CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125499Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125499	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: PLEGRIDY Established/Proper Name: peginterferon beta-1a Dosage Form: pen and pre-filled syringe		Applicant: Biogen Idec, Inc. Agent for Applicant (if applicable):
RPM: Nicole L. Bradley		Division: Division of Neurology Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

Actions	
• Proposed action: August 15, 2014 • User Fee Goal Date is August 15, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, dates 08/04/2014
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☒ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 08/15/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 6/25/14
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 6/25/14 medguide 6/12/14 IFUs
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 6/11/14
Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	08/13/2013 08/09/2013
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None 07/09/2013 DMEPA: ☒ None 06/16/2014 06/11/2014 04/16/2014 10/17/2013 DMPP/PLT (DRISK): ☒ None 2/27/2014 OPDP: ☒ None 03/05/2014 SEALD: ☐ None CSS: ☐ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	07/09/2013 ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 2/26/2014 If PeRC review not necessary, explain: _____	Review under clinical (PMHS)
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	BLA Ack: 05/2/2013 Filing: 07/15/2013 Midcycle comm: 11/05/2013 LCM package: 01/28/2014 LCM minutes: 02/26/2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 04/11/2013
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 12/12/2008
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 10/10/2013
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 02/10/2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 8/18/14
Division Director Summary Review *(indicate date for each review)*	☐ None 8/13/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 8/13/14
PMR/PMC Development Templates *(indicate total number)*	☐ None 5
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	01/16/2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	05/20/2014
Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None Safety TL: 01/23/2014 Safety primary: 01/13/2014 Maternal health:

	PMHS: 10/18/2014
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A 10/10/2013 08/16/2013 07/03/2013
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 03/03/2014
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 01/17/2014
Clinical Pharmacology ☐ None	
Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 07/10/2013
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 07/31/2014
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 02/07/2014
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 01/24/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 01/30/2014
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 01/16/2014 8/13/2014
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None BMAB (DS): 4/11/2014 01/14/2014 BMAB (DP): 01/17/2014 05/05/2014 CDRH (OC): 01/16/2014 07/18/2013 CDRH (engineering): 02/21/2014 01/21/2014 01/17/2014 07/17/2013 CDRH (HF): 04/09/2014 06/28/2013
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	2/3/14 (CMC Executive Summary) 1/14/14 (BMAB Primary DS)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☑ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125499

MID-CYCLE COMMUNICATION

Biogen Idec, Inc.
Attention: Nadine D. Cohen, PhD
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Plegridy (peginterferon beta-1a), for subcutaneous injection.

We also refer to the teleconference between representatives of your firm and the FDA on October 10, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 10, 2013

Application Number: BLA 125499
Product Name: Plegridy **(**peginterferon beta-1a)
Indication: Multiple Sclerosis
Applicant Name: Biogen Idec, Inc.

Meeting Chair: Billy Dunn, MD
Meeting Recorder: Nicole Bradley, PharmD

FDA ATTENDEES

Billy Dunn, MD, Acting Deputy Director, Division of Neurology Products
John Marler, MD, Acting Clinical Team Leader, Division of Neurology Products
Lawrence Rodichok, MD, Clinical Reviewer, Division of Neurology Products
Nicole Bradley, PharmD, Senior Regulatory Project Manager, Division of Neurology Products
Irene Z. Chan, PharmD, Team Leader, Division of Medication Error Prevention and Analysis
Quynh Nhu Nguyen, Human Factors Reviewer, CDRH/Office of Device Evaluation
Jaqueline Ryan, Medical Officer, CDRH/Office of Device Evaluation
Clarence Murray III, Biocompatibility, CDRH
Keith Marin, Team Leader/CDRH/Office of Device Evaluation

APPLICANT ATTENDEES

Heather Faulds, Director, Regulatory Affairs
Nadine Cohen, SVP, Regulatory Affairs
John Barry, Director, Regulatory Affairs
Kimberly Wolfram, Director, Regulatory CMC
Suzanne Zuraski, Director, Regulatory CMC
Rohin Mhatre, VP, Technical Development
Atul Patel, Director, Technical Development
Kasra Kasraian, Sr. Director, CMC
Serena Hung, Medical Director, Clinical Development
Aaron Deykin, Sr. Medical Director, Clinical Development
Ying Zhu, Director, Biostatistics
Shifang Liu, Director, Biostatistics
Ali Seddighzadeh, Medical Director, Safety and Benefit Risk Management
Gary Bloomgren, VP, Safety and Benefit Risk Management

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

A. Device - Engineering

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

B. Device - Biocompatibility

5. **Composite Sample Preparation**
   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.

6. **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.

C. Human Factors

You have not demonstrated safety of the Plegridy Prefilled Syringe (PFS) for its intended users, uses, and use environments. You did not achieve your second objective of demonstrating that 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 PFS, it is unlikely that further design changes to the syringe can mitigate the failures and performance difficulties observed in the validation study. We will provide, in a separate information request, recommendations 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. Please note that changes that are directly related to reported use errors and difficulty that could result in patient harm (i.e., clinically relevant delay of therapy or sub-optimal therapy) should be validated prior to approval of the PFS.

You have not demonstrated safety of the Plegridy Pen for its intended users, uses, and use environments. Review of the supplemental IFU validation study for the Pen device showed that the revised IFU continued to show use errors and difficulties that were previously reported. Based on the results of the supplemental IFU validation study, we find that the use errors and difficulties seen in the validation study for the Pen device have not been effectively minimized (i.e., recurrence of the same use errors) and demonstrated difficulties that can impact dosing and can result in patient harm. In addition, you have not provided a rationale for why you believe that only IFU changes should be made to address the use errors and reported difficulties. 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. Please note that changes made to address use errors and difficulties that could result in patient harm (i.e., clinically relevant delay of therapy or sub-optimal therapy) should be validated in another usability study with the intended-to-market commercial presentation of the product and associated labels and labeling. We will provide additional recommendations for your labels and labeling in a separate information request.

Please address the engineering aspects of your Pen device (see Section A above) prior to any additional human factors evaluation/study. From a human factors' perspective, when we review a human factors validation study report, we assume that the device works as intended so the study results do not mix issues associated with device performance and issues associated with human factors/usability.

3.0 INFORMATION REQUESTS

There are no information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

We are not currently planning to hold an advisory committee meeting to discuss this application.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is May 16, 2014. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 16, 2014. In addition, the planned date for the Late-Cycle Meeting is February 10, 2014, at 1 PM EST.

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

/s/

WILLIAM H Dunn
11/05/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125499

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Biogen Idec, Inc.
14 Cambridge Center
Cambridge, MA 02142

ATTENTION: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs

Dear Dr. Cohen:

Please refer to your Biologics License Application (BLA) dated May 15, 2013, received May 16, 2013, submitted under section 351 of the Public Health Service Act, for Peginterferon beta-1a Injection, 63 mcg/0.5 mL, 94 mcg/0.5 mL, and 125 mcg/0.5 mL.

We also refer to your correspondence, dated and received May 17, 2013, requesting review of your proposed proprietary names, Plegridy and Plegridy Pen. We have completed our review of the proposed proprietary names and have concluded that they are acceptable.

The proposed proprietary names, Plegridy and Plegridy Pen, will be re-reviewed 90 days prior to the approval of the BLA. If we find the names unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 17, 2013 submission are altered prior to approval of the marketing application, the proprietary names should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Nicole Bradley, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

FRANKLIN T STEPHENSON
08/13/2013

IRENE Z CHAN on behalf of CAROL A HOLQUIST
08/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125499

FILING COMMUNICATION

Biogen Idec, Inc.
Attention: Nadine D. Cohen, PhD
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Biologics License Application (BLA) dated May 15, 2013, received May 16, 2013, submitted under section 351(a) of the Public Health Service Act for Plegridy (peginterferon beta-1a), for subcutaneous injection.

We also refer to your amendments dated June 10, 2013, June 11, 2013, and June 14, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is May 16, 2014.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 16, 2014. In addition, the planned date for our internal mid-cycle review meeting is October 2, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. The significant compensation given to clinical investigators at some sites may be a review issue because our preliminary review of the safety data suggests that the double-

blinding may have been compromised to some extent by side effects associated with interferon. See our request for additional information below.

2. The relevance of non-U.S. clinical data to the U.S. population will be a review issue because over 90% of the clinical data is reported from non-U.S. sites.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Clinical

1. Provide an analysis and a summary addressing the extent to which the sites with clinical investigators who disclosed financial interests contributed to the outcome of the trial. (The analysis and summary should include a comparison of the primary outcome for the 301MS105 trial at sites which had investigators who disclosed financial interests to those sites that did not. Also, please discuss the significance of the percentage of US sites with investigators who made disclosures compared to non-U.S. sites.)

2. Provide a rationale for assuming the applicability of foreign data in the submission to the U.S. population or practice of medicine.

Clinical Pharmacology

3. In Study 105HV103, you concluded that there is similarity in pharmacokinetic profiles between the pre-filled syringe and the auto-injector by comparing the percent difference in geometric means of AUC and Cmax values. However, the Agency recommends using the 90% CI of ratios of log-transformed exposure measures, judged by the 80-125% range, for assessing the comparability of two products. Please re-analyze the data accordingly and submit the results. If the results fall out of the 80-125% range, the clinical impact should be addressed.

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.

Labeling

5. During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

    a. Each summarized statement in the Highlights section must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. Provide the reference for the "injection site reaction" bullet under the Warnings and Precautions heading in Highlights.

    b. A horizontal line must separate the Table of Contents (TOC) from the FPI.

    c. The section headings and subheadings in the TOC must match the headings and subheadings in the FPI. The subheadings in Section 16 require revisions to maintain consistency between the TOC and FPI.

    We request that you resubmit labeling (in Microsoft Word format) that addresses the labeling format issues by August 12, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-796-1930.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ERIC P BASTINGS
07/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125499

BLA ACKNOWLEDGEMENT

Biogen Idec, Inc.
Attention: Nadine D. Cohen, PhD
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: peginterferon beta-1a

Date of Application: May 15, 2013

Date of Receipt: May 16, 2013

Our Secondary Tracking Number (STN): 125499-0

Proposed Use: Multiple Sclerosis

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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
05/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100110

MEETING MINUTES

Biogen Idec, Inc.
Attention: Nadine D. Cohen, PhD
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BIIB017 (PEGylated interferon beta-1a).

