sponsor's pre-BLA Meeting (March 12, 2013), the study will be conducted as part of a post-marketing requirement for subsequent evaluation.

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/s/

LORI A LOVE
08/16/2013

SILVIA N CALDERON
08/16/2013

LORI A LOVE on behalf of MICHAEL KLEIN
08/16/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125499	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Plegridy Established/Proper Name: peginterferon beta-1a Dosage Form: solution for SC injection Strengths: 63, 94, 125 micrograms		
Applicant: Biogen Idec Inc. Agent for Applicant (if applicable):		
Date of Application: May 15, 2013 Date of Receipt: May 16, 2013 Date clock started after UN:		
PDUFA Goal Date: May 16, 2014		Action Goal Date (if different):
Filing Date: July 15, 2013		Date of Filing Meeting: July 2, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): PLEGRIDY is a beta interferon indicated for the treatment of patients with relapsing forms of multiple sclerosis.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 100110				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?			X	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?		X		
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>		X		
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff: 5/17/2013</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	X			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			PeRC date has been scheduled
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			Waiver <10yo and deferral 10-17yo
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>			X	
<p><u>Proprietary Name</u></p> <p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	X			PLEGRIDY PLEGRIDY PEN
<p><u>REMS</u></p> <p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>		X		
<p><u>Prescription Labeling</u></p> <p>Check all types of labeling submitted.</p>	<input type="checkbox"/> Not applicable			
<p>Check all types of labeling submitted.</p>	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			CDRH
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): November 12, 2008	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): March 12, 2013	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): February 6, 2009 (no agreement) March 3, 2010 (agreement)	X			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 2, 2013

BLA/NDA/Supp #: 125499

PROPRIETARY NAME: Plegridy

ESTABLISHED/PROPER NAME: Pegylated Interferon beta-1a (BIIB017)

DOSAGE FORM/STRENGTH: Solution for SC Injection/63, 94, & 125 micrograms

APPLICANT: Biogen Idec, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): PLEGRIDY is a beta interferon indicated for the treatment of patients with relapsing forms of multiple sclerosis.

BACKGROUND: BIIB017 is a pegylated form of interferon beta-1a (IFN β -1a) that belongs within the interferon beta class (Avonex, Rebif) that are among the commonly used first-line injectable multiple sclerosis (MS) therapies. BIIB017 provides a more optimized, less-frequent dosing regimen, that has efficacy and safety profiles comparable with currently approved first-line injectable therapies.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nicole Bradley, Pharm.D.	Y
	CPMS/TL:	Jacqueline Ware, PharmD	Y
Cross-Discipline Team Leader (CDTL)	Billy Dunn, MD		Y
Clinical	Reviewer:	John Marler, MD	Y
	TL:	Billy Dunn, MD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial</i>)	Reviewer:		

<i>products)</i>			
	TL:		

Clinical Pharmacology	Reviewer:	Ta-Chen Wu	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Tristan Massie	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Rick Houghtling	Y
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ralph Bernstein	Y
	TL:	Susan Kirshner	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Liu Liu	
	TL:	Irene Chan	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Stephen Sun	Y
	TL:	Michael Klein	N
Other reviewers	Jerry Boehm, Safety Reviewer Sally Yasuda, Safety Team Leader Denise Pico-Branco, Pediatric RPM Irene Chan, DMEPA Team Leader Liu Liu, DMEPA reviewer Lakshmi Narasimhan, BMAB reviewer Patricia Hughes, BMAB Team Leader Ethan Hausman, Pediatric Reviewer Kimberly Rains, CMC labeling reviewer Jaqueline Ryan, CDRH/Devices Team Leader Antoine El Hage, OSI reviewer Ellis Unger, ODEI Director Eric Bastings, DNP Acting Director		Y
Other attendees	Colleen Locicero, ODEI ADRA George Neyarapally, DRISK reviewer Steven Bird, DPV reviewer		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies): 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This biologic is not the first in its class
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Information request for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO To be determined
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES

of sterilization? (NDAs/NDA supplements only) Comments:	<input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments: Information request for 74-day letter	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments:	<input type="checkbox"/> Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	None

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ellis Unger, MD, ODEI Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): October 2, 2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Key Dates

Stamp Date: May 16, 2013
Filing Date: July 15, 2013
Day 74 Letter Date: July 29, 2013

Mid-Cycle meeting: October 2, 2013
Mid-Cycle Communication: October 10, 2013
Label planning meeting: October 21, 2013
Late-Cycle Sponsor Meeting: February 4, 2014
Wrap-up meeting: March 11, 2014

Review completion Goal Date according to GRMP

Primary reviews: January 16, 2014
Secondary reviews: January 23, 2014
CDTL: April 4, 2014
Division Director: April 25, 2014

PDUFA Action Date: May 16, 2014

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.