We also refer to the meeting between representatives of your firm and the FDA on March 12, 2013. The purpose of the meeting was to discuss the planned Biologics License Application (BLA) for BIIB017.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: March 12, 2013; 11:00 am EST
Meeting Location: White Oak Campus; Bldg 22; Room 1315

Application Number: IND 100110
Product Name: BIIB017 (PEGylated interferon beta-1a)
Indication: Multiple Sclerosis
Sponsor/Applicant Name: Biogen Idec, Inc.

Meeting Chair: Russell Katz, MD
Meeting Recorder: Nicole Bradley, PharmD

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director
Colleen Locicero, RPh, Associate Director of Regulatory Affairs

Division of Neurology Products
Russell Katz, MD, Director
Eric Bastings, MD, Deputy Director
Billy Dunn, MD, Clinical Team Leader
John Marler, MD, Clinical Reviewer
Sally Yasuda, MS, PharmD, Safety Team Leader
Gerard Boehm, MD, Safety Reviewer (via phone)
Lois Freed, PhD, Supervisory Pharmacologist
Richard Houghtling, PhD, Nonclinical Reviewer
Nicole Bradley, PharmD, Regulatory Project Manager
Jacqueline Ware, PharmD, Chief, Project Management Staff
Hamet Touré, PharmD, Regulatory Project Manager
Heather Bullock, RN, Regulatory Project Manager
Taura Holmes, PharmD, Regulatory Project Manager

Office of Clinical Pharmacology I
Angela Men, PhD, Team Leader
Jagan Parepally, Clinical Pharmacology Reviewer

Office of Biostatistics I

Sharon Yan, PhD, Statistical Reviewer

Controlled Substance Staff
Stephen Sun, MD, Reviewer
Rylan Hanks, visiting student

Pediatrics and Maternal Health Staff
Jeanine Best, MSN, RN, PNP, Clinical Reviewer
Denise Pica-Branco, Ph.D., Pediatric Senior Regulatory Health Project Manager

Division of Medication Error Prevention and Analysis
Irene Z. Chan, PharmD, Team Leader
Liu (Sue) Liu, PharmD, Reviewer (via phone)

Division of Risk Management
Kendra Worthy, PharmD, Team Leader (via phone)

Division of Epidemiology I
Steven Bird, Epidemiologist

Office of Business Informatics
Doug Warfield, Regulatory Information Specialist

Office of Scientific Investigations
Antoine El Hage, PhD, Good Clinical Practices Assessment Branch

Office of Biotechnology Products
Susan Kirshner, PhD, CMC Team Leader
Ralph Bernstein, PhD, Product Quality Reviewer (via phone)

Center for Devices and Radiological Health
Felicia Brayboy, Office of Compliance, Consumer Safety Officer

Office of Compliance/Biotechnology Manufacturing Assessment Branch
Patricia Hughes, PhD, Team Leader
Lakshmi Narasimhan, PhD, Microbiology Reviewer

Office of Operations
Kim Taylor, Research Analyst

EASTERN RESEARCH GROUP ATTENDEES
(b) (6), Independent Assessor

SPONSOR ATTENDEES

Biogen Idec, Inc.
Aaron Deykin, MD, Sr. Medical Director, Clinical Development
Sarah Sheikh, MD, MSc, MRCP, Associate Director, Clinical Development
Ali Seddighzadeh, MD, Medical Director, Drug Safety and Risk Management
Gary Bloomgren, MD, VP, Drug Safety and Risk Management
Xiao Hu, PhD, Sr. Pharmacometrician, Clinical Pharmacology and Pharmacometrics
Ying Zhu, PhD, Director, Biostatistics
Shifang Liu, PhD, Lead Biostatistician, Biostatistics
Lynn Difinizio, Sr. Director, Statistical Programming and Operations
Sarah McLaughlin, Principal Analyst, Statistical Data Standards
Suzanne Zuraski, Director, Regulatory CMC
Robert Kenyon, Director, CMC Team Leader
Heather Faulds, Director, Regulatory Affairs
Minnie Mildwoff, JD, Manager, Regulatory Affairs
Paula Sandler, PhD, VP, Regulatory Affairs
John Stofko, VP, Program Leadership and Management

1.0 BACKGROUND

Biogen Idec has developed BIIB017 (PEGylated interferon beta-1a) for the treatment of multiple sclerosis.

A Type C, CMC only, meeting was held on August 29, 2012, to discuss the CMC aspects of the proposed BLA plan for BIIB017. Subsequently, Biogen requested a pre-BLA meeting on December 19, 2012. The meeting was granted and held on March 12, 2013. The purpose of the meeting was to discuss the format and content of the BIIB017 marketing application.

2.0 DISCUSSION

Question 1:
Does the Agency agree that the Phase 3 study (105MS301) is adequate to establish BIIB017 safety and effectiveness for the treatment of multiple sclerosis (MS)?

FDA Preliminary Response to Question 1:

Efficacy
On face and subject to full review of a complete application, we agree that the 1-year results of 105MS301 appear adequate to contribute to and potentially provide a demonstration of substantial evidence of effectiveness of BIIB017 for the treatment of relapsing MS. We do not have a complete understanding of the role that the incomplete 2-year results of 105MS301 will play with regard to safety, effectiveness, and dosage. It is conceivable that the 2-year results could alter the interpretation of the 1-year results. There should be a clear plan for analysis before any 2-year data is analyzed or unblinded.

Safety
This is a matter of review. We request that you submit an analysis of compliance with study treatment. This analysis should include a description of delayed and missed injections. We ask that you identify the number of patients that actually received all planned injections in the first year of trial 301, in the second year of trial 301, and in trial 302. Please also provide a summary of the number of patients who received fewer than the assigned number of injections and the number of injections each of these patients missed.

Given that the total number of subjects exposed to BIIB017 is near the minimum ICH recommended exposure for chronically administered treatments, we are concerned about the possibility that non-compliance would result in even lower actual exposure than you reported in your briefing document.

Meeting Discussion:
None.

Question 2:
Does the Agency agree with the proposed approach to summarizing and presenting efficacy data in the BLA (Section 7.2)?

FDA Preliminary Response to Question 2:

Clinical
You plan to use the clinical study report (CSR) from 105MS301 as the integrated summary of effectiveness (ISE). Be sure that the BLA contains all the information outlined in 314.50(d)(5)(iv) and (v) and provide a clear pathway to those sections in the reviewer guide. The application should contain a section which discusses the similarities and differences between BIIB017 and other FDA-approved interferons. The discussion should include (1) a comparison of clinical pharmacological, safety, and effectiveness data as well as baseline characteristics from BIIB017 studies compared to published data from clinical trials and other clinical studies of FDA-approved interferons and (2) a summary regarding the extent to which BIIB017 behaves like other interferons. See also additional clinical comments below.

Statistics
We request that you provide a detailed presentation of analyses of the primary endpoint, including pre-specified sensitivity analyses and a thorough analysis of relapse rate by subgroups as planned. Please also include an additional analysis of time to first relapse and a sensitivity analysis to evaluate the impact of early discontinuation.

Office of Business Informatics
Yes.

Meeting Discussion:

Statistics
The sponsor confirmed that a detailed presentation of the primary analysis along with sensitivity and subgroup analyses will be provided. The sponsor asked FDA to clarify the analysis to evaluate the impact of early discontinuation. FDA responded that an analysis with conservative imputation could be explored based on the pattern of discontinuation, particularly for MRI data, which normally have more missing data. For the primary endpoint and disability progression, descriptive statistics with a summary comparing the treatment groups in discontinuation before and after an event and event number (percentage) could also be used.

Question 3:

Does the Agency agree with the proposed approach to integrate safety data in the BLA (Section 7.3)?

FDA Preliminary Response to Question 3:

Clinical
Yes. We also agree with the list of AEs of special interest that you have identified. Please also include a review of safety for those patients who developed interferon and/or PEG antibodies.

We ask that in your review of each of the AEs of special interest for PEGylated interferon beta-1a, you include a summary of available information for interferon beta-1a. These summaries should include a discussion of the currently available safety related data for each event of interest as well as a discussion of evidence regarding any differences in risk for these events when comparing PEGylated interferon beta-1a to interferon beta-1a.

Office of Business Informatics
Yes.

Meeting Discussion:
None.

Question 4:
Does the Agency agree with the proposed approach to split the Integrated Summary of Safety (ISS) to include data tables in Section 5.3.5.3 and text in Section 2.7.4 (Section 7.3.3)?

FDA Preliminary Response to Question 4:

Clinical
Yes. For those instances when in section 2.7.4 you reference a table included in 5.3.5.5, we ask that you provide a hyperlink.

Office of Business Informatics
Yes.

Meeting Discussion:
None.

Question 5:
Does the Agency agree with the proposed provision for case report forms (CRFs) and safety narratives in the BLA (Section 7.3)?

FDA Preliminary Response to Question 5:

Clinical (Efficacy)
The application should include a list of patients who did not complete the study or discontinued study medication because of relapse events or sustained accumulation of disability in the 301 trial and 302 study. If the list is not extensive, then the list should be linked to individual case narratives. If it is extensive, there should be an ISE or CSR discussion and analysis of the baseline characteristics and one and two year outcomes for this subpopulation to explore the extent of any bias.

Clinical (Safety)
Yes.

Office of Business Informatics
Yes.

Meeting Discussion:
None.

Question 6:
Does the Agency agree with the proposed presentation of electronic data for the clinical studies (Section 7.1)?

FDA Preliminary Response to Question 6:

Clinical Pharmacology
Yes.

Clinical (Efficacy)
See additional comments below for specific requirements for efficient review related to this application.

Clinical (Safety)
Yes. We request that prior to submission that you verify that the safety datasets can be opened using JMP, version 9.0.2

Statistics
In order to answer this question, we need a draft define document for the datasets. We offer you the opportunity for a preliminary review of the define document for relapse and disability data before your submission (or before the meeting if it is ready). Please follow the CDER Common Data Standards Issues Document and Study Data Specifications (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm) in constructing and organizing datasets.

Office of Business Informatics
Yes.

Meeting Discussion:

Statistics
FDA and the sponsor discussed and clarified questions with regard to data structure. FDA asked for some additional variables to be added to the relapse and disability progression data and the sponsor agreed to provide the datasets with the requested variables. FDA agreed that analysis programs that work with the current prepared datasets need not be changed.

Question 7:
Does the Agency agree with the proposed presentation of electronic data for the population PK analysis (Section 4.4.3)?

FDA Preliminary Response to Question 7:

Clinical Pharmacology
Yes.

Office of Business Informatics
Yes.

Meeting Discussion:
FDA reiterated that a justification should be provided as to why a bridging study is not needed between the drug substances BIIB017-A (used in the Phase 1 study) and BIIB017-B (used in pivotal study). The sponsor agreed to provide an explanation and indicated that there were no changes in the formulation during the development program.

Question 8:
We plan to include a comprehensive list of all clinical sites and manufacturing facilities in the BLA. The list of manufacturing facilities will be provided in the 356H Form, item 29. The list of clinical sites will be appended to the cover letter in Module 1 (Section 1.2). Does the Agency agree with the location of these lists within the BLA?

FDA Preliminary Response to Question 8:

Clinical
See additional comments below for a description of a site dataset to be included among the ISE/CSR datasets for review of effectiveness.

Biotechnology Manufacturing Assessment Branch (BMAB)
The list of the manufacturing and testing sites of drug substance and drug product with their FEI numbers should be included in Section 3.2.S.2.1 and 3.2.P.3.1, respectively.

CDRH – Compliance
It is acceptable to submit the manufacturing facilities in the 356H Form, item 29. This information should also be included in Module 3. Clearly identify the manufacturing site for the final combination product.

Meeting Discussion:
None.

Question 9:
The proposed Table of Contents for the BLA is provided in Appendix A. Does the Agency agree that the documentation and data as outlined in the Table of Contents constitute a complete application?

FDA Preliminary Response to Question 9:

Nonclinical
The embryo-fetal development study for Avonex may be used to support a BLA for BIIB017 if comparability between the interferon beta-1a used to manufacture Avonex and the interferon beta-1a starting material used to manufacture BIIB017 (b) (4) is demonstrated. The comparability data should be provided in the BLA. If comparability cannot be demonstrated, then an embryo-fetal development study will need to be conducted for BIIB017.

Clinical
See responses to questions 2 and 8 above. See also additional clinical efficacy comments below.

BMAB
For additional information related to Quality Microbiology content, please refer to the table below in Section 3.0 Additional Preliminary Comments.

Meeting Discussion:

Nonclinical
FDA asked for clarification regarding the discrepancy between the proposed BLA Table of Contents and the meeting package narrative as to what reproductive toxicology studies would be included in the BLA. The sponsor noted that only a hormonal study would be included, stating that FDA had agreed to this plan at the End of Phase 2 meeting. FDA noted that concurrence on such a plan was not given.

[Post-Meeting Note added: See Meeting Discussion under Question 11, End of Phase 2 Meeting Minutes issued on December 12, 2008.]

BMAB
See meeting discussion in Section 3.0, Additional Preliminary Comments #33.

Question 10:
Biogen Idec plans to submit additional CMC stability data and final shipping validation data as outlined in the briefing package within 30 days after submission of the BLA. Does the Agency agree with this approach?

FDA Preliminary Response to Question 10:

BMAB
We agree with the approach of submitting some final shipping data, as outlined in your February 13, 2013, email communication, within 30 days after submission of the BLA.

CDRH – Compliance
Per the briefing package, you intend to submit both the low and high capacity validation data. Additionally, you plan to submit 3 months of stability data from the low capacity validation runs and 24 months of development stability data, representative of the commercial process. Within 30 days of the original submission, you plan to submit 3 months of stability data for the prefilled pen from the high capacity validation runs.

CDRH/OC's position is that this approach is acceptable. The table of contents was reviewed and it appears that there will be manufacturing information for the drug substance, drug product, and pen. CDRH interprets pen to mean the prefilled pen [final combination product (pen and drug product)]. CDRH/OC will review the manufacturing for the pen.

Meeting Discussion:
None.

Question 11:
Does the Agency concur with Biogen Idec's proposal to waive clinical trials in children less than 10 years old and defer clinical studies in children 10-17 years old until the product has been approved in the adult population (Section 9)?

FDA Preliminary Response to Question 11:

Yes.

You should note that all waivers and deferrals for required pediatric studies must be discussed by the Pediatric Review Committee (PeRC). The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, changes the timeline for submission of a Pediatric Study Plan and includes a timeline for the implementation of these changes. Because your End-of-Phase 2 (EOP2) Meeting occurred prior to November 6, 2012, the following apply to you regarding submission of a Pediatric Plan or a Pediatric Study Plan (PSP):

- If you plan to submit your BLA prior to January 5, 2014, FDAAA rules still apply and your Pediatric Plan must be submitted with your application. Alternatively, you may submit a PSP rather than a Pediatric Plan; however, a PSP should be submitted no later than 210 days prior to submission of your application;

Or

- If you plan to submit your BLA on or after January 5, 2014, your Pediatric Study Plan (PSP) must be submitted no later than 210 days prior to submission of your application.

A PSP must include the following:

- An outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach). Appropriate juvenile animal toxicity studies will be needed to support the initiation of any pediatric studies.

- Any request for a deferral, partial waiver or waiver, along with supporting information. (Note: Although requests must be submitted with a pediatric plan, decisions on whether or not waivers and deferrals will be granted do not become final until approval.)

A template is available to aid sponsors in formulating a Pediatric Study Plan: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf.

Although not required for a Pediatric Plan submitted under FDAAA, the Pediatric Study Plan template contains elements that will assist FDA in reviewing a Pediatric Plan that is submitted under FDAAA.

Meeting Discussion:
None.

Question 12:
The Food and Drug Administration Amendments Act of 2007 (FDAAA) requires the submission and implementation of a risk evaluation and mitigation strategy (REMS) if it is determined that one is necessary to ensure that a drug's benefits outweigh the risks. Given the benefit/risk profile of BIIB017 (PEGylated IFN β-1a), we do not plan to include a REMS or other risk management actions beyond the Prescribing Information and Medication Guide. Does the Agency agree?

FDA Preliminary Response to Question 12:

We agree with your plan; however, we have insufficient information to determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks. We will determine the need for a REMS during the review of your application.

Meeting Discussion:
None.

Question 13:
Does the Agency anticipate convening an Advisory Committee to discuss BIIB017?

FDA Preliminary Response to Question 13:

There is no obvious reason to convene an advisory committee at this time. The decision will not be made until the complete application has been received and preliminary review completed.

Meeting Discussion:
None.

Question 14:
Biogen Idec plans to request priority review of the BIIB017 BLA based on the potential for BIIB017 to address an unmet medical need for a new first-line agent with a favorable efficacy and safety profile and a more optimized, less-frequent dosing regimen as compared to currently approved first-line injectable therapies. Does the Agency agree that BIIB017 should be considered for priority review based on this rationale?

FDA Preliminary Response to Question 14:

Suitability for priority review will not be determined before the application is submitted. We will comment, however, that in the time since Fast Track designation was granted for BIIB017, FDA has approved so-called first-line MS treatments which do not require frequent injections.

Meeting Discussion:

None.

3.0 ADDITIONAL PRELIMINARY COMMENTS

Clinical (Efficacy)

An application adequate to review efficacy will:

1. Provide full reports of all data collected and appropriate analyses to evaluate compliance with the protocol procedures for the identification and evaluation of all possible relapse events. The datasets and reports should include the times that the events were first reported by subjects, and when the events were evaluated by investigators, and also the times the events were first reported and entered into the electronic database. In addition, the application should provide analyses and datasets that establish the extent of any bias in reporting corrections or changes to the primary outcome data (relapses and EDSS) after the initial reports, when the changes were made, and what the changes were.

   Meeting Discussion:
   The sponsor stated that some of the data requested (viz., the time that events were first reported in the electronic database) were available but would not be included in the planned submission. FDA explained that it remained unclear why the data would not be reported if they were available and that their inclusion would contribute significantly to an understanding of the degree of protocol compliance for key outcome measures for this application in which substantial evidence of effectiveness would be based on a single trial.

2. Include a dataset and table in the IDE/CSR that identifies the time of milestones in the two parts of the 301 trial and the 302 extension study. In the table and dataset include 4 columns/fields that report the (i) proportion of patients randomized, (ii) the proportion that had completed the 301-Part 1 placebo-controlled trial at the time of the milestone, (iii) the number of randomized or continuing in 301-Part 2 at the time of the milestone, and (iv) the number that had completed 301-Part-2. Milestones include (please add others that you regard as relevant):
   - protocol approvals
   - protocol amendments
   - statistical analysis plan approvals
   - changes to statistical analysis plans
   - first patient randomized
   - last patient randomized
   - first patient completes follow-up
   - last patient completes follow up
   - data locks at different stages
   - any interim analyses (labeled as blinded or not, and efficacy or safety, or both)

- DSMC meetings and teleconferences
- Any adjudication committee meetings and teleconferences.

Meeting Discussion:
None.

3. Describe the site monitoring process and document when monitoring visits occurred and the personnel who made the site visit.

Meeting Discussion:
None.

4. Describe the EDSS certification process and summarize all certification and recertification test results. Also, document how you checked the EDSS for internal consistency with the algorithms for determining each FS score and the final EDSS. Provide a discussion and analysis of all the EDSS scores changed after the first data was recorded by the blinded examiner.

Meeting Discussion:
None.

5. Include datasets and analyses of the times of certain milestones for each patient so that the process for determination of clinical and MRI outcomes can be reviewed in the 301 and 302 trials. These milestone parameters include:
   - randomization in 301-Part 1 trial
   - transition/randomization to 301-Part 2 trial
   - transition to 302 trial
   - dispensing of medication to patient
   - medication discontinuation
   - rescue or other MS medication administration (with name of medication)
   - patient reports of possible relapse
   - relapse visit (whether declared an outcome event relapse or not)
   - date of protocol-defined outcome event relapse
   - EDSS determination (with score)
   - any adverse event (with severity)
   - protocol MRI scan
   - last contact with patient during 301-Part 1 trial
   - last contact with patient during 301-Part 2 trial
   - last contact with patient during 302 trial

   Consolidate these patient milestones in a single dataset that is designed to accommodate a different number of events for different patients with a single field in each record that indicates the date and time of the event and the associated visit name and another field indicating the type of event and a description (for example, EDSS score).

Meeting Discussion:
The sponsor asked FDA for further information about the requested table/dataset. FDA explained that the purpose of the dataset was to consolidate all the important clinical data from multiple datasets into one dataset in order to present a timeline of all important events for each patient. FDA agreed to provide a table format for the dataset.