	<p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

NICOLE L BRADLEY
07/09/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: BLA 125499

Application Type: Original BLA

Name of Drug: Plegridy (peginterferon beta-1a) for subcutaneous injection

Applicant: Biogen Idec, Inc.

Submission Date: May 15, 2013

Receipt Date: May 16, 2013

1.0 Regulatory History and Applicant's Main Proposals

BLA 125499 was submitted on May 15, 2013, and received on May 16, 2013, as a new original BLA. This review was conducted using the Applicant's labeling provided on May 16, 2013.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 12, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

Injection Site Reaction bullet under Warnings and Precautions does not contain the section reference

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *FDA internet address should not be underlined*

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment: *No horizontal line separating TOC from FPI*

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
Section 16.3 in TOC says [REDACTED]^{(b) (4)} and in the FPI it says Storage and Handling. There is also an additional subsection, 16.4, in the FPI that is not listed in the TOC
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery

Selected Requirements of Prescribing Information (SRPI)

8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

NICOLE L BRADLEY
07/09/2013



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 3, 2013

To: Eric Bastings, MD, Acting Director
Division of Neurology Products (DNP)

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Stephen Sun, M.D., M.P.H., Medical Officer
Controlled Substance Staff

Subject: **Topic:** Abuse Potential Assessment of Investigational New Drug
Application: BIIB017 (BLA 125,499), 125 µg Q2W as a Single-Dose Subcutaneous Injection as a Prefilled Syringe and Pen
Proposed Indication: Relapsing Multiple Sclerosis
Sponsor: Biogen Idec

Materials reviewed: 1. Biogen Idec. Abuse Potential Report.
2. Sun S. Abuse potential assessment of investigational new drug. BIIB017 (IND100110). Memorandum. March 14, 2013.

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I. Summary

A. Background:

This memorandum is in response to a consult request dated May 17, 2013, from the Division of Neurology Products (DNP) pertaining to BLA125,499 for BIIB017 (PEGylated interferon beta-1a) under development by Biogen Idec for the treatment of patients with relapsing multiple sclerosis (b) (4)

The consult requests CSS participation in the internal meeting and industry BLA meetings.

B. Conclusions:

1. The following are abuse-related highlights:
 - a. BIIB017 is a pegylated form of interferon beta-1a (IFN β -1a) proposed for the treatment of multiple sclerosis. Interferon is currently not a scheduled drug substance. The product is intended to be packaged as a pre-filled, (b) (4) dose syringe and as a pre-filled pen to be administered subcutaneously every 2 (b) (4)
 - b. No abuse-related receptor binding study was performed.
 - c. Evaluation of abuse-related adverse events during the controlled clinical studies showed no differences between subjects exposed and not exposed to the study drug.
 - d. No animal or human abuse potential study was performed.
 - e. Clinical withdrawal events after drug discontinuation were not identified in the phase 3 studies.
 - f. An analysis of a Sponsor's similar class product, Avonex (interferon beta-1a), based upon over 400,000 patient exposure in 15 years of global safety data did not show a pattern similar to other drugs of abuse.
 - g. Sponsor has submitted a recommendation for no drug scheduling of this drug.
2. The indicated population of patients with multiple sclerosis and dosing schedule of once-every-2 weeks are not likely conditions associated with abuse and diversion.
3. The results of an abuse-related receptor binding panel have not been provided.

C. Recommendations (to Division):

1. Sponsor should be made aware that data from the abuse-related receptor binding panel was not addressed in the abuse potential materials that were submitted. Therefore, the Sponsor should explain if it intends to submit the study data during the review cycle or as a postmarketing requirement.
2. Upon review of the submitted materials, the Sponsor may perform the abuse-related receptor binding panel as a post-marketing requirement because of the following product features:
 - Product is intended to be prescribed on a very limited basis and only to multiple sclerosis patients,
 - Product is to be administered on a limited basis, i.e., approximately every-two-weeks,
 - Sponsor's review and analysis of abuse- or withdrawal-related adverse events did not reveal abuse concerns
 - Cases of abuse and diversion were not observed in the Avonex product (interferon beta-1a)
 - The large molecule size of BIIB017 is approximately ^(b)₍₄₎kDa (20kDa for interferon, 20 kDa for pegylation) with no precedence for abuse.
3. Sponsor should be advised that if data exists to show there is no drug present in the brain, no further abuse potential assessment is required.
4. Sponsor should make the DNP aware if abuse-related post marketing surveillance signals arise.