6. Provide a clear discussion in the CSR/ISE of the number of missing values for each of the primary and secondary outcomes by treatment group. In the CSR/ISE analysis tables, flag any dataset items that are imputed, carried forward, or otherwise estimated and vary from what is entered in the CRF tabulation files. Describe imputation rules in the dataset documentation, including those for date and time. For times, use standard formats that will allow you to include all available time information, i.e., do not truncate or round down date or time information. Mention briefly how the different time zones are accounted for in the datasets and data analyses.

Meeting Discussion:
The sponsor asked FDA for further information about the requested data. FDA explained that the comment was a general comment regarding FDA expectations for the presentation of data in tables and figures throughout the clinical sections of the application. The sponsor explained that confidence intervals on survival curves might make them difficult to interpret. FDA agreed that in some cases the confidence intervals could make the survival curves more difficult to read. FDA explained the need to show the actual number of data points used to calculate a specific table entry. Table 1 from the meeting material was used as an example. In that table, it was not clear how many one-year Gd-enhanced MRI scans contributed to the calculation of the "% reduction vs. placebo." Without knowledge of the amount of missing or imputed data it is more difficult to assess the credibility of the data.

7. Include the following MRI data in datasets and tables with accompanying analysis for MRI scans:
    - the date the MRI scan was performed
    - the date the MRI scan was received at the reading center
    - performance site
    - machine description
    - MRI protocols for sites, data center, and reading centers
    - Baseline values and actual readings as well as the change from baseline for the different MRI parameters.

    Report and analyze the extent that MRI scans are missing by treatment group and all subjects for each of the different MRI outcomes reported in the CSR/ISE and whether MRIs were done on schedule or not and on the same machine for a given subject.

Meeting Discussion:
See discussion of Clinical (Efficacy) additional comment #1, above.

8. Analyze efficacy outcomes by the relevant clinical protocol version if there were significant protocol changes.

Meeting Discussion:
None.

9. Discuss the credibility of the results and the choice of dose with respect to the impact on the risk-benefit assessment of possible bias due to unblinding by treatment-related side effects and the various sensitivity analyses for missing clinical outcome data.

Meeting Discussion:
None.

10. Provide clear documentation of the dataflow from raw data to efficacy results. Data should include the time a patient or clinician first reported a possible relapse, and the date of associated post-relapse evaluations. The ISE narrative should describe and evaluate in detail the processes for identifying how possible relapses were identified and screened. This narrative should contain relevant links to site training material and procedure manuals. The narrative should include tables that show how each possible relapse identified by patients or clinicians was eventually categorized (relapse or not by protocol criteria). The number and severity of possible relapses should be summarized by treatment arm. The subsets of possible relapse events that did and did not meet protocol criteria as relapses should be compared across treatment groups. In addition, the EDSS and other data fields should be used to identify possible clinical events that were relapses but not identified as such in the trial. Compliance with the 72-hour and 5-day rules to evaluate a relapse should also be discussed. Tables should compare compliance in treatment arms.

Meeting Discussion:
See discussion of Clinical (Efficacy) additional comment #1, above.

11. Document both the date and the visit classification ("Visit 1") for each observation in the analysis and tabulation datasets. Provide notice and explanation in the reviewer guide if across datasets the same visit classification is associated with multiple dates in a single patient.

Meeting Discussion:
None.

12. For the 301 and 302 trials combined, please include a detailed CONSORT diagram of patient disposition with footnotes identifying flags used in the datasets to identify each of the subject subsets in the diagram.

Meeting Discussion:
None.

13. Avoid unnecessary repetition of records in the ADSL analysis dataset. This dataset should contain one record per randomized/enrolled patient per trial part (301-1, 301-2) or study (302). For this application, we prefer that different patient sub-populations within trial parts be indicated by separate flag fields rather than multiple records for patients.

Meeting Discussion:
None.

14. Avoid confusion and errors by presenting coded variables as meaningful strings in datasets, (viz., "Yes" or "No" instead of 1 and 0) whenever possible.

Meeting Discussion:
None.

15. Compare relapse, EDSS, and MRI outcomes in the BIIB017 treatment arms in patients who had symptoms that may have unblinded the patients or treating physicians to those who did not.

Meeting Discussion:
None.

16. Determine if there is any difference in the time from onset of relapse to the first eCRF data entry by treatment group.

Meeting Discussion:
See discussion of Clinical (Efficacy) additional comment #1, above.

17. Report baseline and measured values for MRI scan parameters as well as differences from baseline.

Meeting Discussion:
None.

18. Report and discuss any changes in the overall relapse, SAD, and AE rates observed in the three treatment groups during the three periods of the clinical observations: 301-1, 301-2, 302.

Meeting Discussion:
None.

19. Document any CRF fields that are not in the tabulation datasets.

Meeting Discussion:
None.

20. Display confidence intervals in survival curves and identify the extent of missing data in graphs, figures, and tables. Every analysis, table, or figure that includes imputed data values should describe the imputation and number of imputed values in the appropriate caption or legend.

Meeting Discussion:
See discussion of Clinical (Efficacy) additional comment #6, above.

21. In order to document the effectiveness of the double blinding, include samples of the placebo and active treatments packaged and labeled as received at the centers in labeled plastic bags. Put labels to indicate placebo or BIIB017 on the plastic bags and not on the study drug packaging or container inside the bag.

Meeting Discussion:
None.

22. Provide a dataset with a row for each site with fields in each row that are needed to evaluate the extent of participation at the different sites. The fields to include in the new table are the following: SiteID (that maps to the ADSL table), contact individual, address, city, (state/territory/province), country, mail code, region, telephone number, fax number, email address for contact individual, 6 fields equal to the number of subjects randomized to the 3 arms in the 301 Part 1 trial and the two arms of the 301 Part 2 trial, and enrolled in the 302 extension, 10 fields showing the number of randomized patients in the 5 arms of the two parts of the 301 trial who experienced SAD events (5 fields) and relapses (5 fields), 10 fields to list the total number of SAD events (5 fields) and total number of relapses (5 fields) for all 301 trial patients, 5 fields with the number of patients who did not complete the trial in each of the 5 arms, 5 fields to provide the number of patients who completed the 48-week MRI with acceptable quality in each arm, and 5 fields to describe the number of patients to complete the 96-week MRI with acceptable quality.

Meeting Discussion:
None.

Additional Meeting Discussion for Clinical (Efficacy):
In general, FDA explained that because this application would be supported by a single relatively short duration trial, the review would assess with particular importance the quality of the trial conduct and consider the apparent consistency of the results with other trials of approved interferon drugs for relapsing multiple sclerosis. These additional comments should be considered in the context of the specific comments above.

Clinical (Safety)

23. Please provide a single dataset with all AEs in phase 1 studies.

24. Please provide a table which summarizes the outcomes of all pregnancies. Include a narrative that includes the outcome of each pregnancy, including the reasons for termination if this occurred. Provide a table which summarizes all known adverse events in subject offspring.

25. Please clarify the criteria for reporting MS relapse as an adverse event (versus lack of efficacy).

Narratives and CRFs:

26. Please include in your submission an index listing all submitted narratives with links to the narratives. Include a similar index for all submitted case report forms.

27. Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; and provide more specific information regarding the discontinuation.

28. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not be limited to):
    - Patient age and gender
    - Adverse event onset and stop dates (presented as relative Study Day number)
    - Signs and symptoms related to the adverse event being discussed
    - An assessment of the relationship of exposure duration to the development of the adverse event
    - Pertinent medical history
    - Concomitant medications with start dates relative to the adverse event
    - Pertinent physical exam findings
    - Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
    - Discussion of the diagnosis as supported by available clinical data
    - For events without a definitive diagnosis, a list of the differential diagnoses
    - Treatment provided
    - Re-challenge results (if performed)
    - Outcomes and follow-up information

Meeting Discussion for Clinical (Safety):

The sponsor raised an issue about Clinical (Safety) request #23. The sponsor did not feel that providing a pooled dataset for AEs from Phase 1 studies would be appropriate, given the differences in study designs and populations among the various trials. FDA responded that such a dataset would not be used to estimate frequencies for events, but rather as an aid to be able to quickly look for specific types of AEs in the Phase 1 studies. Without such a pooled dataset, the safety reviewer would need to open multiple datasets to look for AEs. In addition, the sponsor noted that the AEs in the different Phase 1 studies were coded using different versions of MedDRA dictionaries. FDA will not require that these events be re-coded using a single dictionary since the dataset will be used as an exploratory tool and not to estimate frequencies for events.

Statistics

29. Please include in the submission complete documentation of the futility analysis performed (including report of futility analysis results to the DSMB and DSMB meeting minutes) and any documentation related to the decision to increase the sample size.

Meeting Discussion for Statistics:
None.

Controlled Substance Staff

30. You should refer to the FDA draft guidance for Industry, "Assessment of Abuse Potential of Drugs" (January 27, 2010) for the framework of nonclinical and clinical data and studies that are necessary to evaluate the abuse potential of BIIB017 and any active, major metabolites. The following information should be submitted as part of your assessment of abuse potential for your BLA submission:

    a. Include the source data of any in-vitro abuse-related, receptor binding studies. If information suggests a relationship to drugs of abuse, additional studies, such as animal self-administration and drug discrimination studies, may be subsequently required.

    b. Compile any adverse events related to misuse, abuse, addiction, and overdose in all clinical studies. Any issues regarding drug accountability and study patient withdrawal should be evaluated for potentially inappropriate reasons of misuse, abuse, and diversion. Relevant adverse events may be found in the draft guidance for abuse assessment.

    c. Provide an assessment on drug dependence and withdrawal.

    d. Provide a recommendation for drug scheduling.

Meeting Discussion for Controlled Substance Staff:
The sponsor must submit the Assessment for Abuse Potential of BIIB017 that should include: (1) existing abuse-related, nonclinical, and clinical data for BIIB017, (2) abuse-related post-marketing surveillance information for interferon-beta, and (3) a proposal for DEA drug scheduling for BIIB017 as part of the application review. This Assessment for Abuse Potential should be included with the original application at the time of initial submission. If an abuse-related receptor binding panel is not submitted with the original application, it must be submitted as part of a post-marketing requirement for subsequent evaluation.

CDRH – Human Factors

31. You did not include any Human Factors information in the pre-BLA meeting briefing package. Please note that we expect your Human Factors protocol and report to address the concerns that we communicated to you at the August 29, 2012, Type C CMC meeting. Guidance on Human Factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to Human Factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

Meeting Discussion for CDRH-Human Factors:
None.

Office of Scientific Investigations

32. Please refer to information provided in Appendix A.

Meeting Discussion for Office of Scientific Investigations:
FDA informed the sponsor that Item 1 in Appendix A was a regulatory requirement, whereas Items 2 and 3 were optional. The sponsor agreed to provide the information in Item 1; however, they stated that Items 2 and 3 would be too much information to provide in light of the issues raised during the meeting. FDA and the sponsor agreed that once the sites were selected for inspection, OSI will make specific requests for the selected sites.

BMAB

33. Please refer to the table below.

ECTD section	
Module 1	***Administrative information***
1.1	Forms
1.2	Cover letter
1.3	Administrative information ➢ *A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections.*
1.4	Reference Section
1.6	Meetings
1.12	Other correspondence
1.14	Labeling
1.16	Risk management plans
Module 2	***Technical Document Summaries***
Module 3	***Quality***
3.2.S	**Drug Substance**
3.2.S.1	**General information**
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure

3.2.S.1.3	General properties
3.2.S.2	**Manufacture**
3.2.S.2.1	Manufacturer(s) ➢ *A complete list of the manufacturing and testing sites with their corresponding FEI numbers*
3.2.S.2.2	Description of Manufacturing Process and Process Controls
3.2.S.2.3	Control of Materials
3.2.S.2.4	Controls of Critical Steps and Intermediates ➢ *Pre-determined* (b) (4) *limits and data*
3.2.S.2.5	Process Validation and/or Evaluation ➢ *Three successful consecutive product* (b) (4) *validation runs at manufacturing scale.* ➢ (b) (4) *and storage validation* ➢ *Bioburden and endotoxin data obtained during manufacture of the three conformance lots* ➢ *Data summaries of shipping validation studies*
3.2.S.2.6	Manufacturing Process Development
3.2.S.3	**Characterization**
3.2.S.4	**Control of Drug Substance**
3.2.S.4.1	Specification ➢ Bioburden and endotoxin
3.2.S.4.2	Analytical Procedures ➢ Bioburden and endotoxin
3.2.S.4.3	Validation of Analytical Procedures ➢ *Bioburden and endotoxin test qualifications*

3.2.S.4.4	Batch Analyses
3.2.S.4.5	Justification of Specification
3.2.S.5	**Reference Standards or Materials**
3.2.S.6	**Container Closure System**
3.2.S.7	**Stability**
3.2.S.7.1	Stability Summary and Conclusions
3.2.S.7.2	Post-approval Stability Protocol and Commitment
3.2.S.7.3	Stability Data
3.2.P	**Drug Product**
3.2.P.1	**Description and Composition of the Drug Product**
3.2.P.2	**Pharmaceutical Development**
3.2.P.2.3	Manufacturing Process Development
3.2.P.2.4	Container Closure System
3.2.P.2.5	Microbiological Attributes ➢ *Container Closure Integrity test validation and data* ➢ *The worst-case* (b) (4) *parameters validated for the container closure integrity*
3.2.P.2.6	Compatibility
3.2.P.3	**Manufacture**
3.2.P.3.1	Manufacturer(s) ➢ *A complete list of the manufacturing and testing sites with their corresponding FEI numbers*
3.2.P.3.2	Batch Formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls

3.2.P.3.4	Controls of Critical Steps and Intermediates
3.2.P.3.5	Process Validation and/or Evaluation ➢ (b) (4) ➢ (b) (4) ➢ (b) (4) ➢ (b) (4) ➢ *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs,* ➢ *A description of the routine environmental monitoring program* ➢ *Shipping validation*
3.2.P.4	**Control of Excipient**
3.2.P.4.1	Specification
3.2.P.4.2	Analytical Procedures
3.2.P.4.3	Validation of Analytical Procedures
3.2.P.4.4	Justification of Specification
3.2.P.4.5	Excipients of Animal Origin
3.2.P.4.6	Novel Excipient
3.2.P.5	**Control of Drug Product**
3.2.P.5.1	Specification ➢ *Bioburden,* (b) (4) *and endotoxin*
3.2.P.5.2	Analytical Procedures ➢ *Bioburden,* (b) (4) *and endotoxin*
3.2.P.5.3	Validation of Analytical Procedures ➢ *Bioburden, endotoxin, ana* (b) (4)
3.2.P.5.4	Batch Analyses

3.2.P.5.5	Characterization of Impurities
3.2.P.5.6	Justification of Specification
3.2.P.6	**Reference Standards or Materials**
3.2.P.7	**Container Closure System**
3.2.S.8	**Stability**
3.2.P.8.1	Stability Summary and Conclusions ➢ *Microbial attributes*
3.2.P.8.2	Post-approval Stability Protocol and Commitment ➢ *Include container closure integrity*
3.2.P.8.3	Stability Data
3.2.A	**Appendices**
3.2.A.1	Facilities and Equipment
3.2.A.2	Adventitious Agents Safety Evaluation
3.2.R	**Regional Information**
3.3	**Literature References**

Meeting Discussion for BMAB:

The sponsor inquired (b) (4) However, there are various approaches that can be followed to establish acceptable hold conditions from a microbial perspective. FDA referenced a PDA presentation from Kalavati Suvarna at the Global Microbiology PDA conference in October 2012 describing strategies for establishing acceptable hold conditions. During the post meeting discussion, the sponsor stated (b) (4) FDA stated that the studies should be conducted under protocol and that the protocol should be included in the BLA and executed during the next manufacturing campaign.

4.0 POST-MEETING DISCUSSION

CMC
On March 8, 2013, FDA notified the sponsor that we would reference the agreements made during the August 29, 2012, CMC only Type C meeting in the meeting minutes for the March 12, 2013, meeting. The sponsor provided the comments below in a March 11, 2013, e-mail. Those comments were discussed with the sponsor in a post-meeting discussion.

Biogen comment 1
In addition, we have a comment on the FDA preliminary comments received today regarding question 10 (the proposal to submit additional CMC data during the 30 day review). If time allows, we are happy to discuss these comments at the meeting tomorrow.

- Biogen Idec would like to confirm that it is acceptable to submit some mPEG stability data within 30 days of submission of the BLA (Question 10). A response was not included with the Preliminary Comments.
    - BIIB017 mPEG pilot scale stability data: At the Type C meeting in August 2012, the FDA requested that Biogen Idec include stability data for 3 lots of BIIB017 drug substance and drug product produced from lots of mPEG sourced from each mPEG supplier, (b) (4). As agreed with the FDA, this dataset will include 2 batches manufactured with (b) (4) mPEG at pilot scale, representative of the commercial manufacturing process. Comparability of stability trends with respect to mPEG supplier will be evaluated using available accelerated and/or stressed storage stability data. The original submission will contain 24 months of BIIB017 drug substance and 18 months of BIIB017 drug product long-term storage stability data generated from 3 lots of mPEG sourced from (b) (4) and 1 lot of mPEG sourced from (b) (4) Biogen Idec plans to submit additional stability data from the pilot scale batches manufactured with (b) (4) mPEG within 30 days of the initial submission.

FDA response to comment 1:
It is acceptable to submit simple stability updates within 30 days of submission of the BLA.

Biogen comment 2
Biogen Idec would like to make a clarification to Question 5 of the Meeting Minutes from the Type C Meeting held on August 29, 2013.

As a clarification to the FDA feedback, at the time that the meeting package was submitted, Biogen Idec stated that 48 months of DS stability data was currently available for 1 DS batch (b) (4) mPEG), 18 months for 3 DS batches ((b) (4) mPEG), and 12 months for 1 drug substance lot ((b) (4) mPEG).

Biogen Idec will submit all available stability data for these lots at the time of filing (60 months for 1 DS batch and 24 months for the other 4 DS batches), as well as, the available stability data for the two newly manufactured pilot scale DS lots manufactured with (b) (4) mPEG.

FDA response to comment 2:
This plan is acceptable.

5.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  In addition, we note that a CMC pre-submission Type C meeting was held on August 29, 2012. We refer you to the meeting minutes, dated September 28, 2012, for any additional agreements that may have been reached.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

- A preliminary discussion on the need for a REMS was held and it was concluded a REMS is not necessary at this time.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

  - Simple stability update for mPEG
  - Some final shipping data (as outlined in your February 13, 2013, email communication) from the transportation qualification studies for the prefilled syringe, prefilled pen, and finished product
  - 3 months of stability data for the prefilled pen from the high capacity validation runs

  Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  BLA NUMBER: LATE COMPONENT - QUALITY

6.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

1. Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

2. The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

3. The preferred presentation for cross-references in the 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)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

7.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

APPENDIX A

Please note the requested information outlined below is Optional/Voluntary

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

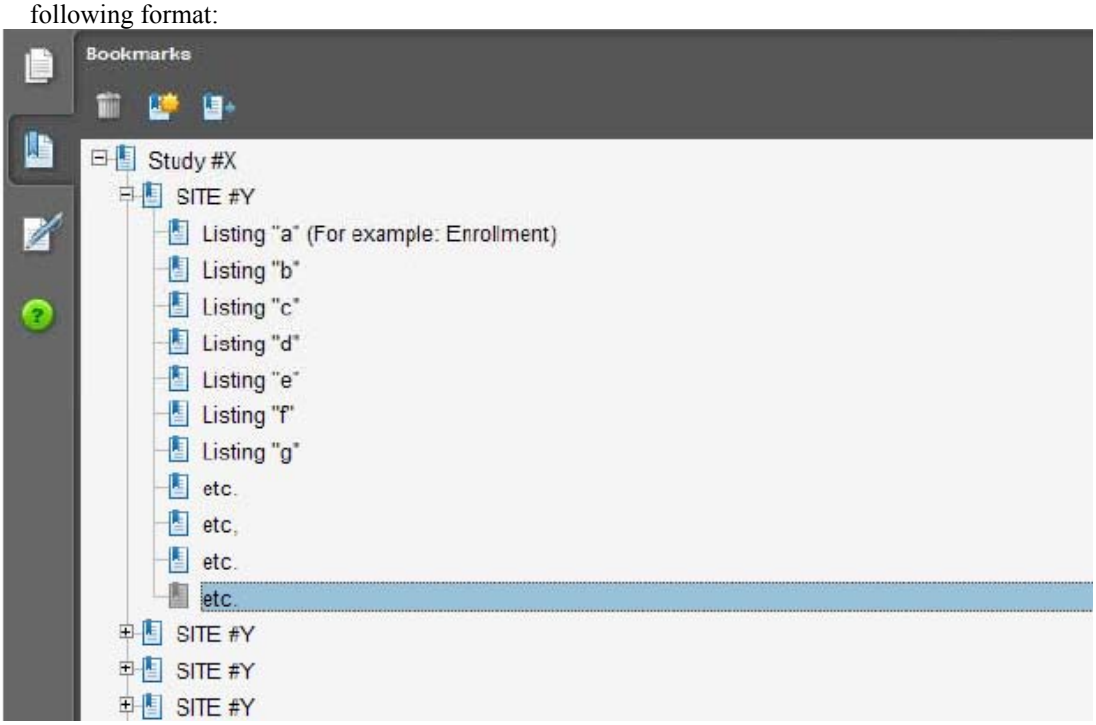
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters (relapse, EDSS, MRI). For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring
   k. By subject listing of MRI scans performed

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We

request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

I. Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

INTRODUCTION

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

II. Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter “1”.	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to descr be the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

III. Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

IV.