II. Discussion

A. Chemistry:

1. BIIB017 is a pegylated form of interferon beta-1a (IFN β -1a) (a.k.a. peginterferon) proposed for the treatment of relapsing multiple sclerosis. Peginterferon beta-1a is a glycosylated recombinant interferon beta-1a that is pegylated with a single 20kDA methoxypoly (ethyleneglycol)-O-2 methylpropionaldehyde (mPEG) moiety at the N-terminus. The Sponsor has marketed Avonex (IFN β -1a) for the treatment of multiple sclerosis since 1997. Pegylation to an existing therapeutic molecular is intended to shield a protein from enzymatic degradation or other clearance mechanism resulting

in a longer half-life. PEG [REDACTED] (b) (4)

2. [REDACTED] (b) (4)
3. BIIB017 will be provided in a pre-filled syringe (PFS) and a pre-filled pen (PFP) as a sterile, liquid for subcutaneous injection. Each 0.5 mL of BIIB017 contains 125 mcg of peginterferon beta-1a [REDACTED] (b) (4)

B. Pharmacology of drug substance and active metabolites:

1. In vitro studies

- a. No abuse-related, receptor-binding or functional assays were performed or discussed.
- b. Sponsor provided only discussions on the binding of interferon beta-1a or BIIB017 for the IFNAR1 and IFNAR2 chains of Type 1 interferon receptors.

2. Animal behavioral studies

- a. No abuse-related, animal behavioral studies were performed.

C. Clinical Pharmacology:

1. Pharmacology studies in healthy volunteers (3 studies) and subjects with renal impairment (1 study) were performed to characterize the pharmacokinetics and pharmacodynamics, and the safety profile of BIIB017, and to inform dose selection for the pivotal Phase 3 study.
2. **Pharmacokinetics / pharmacodynamics parameters of parent drug & active metabolites**

- C_{max} was reached between 1 to 1.5 days post-dosing (T_{max}) (compared to Avonex T_{max}: 15 hrs)
- Half-life is approximately 2 to 3 days in MS patients (compared to Avonex's ½ life: 19 hours)

D. Clinical Studies:

1. No human abuse potential studies were conducted.
2. Adverse event profile through all phases of development
 - a. No phase 2 studies were performed based upon the sufficiency of Phase 1 and the efficacy/safety Phase 3 studies as agreed with the review division.
 - b. The results summarized in this document include data available at the time of the planned data cut-off (24 October 2012) for Studies 301 and 105MS302 (Study 302; an ongoing safety extension study to Study 301). The data cut-off date corresponds to the date that all subjects had completed the placebo-controlled period (Year 1) of Study 301 and thus the last visit required for the assessment of the primary endpoint, the annualized relapse rate. As of the data cut-off date, these studies comprise 1,512 subjects with at least 1 dose exposure to placebo or BIIB017, 1,468 subjects with at least one dose exposure to BIIB017, 1,093 subjects with ≥1 year (48 weeks) BIIB017 exposure, 694 subjects with ≥18 months (72 weeks) BIIB017 exposure, and 415 subjects with ≥2 years (96 weeks) exposure to BIIB017.
 - c. Based on a Sponsor's analysis of placebo-controlled BIIB017 experience using a reference list of MedDRA terms associated with drugs of abuse, the most common term were noted to be dizziness, insomnia, depression, somnolence, and depressed mood which were commonly seen in the MS population and occurred with an incidence of ≤1%. No evidence of abuse potential appears to exist based on Sponsor's analysis (See Table 1).

Table 1: Comparison of Abuse-Related Adverse Events in BIIB017 Placebo-Controlled Studies

	Placebo # (%)	BIIB017 Q4W	BIIB017 Q2W	Total
# of subjects in safety pop	500 (100)	500 (100)	512 (100)	1012 (100)

# of subjects with an event	97 (19)	87 (17)	107 (21)	194 (19)
Euphoria-related terms	49 (10)	40 (8)	67 (13)	107 (11)
Dizziness	31 (6)	22 (4)	35 (7)	57 (6)
Insomnia	19 (4)	18 (4)	28 (5)	46 (5)
Nervousness	3 (<1)	1 (<1)	5 (<1)	6 (<1)
Agitation	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Initial insomnia	0	0	1 (<1)	1 (<1)
Impaired attn, cogn, mood, psychomotor	56 (11)	54 (11)	53 (10)	107 (11)
Depression	20 (4)	25 (5)	21 (4)	46 (5)
Somnolence	5 (1)	13 (3)	10 (2)	23 (2)
Depressed mood	14 (3)	12 (2)	7 (1)	19 (2)
Irritability	6 (1)	6 (1)	5 (<1)	11 (1)
Memory impairment	1 (<1)	4 (<1)	4 (<1)	8 (<1)
Affect lability	2 (<1)	0	5 (<1)	5 (<1)
Mood altered	1 (<1)	1 (<1)	4 (<1)	5 (<1)
Affective disorder	3 (<1)	2 (<1)	2 (<1)	4 (<1)
Disturbance in attention	2 (<1)	2 (<1)	0	2 (<1)
Mood swings	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Bradyphrenia	0	0	1 (<1)	1 (<1)
Cognitive disorder	0	0	1 (<1)	1 (<1)
Dysphoria	0	1 (<1)	0	1 (<1)
Emotional disorder	0	1 (<1)	0	1 (<1)
Major depression	0	0	1 (<1)	1 (<1)
Personality disorder	0	1 (<1)	0	1 (<1)
Crying	1 (<1)	0	0	0
Depressive symptom	1 (<1)	0	0	0
Frustration	1 (<1)	0	0	0
Lethargy	2 (<1)	0	0	0
Restlessness	2 (<1)	0	0	0
Dissociative/Psychotic terms	13 (3)	12 (2)	11 (2)	23 (2)
Sensory disturbance	7 (1)	4 (<1)	4 (<1)	8 (<1)
Affective disorder	3 (<1)	2 (<1)	2 (<1)	4 (<1)
Speech disorder	1 (<1)	2 (<1)	2 (<1)	4 (<1)
Agitation	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Confusional state	0	1 (<1)	1 (<1)	2 (<1)
Bradyphrenia	0	0	1 (<1)	1 (<1)
Formication	0	1 (<1)	0	1 (<1)

Muscle rigidity	1 (<1)	1 (<1)	0	1 (<1)
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- d. In an analysis of subjects who discontinued BIIB017, the incidence of abuse-related AEs was low and showed no increase over placebo-treated subjects.
- e. In an analysis of subjects with overall BIIB017 experience, the incidence of abuse-related AEs did not show an increase over placebo-treated subjects.
- f. No cases of intentional overdose or drug abuse were reported in any of the clinical studies of BIIB017.
- g. To evaluate dependence and withdrawal in an analysis of subjects who were discontinued from the study treatment and continued to be followed, the incidence of AEs was similar between BIIB017- and placebo-treated subjects with the most common AEs being depression, headache and MS relapse. No rebound or withdrawal effects were observed.

E. Integrated assessment:

- 1. Sponsor referenced Avonex’s (interferon beta-1a) postmarketing experience to anticipate the exposure effects of BIIB017.
 - a. A review of Avonex’s population exposure from 1997 (international birth date, IBD) to April 30, 2012 showed that approximately (b)(4) patients have been treated in a commercial setting with an estimated 1,632,834 person-years of exposure to Avonex.
 - b. Based on their evaluation of 33,217 unique cases comprising of 40,873 events, the most frequent events by System Organ Class were System Organ Class were Psychiatric Disorders, (51%), Nervous System Disorders (42%), and General Disorders and Administration Site Conditions (7%).
 - c. The most frequently reported AE by preferred terms were depression (20%), dizziness (14%), insomnia (11%), and memory impairment (9%). All other events were reported in <4% of patients.
 - d. Medical review of narratives of all cases showed no cases of potential abuse or intentional overdose with Avonex.

2. Sponsor's Avonex product information is absent Section 9.0 for Abuse and Dependence.
3. Sponsor has proposed that the current formulation is intended to be better than the existing formulation (and other therapies) due to the following:
 - a. (compared to Sponsor's Avonex) frequency of once-every-2-weeks instead of once-every week
 - b. (compared to Sponsor's Avonex) administration route of subcutaneous dosing instead of intramuscular dosing
 - c. (compared to recently approved oral formulations) frequency of once-every-2-weeks instead of daily administration with an unknown long-term safety profile
4. No member of the interferon-beta class is known to have abuse potential, be scheduled, or require special use, handling, or disposal.
5. Published literature:
 - a. Abuse potential of interferon was not found in the published literature (Pubmed search conducted on June 6, 2013).
 - b. (Falcone et al., 2005) 38M with multiple sclerosis attempted suicide by taking an overdose of interferon beta-1a (6 or 7 prefilled syringes). Causality, as determined by the authors, was a consequence of spontaneous, patient discontinuation of citalopram prescribed for depression. Depression is a known adverse event of interferon.
6. Sponsor proposes no scheduling for this product.

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/s/

STEPHEN W SUN
07/03/2013

MICHAEL KLEIN
07/03/2013