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

V. Attachment 2

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

ERIC P BASTINGS on behalf of RUSSELL G KATZ
04/11/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 100,110

Biogen Idec, Inc.
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BIIB017, PEGylated Interferon β-1a.

We also refer to the meeting between representatives of your firm and the FDA on November 12, 2008.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call James H. Reese, Regulatory Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 12, 2008
TIME: 3:00-4:00PM EST
LOCATION: CDER WO Room 1309
APPLICATION: IND 100,110
DRUG NAME: BIIB017, PEGylated Interferon β-1a
TYPE OF MEETING: Type B/End of Phase II (EOP2)

MEETING CHAIR: Russell Katz, M.D.

MEETING RECORDERS: James Reese, Ph.D.
Stephanie N. Keefe

FDA ATTENDEES:

Russell Katz, MD, Division Director, DNP
Eric Bastings, MD, Deputy Division Director & Clinical Team Leader, DNP
Billy Dunn, MD, Clinical Team Leader, DNP
Teresa Podruchny, MD, Clinical Reviewer, DNP
Lois Freed, PhD, Non-Clinical Team Leader, DNP
Barbara Wilcox, PhD, Non-Clinical Reviewer, DNP
Susan Kirshner, PhD, CMC Pharmaceutical Assessment Lead, DNP
Ralph Bernstein, PhD, CMC Pharmaceutical Assessment Reviewer, DNP
Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer, DNP
Sharon Yan, PhD, Biostatistics Reviewer, DNP
James Reese, PhD, Regulatory Project Manager, DNP
Stephanie N. Keefe, Consumer Safety Officer, DNP
Vandna N. Kishore, Regulatory Project Manager, DNP

BIOGEN IDEC, INC. ATTENDEES:

Clinical:
Gudarz Davar
Michael Panzara
Meena Subramanyam
Leila Jalinous
Sandra Richman

Non-Clinical:
Janice Lansita
Lisa Beebe

Clinical Pharmacology:
Ivan Nestorov

Clive Patience

Statistics:
Ying Zhu
Young-Chen Wang

Regulatory Affairs:
Heather Faulds
Gita Dittmar
Paula Sandler
Iftikhar Ali
Ann Dodds-Frerichs
Kimberly Wolfram

BACKGROUND:

Biogen Idec, Inc. is developing BIIB017 (PEGylated Interferon β-1a) for multiple sclerosis. BIIB017 is a PEGylated form of the same interferon β-1a molecule found in Avonex®, a drug used to treat patients with MS for over 10 years. Biogen Idec, Inc. has completed single and multiple dose safety and tolerability studies in healthy volunteers and plans to initiate a pivotal study to enable registration of BIIB017 in MS patients. The sponsors' objectives are to gain guidance on the following:

- To gain agreement regarding the design of the pivotal study of BIIB017, including the patient population, endpoints, and statistical plan, to treat relapsing forms of MS.
- To gain agreement regarding the adequacy of the planned clinical exposure to support the registration of BIIB017 for the proposed indication.
- To gain agreement regarding the adequacy of the nonclinical package to support the registration of BIIB017 to treat relapsing forms of MS.
- To gain agreement that a pediatric deferral is appropriate for BIIB017.
- To gain agreement with the Agency regarding the comparability of drug substance and drug product used in early clinical studies and the drug substance and drug product to be used in pivotal study.

QUESTIONS:

*I. [Questions regarding the **REGULATORY PLANS** that were submitted in the October 9, 2008 Briefing Document]*

QUESTION 1a: Does the FDA agree that the achievement of superiority over placebo at 1 year based on ARR, along with safety and immunogenicity data from 940 patients who have been exposed to BIIB017 for 1 year and 200 patients with 2 years of exposure, will support registration of BIIB017 for RMS?

FDA Preliminary Response

Yes, when taken in the context of the answer to question 1b.

Meeting Discussion

No additional discussion.

QUESTION 1b: Does the FDA concur with the overall design of the proposed Phase 3 trial?

FDA Preliminary Response

We strongly advise you to include an active comparator arm (Avonex) in the study and submit a modified, detailed statistical analysis plan that incorporates this change. We suggest that you submit your revised protocol as a Special Protocol Assessment.

Regarding your plan to conduct an interim analysis for futility purpose, you should include a stopping rule in the protocol. In addition, details of the plan for the interim analysis need to be documented in the charter and submitted for review.

Meeting Discussion

The sponsor enquired as to why FDA would want an active comparator arm in the study. FDA noted that it was not requesting a formal superiority or non-inferiority analysis but rather a sense of how this pegylated version of Avonex compares to Avonex. The sponsor stated that inclusion of an Avonex arm would be logistically challenging and burdensome to patients, and it would be more efficient to establish efficacy with the proposed trial. The sponsor indicated that given the long history of interferon use in MS, a placebo-controlled trial was adequate.

FDA and the sponsor agreed it would be useful to the clinical community and desirable to have the type of information that an active comparator could provide. The sponsor enquired as to the absolute requirement for approval of an NDA for BIIB017 and asked specifically for confirmation that a placebo-controlled trial would be sufficient for approval. FDA confirmed that such a trial would meet the basic requirements but reiterated that the addition of an active comparator is strongly advised. FDA also noted that the absence of an active comparator may have labeling and marketing implications.

The sponsor and FDA agreed that the sponsor will provide the stopping rule(s) for the interim analysis and a SAP before un-blinding. FDA noted that the further before the interim analysis the sponsor could submit such plans, the better. The sponsor agreed that an interim analysis plan will be submitted prior to the interim analysis with sufficient time to allow the Division for review and comments.

*II. [Questions regarding the **DOSE and TITRATION** that were submitted in the October 9, 2008 Briefing Document]*

QUESTION 2: Does the FDA concur with the BIIB017 dosing regimens proposed for the Phase 3 study?

FDA Preliminary Response

While your dosing regimen is not unacceptable, please justify your specific choice of dose and dosing interval.

Meeting Discussion

FDA noted the submission's description of Cmax and t1/2 of the 63mcg pegylated product when compared to Avonex 30mcg (higher and longer with pegylated product). FDA noted that it is not suggesting 63mcg is the preferred dose but requested that the sponsor provide a more detailed discussion of the dosing choice. The sponsor will include this in the forthcoming submission.

QUESTION 3: If the trial is successful, we believe that the titration schedule will be reflected in the Dosage and Administration section of the label. Does the FDA concur?

FDA Preliminary Response

The Dosage and Administration section of the label will reflect the dosage and administration (including, for example, a titration schedule) that were used in the trial leading to approval.

Meeting Discussion

No additional discussion.

*III. [Questions regarding the **SAFETY DATABASE** that were submitted in the October 9, 2008 Briefing Document]*

QUESTION 4: Does the FDA agree that the proposed safety database is acceptable?

FDA Preliminary Response

Yes.

Meeting Discussion

No additional discussion.

*IV. [Questions regarding the **PATIENT POPULATION** that were submitted in the October 9, 2008 Briefing Document]*

QUESTION 5: Does the FDA concur that the proposed Phase 3 trial design supports the registration of BIIB017 in the patient population for (b) (4)

FDA Preliminary Response

No. [redacted] (b) (4) Your proposed trial does not include such a population. A second study is required to support an indication for [redacted] (b) (4)

Meeting Discussion

No additional discussion.

*V. [Questions regarding **CLINICAL PHARMACOLOGY** that were submitted in the October 9, 2008 Briefing Document]*

QUESTION 6: Does the FDA agree with the clinical pharmacology plans?

FDA Preliminary Response

On face, the outline of your population PK plan to investigate the potential impact of covariates and intensive PK sampling plan in a subset of patients seems reasonable. However, we have the following comments on your proposal, as well as your clinical pharmacology program, for your consideration:

1. In view of the ranges of Tmax and t1/2 values of the BIIB017 from the Phase 1 study, you should consider more frequent PK timepoints covering the Tmax ranges and a longer PK sampling process beyond the planned 168 hours in the subset of patients to allow a more accurately estimation for the PK parameters in the MS patient population.

2. We recommend that you investigate the impact of renal insufficiency on the PKs of BIIB017, in view of the renal elimination for interferon and the literature-reported significant impact of moderate and severe renal impairment on the approved interferon product. Although the potential impact of renal impairment may be detected via population PK assessment, a sufficient number of patients enrolled in the study to capture the impact of various degrees of renal function may not be possible. The population PK approach, however, will be useful in serving as a confirmatory measure for renal impairment study.

3. We recommend that a PK and PD comparability study in humans be considered to bridge BIIB017-A (Phase 1 study) and BIIB017-B (proposed pivotal study), unless adequate justification is provided that a human study is not necessary.

Meeting Discussion

- *The sponsor has agreed to the OCP recommendations #1 and #2 and plans to investigate the impact of renal insufficiency in a separate renal impairment study with confirmatory results from the population PK analysis in Phase 3 clinical trial.*
- *Regarding the comment #3, the sponsor enquired the rationale for making the recommendation. The Agency responded that the changes between the two processes seem significant per internal discussion with the CMC review team, and a human PK and PD comparability study will be necessary per outcome of the CMC review regarding the significance of the change. CMC review team also enquired whether the study in monkey will be less sensitive for showing PK difference between products from two processes. The sponsor reassured that the changes made between the two processes are not significant and plans to submit robust data and justification for CMC review.*

*VI. [Questions regarding **PEDIATRIC DEFERRAL** that were submitted in the October 9, 2008 Briefing Document]*

QUESTION 7: Does the FDA agree that a pediatric deferral is appropriate?

FDA Preliminary Response

Yes.

Meeting Discussion

No additional discussion.

*VII. [Questions regarding **CMC** that were submitted in the October 9, 2008 Briefing Document]*

QUESTION 8: Does the Agency agree that the comparability plan and data presented demonstrate that the IFN β-1a and BIIB017 made by the BIIB017-A and BIIB017-B processes are comparable?

FDA Preliminary Response

No, this is a review issue, i.e., a complete comparability package with raw data should be submitted to the Agency for review. Please see the initial CMC related comments, below.

Meeting Discussion

No additional discussion.

QUESTION 9: Does the Agency concur with the release test specifications for the BIIB017 drug substance and drug product to be used in the proposed Phase 3 clinical study?

FDA Preliminary Response

No, please see additional comments.

Meeting Discussion

No additional discussion.

QUESTION 10: Does the Agency concur that the plans outlined for the change of container closure to staked needle syringe would be sufficient for approval?

FDA Preliminary Response

Yes, the Agency concurs with the outlined plans.

Additional CMC comments to Sponsor:

1) *Regarding your immunogenicity assays*: Please clarify if the assays were validated for 017, 017-A or 017-B grade material. If the assays were **not** validated for the Phase 3 studies' material (017-B), please provide a scientifically sound rationale why this is acceptable.

2) *Regarding raw materials*:

a. Your 20kDaPEG raw material vendors/sources:

i. Please provide data demonstrating appropriate control of critical raw materials, namely the 20kDaPEG purchased from (b) (4) and (b) (4) Please provide your risk management plan that addresses the qualification and use of the vendor supplied critical component.

ii. Please perform stability (real time and accelerated/ stressed) testing on lots of **drug product** manufactured using the 20kDaPEG from each vendor.

b. The alternate source of (b) (4) process should be appropriately qualified. Please submit data demonstrating drug substance comparability when the alternative source of (b) (4) is used.

3) *Regarding test methods for drug substance release and stability*:

(b) (4)

4) (b) (4)

Meeting Discussion

- *Regarding 2a: Sponsor stated that a comparability study and stability study were to be conducted on raw material of both vendors. The sponsor will implement an audit program regarding the raw material that arrives. The Agency requested information be provided on initial testing. The Agency also inquired as to whether the sponsor would be using both vendors during the phase 3 studies. The sponsor stated they would be using both vendors. The Agency requested the sponsor submit information regarding how they would control variability that has been seen in various batched of PEG-versions. Variability causes varying effects to PK and has been seen in similar situations.*

- *Regarding 3c:* (b) (4) *Sponsor will continue to monitor product during phase 3 trials and continue to evaluate data. The Agency plans to view P3 study data and discuss whether the amount of data provided is sufficient.*

*VIII. [Questions regarding **NONCLINICAL** that were submitted in the October 9, 2008 Briefing Document]*

QUESTION 11: Does the Agency agree that the proposed nonclinical package will support registration of BIIB017?

FDA Preliminary Response

No. Pegylation of protein drugs may result in significant alterations in pharmacokinetics, biodistribution, and immunogenicity. Therefore, it is not clear that the data on INF ß-1a (Avonex®) alone are adequate to assess the nonclinical safety of BIIB017. The presence of the PEG moiety may result in toxicity not observed with the active interferon molecule. Considering the previous human experience with INF ß-1a (Avonex®), it will not be necessary to further characterize the general toxicity of BIIB017. However, you will need to conduct reproductive toxicology studies (embryofetal development, pre- and post-natal development) in a relevant animal model using BIIB017.

Meeting Discussion

The Sponsor asked for clarification of the need for reproductive toxicology studies for BIIB017. According to the sponsor, the plan is to address this concern by submitting data from studies assessing hormone levels and general toxicity. The Division noted that these data might adequately address the issue of fertility, but not potential effects on embryofetal or pre/post-natal development. The Division stated that if the sponsor does not intend to conduct embryofetal and pre/post-natal development studies, justification should be provided for that approach. That justification should address potential differences in plasma exposure due to PEGylation, the relevance of general toxicity findings to reproductive toxicology, and issues regarding the feasibility of conducting these studies in nonhuman primate (which was not discussed by the sponsor).

Linked Applications	Sponsor Name	Drug Name
IND 100110	BIOGEN IDEC INC	PEGylated interferon beta-1a

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

/s/

RUSSELL G KATZ
12/12/2008

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125499

LATE-CYCLE MEETING MINUTES

Biogen Idec, Inc.
Attention: Nadine Cohen, PhD
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Plegridy (peginterferon beta-1a).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 10, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 10, 2014; 1:00 – 2:00 PM EST
Meeting Location: FDA White Oak Campus, Building 22; Room 1309
10903 New Hampshire Avenue
Silver Spring, MD 20993

Application Number: BLA 125499
Product Name: Plegridy (peginterferon beta-1a)
Applicant Name: Biogen Idec, Inc.

Meeting Chair: John Marler, MD
Meeting Recorder: Nicole Bradley, PharmD

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Billy Dunn, MD, Acting Director
John Marler, MD, Acting Clinical Team Leader
Sally Yasuda, PharmD, MPH, Safety Team Leader
Nicole Bradley, PharmD, Regulatory Project Manager

Office of Biotechnology
Susan Kirshner, PhD, Review Chief
Juhong Liu, PhD, Team Lead
Ralph Bernstein, PhD, Reviewer
Ennan Guan, PhD, Reviewer

Office of Manufacturing and Product Quality
Patricia Hughes, PhD, Team Leader
Bo Chi, PhD, Reviewer
Lakshmi Narasimhan, PhD, Reviewer

Center for Devices and Radiological Health
Quynh Nhu Nguyen, Human Factors Reviewer
Ryan McGowan, Biomedical Engineer

Division of Medication Errors Prevention and Analysis
Julie Neshiewat, PharmD, Team Leader

Justine Harris, RPh Safety Evaluator

Pediatric and Maternal Health Staff
Ethan Hausman, MD, Pediatric Reviewer

EASTERN RESEARCH GROUP ATTENDEES
(b) (6), Independent Assessor
(b) (6), Independent Assessor

APPLICANT ATTENDEES

Biogen Idec, Inc.
Serena Hung, Medical Director, Clinical Development
Ali Seddighzadeh, Medical Director, Drug Safety and Risk Management
Atul Patel, Director, Technical Development
Clive Patience VP, Global Quality Assurance
Jess Ballinger, Senior Director, Technical Development
Joanne Nijssen, CMC Team Director
Robert Gronke, Senior Principal Scientist, Technical Development
Kimberly Wolfram, Associate Director, Regulatory Affairs
Ann Dodds-Frerichs, VP, Regulatory Affairs
Suzanne Zuraski, Director, Regulatory Affairs
Tammy Phinney, Senior Director, Regulatory Affairs
John Barry, Director, Regulatory Affairs
Heather Faulds, Director, Regulatory Affairs
Stephanie Melillo, Manager, Regulatory Affairs
Ketan Shah, Director, Quality Control

1.0 BACKGROUND

BLA 125499 was submitted on May 15, 2013, for Plegridy (peginterferon beta-1a)

Proposed indication: Relapsing-remitting forms of multiple sclerosis

PDUFA goal date: May 16, 2014

FDA issued a Background Package in preparation for this meeting on January 28, 2014.

2.0 SUMMARY OF MEETING DISCUSSION

1. Introductory Comments
2. Discussion of Substantive Review Issues

   Each issue will be introduced by FDA and followed by a discussion.

   a. Prefilled syringe and prefilled pen human factors

   Discussion:
   The FDA review team recently received the instructions for use (IFU) validation test reports, but has not yet discussed the adequacy of the information. With regard to the study methodology, the team asked whether the cognitive walkthrough approach included participants performing the critical tasks in addition to demonstrating comprehension of the information contained in the IFUs. Biogen confirmed that the participants performed critical tasks during the study. FDA commented that preliminary evaluation of the results of the IFU validation studies found an improvement in task performance; however, there continue to be failures and use errors. Biogen confirmed that no further changes to the IFUs were made after completion of the validation studies. FDA will perform a detailed review to determine whether there is a need for additional mitigations and/or testing.

   b. Drop test device failures

   Discussion:
   Biogen outlined a proposed response plan for answering FDA's remaining questions concerning freedom from breakage or malfunction after a fall or drop. FDA 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 can only be asserted after evaluation of formal response materials.

3. Discussion of Minor Review Issues

   Office of Manufacturing and Product Quality (OMPQ)

a. There is uncertainty over the reliability of the endotoxin release test results for drug product. An endotoxin spiking study will be conducted using containers of similar composition as those used for sampling and storage of drug product to evaluate the potential for endotoxin masking over time. Results from this study are pending and will be submitted by March 31, 2014.

b. Data demonstrating that the endotoxin sample storage conditions do not impact the recovery of endotoxin will be submitted by March 31, 2014.

c. Drug product [redacted] (b) (4) qualification data with an additional conformance lot will be submitted by March 31, 2014.

d. [redacted] (b) (4) will be provided by January 31, 2014.

e. [redacted] (b) (4) will be provided by January 31, 2014.

f. [redacted] (b) (4) will be provided by January 31, 2014.

Discussion:
FDA accepted the updated commitment dates. Specifically, items (a), (b), (c), and (d) will be provided by March 31, 2014. Item (e) was submitted on January 23, 2014. For item (f), Biogen submitted the [redacted] (b) (4) on January 31, 2014. Biogen plans to provide the endotoxin qualification data of these samples by February 14, 2014.

4. Information Requests

Division of Medication Errors Prevention and Analysis

a. Recommendations for the labels and labeling of the prefilled syringe and pen were sent on January 14, 2014, and we are currently waiting on a response. All recommendations for the labels and labeling should be addressed prior to conducting any human factors study.

Discussion:
Biogen responded to FDA recommendations for the labels and labeling on January 24, 2014. FDA has not completed their review of this submission.

Center for Device and Radiologic Health

b. In your January 15, 2014, response to the Agency, you have provided information to support ISO 11608-1:2012 testing, specifically free fall testing completed by

independent testing laboratory and Notified Body, [redacted] concluded within Report 89203092.03 that the batch they tested did not pass criteria of ISO 11608-1:2012. The Agency has reviewed your claim that the failure which caused [redacted] to conclude the batch did not pass testing requirements constitutes an obvious failure. At this time, we disagree with your position; however, we request additional information in order to understand the purpose and importance of ISO 11608-1:2012 drop testing as it relates to the application:

i. Describe the design requirements and specifications that are in place for your device relevant to freedom from breakage or malfunction after a fall or drop.

ii. Contrast the design requirements and specifications outlined in your response to (i), above, with methods used to verify these requirements and specifications.

iii. If you have determined that the results of the [redacted] Report 89203092.03 adequately verify product requirements and specifications as outlined within your response to (i), above, then provide the rationale for this determination.

iv. Provide an analysis of risks to the user if they have an experience like that described for device sample number F13 in [redacted] Report 89203092.03. Include a listing of current or proposed mitigations you have established (if any) to reduce the risk to the patient in such a scenario.

Discussion:
See discussion under item 2(b).

Office of Biotechnology Products

c. [redacted] To assure safety, revise your [redacted] according to manufacturing history and in concordance with clinical trial material.

Discussion:
The proposed [redacted] rejection limit stated in the response submitted on January 31, 2014, was [redacted] in clinical lots. FDA stated that the rejection limit should be revised to conform to clinical and manufacturing experience.

d. In your primary and working reference standard qualification, you state the potency of the references will be assigned based on a "rigorous protocol driven

testing" but provide no details of the testing. Provide details about your potency assignment strategy and your assessment of how the strategy prevents drift.

e. Your drug product (DP) post-approval stability protocol includes only real temperature stability testing. Revise your annual stability protocol to include stability testing under accelerated storage conditions.

Discussion:
FDA stated that because of long gaps between testing time points in annual stability protocols, an out of specification event may not be discovered in time. To ensure safety, FDA now requests that sponsors include accelerated stability testing as part of their annual stability testing. (b) (4) FDA responded that the accelerated stability testing was generally more sensitive to potential product quality issues. Accelerated stability testing should be an integral part of an annual stability testing program and should stay with the product throughout its entire life cycle.

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

Discussion:
At the time of the late-cycle meeting, the review team had not reviewed Biogen's response received on February 10, 2014. FDA will communicate the evaluation of these materials to the sponsor once the review is completed.

5. Postmarketing Requirements (PMRs)/Postmarketing Commitments (PMCs)

Office of Biotechnology Products

a. The acceptance criteria for release and stability specifications for the Plegridy drug substance and drug product are (b) (4) than your clinical experience and manufacturing experience. Re-evaluate the following acceptance criteria after thirty (30) batches are manufactured or within three (3) years, whichever is sooner:

i. Drug substance:

1. CPE Potency
2. (b) (4)

3. HMW impurities
4. (b) (4)

ii. Drug product:

5. CPE Potency
6. (b) (4)
7. HMW impurities
8. (b) (4)
9. Purity for drug product

b. You have not provided study results showing the level of leachables in the Plegridy drug product at the end of expiry. To ensure safety, evaluate levels of leachables for the components detected in the extractable studies for samples at the end of expiry.

c. You have only conducted subvisible (2-10 microns) particulate testing of Plegridy PFS with HIAC. Because using only one method may bias the actual particulate counts, you need to conduct the study using at least one orthogonal method.

Discussion:
FDA noted that in addition to the PMRs outlined above, they plan to issue a PMR for a pregnancy registry and a PMR for a pediatric study.

6. Review Plans

Discussion:
FDA stated that, as conveyed in the July 15, 2014, Filing Communication letter, the goal date to convey labeling/PMRs/PMCs is April 16, 2014, and the user fee goal date is May 16, 2014.

7. Wrap-up and Action Items

Discussion:
None.

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and, therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

WILLIAM H Dunn
02/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125499

LATE CYCLE MEETING
BACKGROUND PACKAGE

Biogen Idec, Inc.
Attention: Nadine Cohen, PhD
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Plegridy (peginterferon beta-1a).

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 10, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	February 10, 2014; 1:00 – 2:00 PM EST
Meeting Location:	FDA White Oak Campus Building 22; Room 1309 10903 New Hampshire Avenue Silver Spring, MD 20993
Application Number:	BLA 125499
Product Name:	Plegridy (peginterferon beta-1a)
Indication:	Multiple Sclerosis
Sponsor/Applicant Name:	Biogen Idec, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

HUMAN FACTORS
Division of Medication Errors Prevention and Analysis
Center for Devices and Radiologic Health

a. Plegridy Prefilled Syringe (PFS):
As indicated in the November 8, 2013, information request and during the October 10, 2013, mid-cycle communication teleconference, you have not demonstrated safe and effective use of the PFS with representative users. Prior to approval of the PFS, you need to address the concerns described in previous communications. You will be required to validate changes to the Instructions for Use (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 to submit the results of this validation study for review. We ask that you provide a table that outlines all of the IFU changes and link 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.

b. Plegridy Prefilled Pen:
As indicated in the November 8, 2013, information request and during the October 10, 2013, mid-cycle communication teleconference, you have not demonstrated safe and effective use of the pen device with representative users. Prior to approval of the pen device, you need to address the 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, which incorporated IFU changes that were made after the first study, continued to show similar task failures, use errors, and reported difficulties. This indicates that you have not effectively addressed the task failures, use errors, and reported difficulties with those IFU changes. 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 evaluations or studies.

ENGINEERING
Center for Devices and Radiologic Health

c. Drop Test Device Failures
We determined that your response to our September 17, 2013, information request was incomplete because you could not verify that drop testing, per ISO11608-1, had been completed properly by an independent testing laboratory and Notified Body, (b) (4) On January 15, 2014, you subsequently provided an updated test report completed by (b) (4) in which 30 devices were tested and dropped from 3 orientations as specified within ISO11608-1. Of these 30 devices, one device was found to have obvious damage, (b) (4) . An additional 6 devices were noted to have minor damage that did not result in a failure to deliver the product. In total, 23 devices showed no visible damage, of these, 21 devices were chosen for dose accuracy testing, and all passed. However, the test company, (b) (4) considers that this batch did not pass because one of these 21 devices (b) (4) We note that you consider this to be a delivery failure that is not obvious to the user and thus is not compliant with ISO11608-1. You state that this failure should not constitute a batch failure per ISO11608-1, as the failure was obvious to the user during injection; therefore, you believe (b) (4) should be able to consider this a "replaceable device" per ISO11608-1. The Agency's evaluation of the test report confirms (b) (4) findings that a non-compliant delivery occurred with one of the devices and that the device previously represented a non-obvious defect after drop. Considering this, the batch does not meet the ISO11608-1 standard.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. **Introductory Comments** – 5 minutes (Nicole Bradley/John Marler)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. **Discussion of Substantive Review Issues** – 20 minutes (CDRH and DMEPA)

   Each issue will be introduced by FDA and followed by a discussion.

   a. Prefilled syringe and prefilled pen human factors

   b. Drop test device failures

3. **Discussion of Minor Review Issues** – 5 minutes (OMPQ)

   Office of Manufacturing and Product Quality (OMPQ)

   a. There is uncertainty over the reliability of the endotoxin release test results for drug product. An endotoxin spiking study will be conducted using containers of similar composition as those used for sampling and storage of drug product to evaluate the potential for endotoxin masking over time. Results from this study are pending and will be submitted by March 31, 2014.

   b. Data demonstrating that the endotoxin sample storage conditions do not impact the recovery of endotoxin will be submitted by March 31, 2014.

   c. Drug product (b) (4) qualification data with an additional conformance lot will be submitted by March 31, 2014.

   d. (b) (4) will be provided by January 31, 2014.

   e. (b) (4) will be provided by January 31, 2014.

   f. (b) (4) will be provided by January 31, 2014.

4. **Information Requests** – 10 minutes (DMEPA, CDRH, OBP)

   Division of Medication Errors Prevention and Analysis

   a. Recommendations for the labels and labeling of the prefilled syringe and pen were sent on January 14, 2014, and we are currently waiting on a response. All

recommendations for the labels and labeling should be addressed prior to conducting any human factors study.

Center for Device and Radiologic Health

b. In your January 15, 2014, response to the Agency, you have provided information to support ISO 11608-1:2012 testing, specifically free fall testing completed by independent testing laboratory and Notified Body, [redacted] concluded within Report 89203092.03 that the batch they tested did not pass criteria of ISO 11608-1:2012. The Agency has reviewed your claim that the failure which caused [redacted] to conclude the batch did not pass testing requirements constitutes an obvious failure. At this time, we disagree with your position; however, we request additional information in order to understand the purpose and importance of ISO 11608-1:2012 drop testing as it relates to the application:

   i. Describe the design requirements and specifications that are in place for your device relevant to freedom from breakage or malfunction after a fall or drop.

   ii. Contrast the design requirements and specifications outlined in your response to (i), above, with methods used to verify these requirements and specifications.

   iii. If you have determined that the results of the [redacted] Report 89203092.03 adequately verify product requirements and specifications as outlined within your response to (i), above, then provide the rationale for this determination.

   iv. Provide an analysis of risks to the user if they have an experience like that described for device sample number F13 in [redacted] Report 89203092.03. Include a listing of current or proposed mitigations you have established (if any) to reduce the risk to the patient in such a scenario.

Office of Biotechnology Products

c. [redacted] To assure safety, revise your [redacted] according to manufacturing history and in concordance with clinical trial material.

d. In your primary and working reference standard qualification, you state the potency of the references will be assigned based on a "rigorous protocol driven testing" but provide no details of the testing. Provide details about your potency assignment strategy and your assessment of how the strategy prevents drift.

e. Your drug product (DP) post-approval stability protocol includes only real temperature stability testing. Revise your annual stability protocol to include stability testing under accelerated storage conditions.

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

5. Postmarketing Requirements/Postmarketing Commitments – 10 minutes (OBP)

Office of Biotechnology Products

a. The acceptance criteria for release and stability specifications for the Plegridy drug substance and drug product are much (b) (4) your clinical experience and manufacturing experience. Re-evaluate the following acceptance criteria after thirty (30) batches are manufactured or within three (3) years, whichever is sooner:

   i. Drug substance:

      1. CPE Potency
      2. (b) (4)
      3. HMW impurities
      4. (b) (4)

   ii. Drug product:

      1. CPE Potency
      2. (b) (4)
      3. HMW impurities
      4. (b) (4)
      5. Purity for drug product

b. You have not provided study results showing the level of leachables in the Plegridy drug product at the end of expiry. To ensure safety, evaluate levels of leachables for the components detected in the extractable studies for samples at the end of expiry.

c. You have only conducted subvisible (2-10 microns) particulate testing of Plegridy PFS with HIAC. Because using only one method may bias the actual particulate counts, you need to conduct the study using at least one orthogonal method.

6. Review Plans – 5 minutes (John Marler)

7. Wrap-up and Action Items – 5 minutes (ALL)

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/s/

WILLIAM H Dunn
01/28/2014