CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204063Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204063 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Tecfidera Established/Proper Name: dimethyl fumarate Dosage Form: delayed-release capsules		Applicant: Biogen Idec Agent for Applicant (if applicable):
RPM: Nicole L. Bradley		Division: Division of Neurology Products

NDAs and NDA Efficacy Supplements:

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

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (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. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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 • User Fee Goal Date is March 27, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (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., nrew listed drug, patent certification revised).

❖ 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]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug 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
❖ 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
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[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.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
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 - March 27, 2013
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.	
• Original applicant-proposed labeling	02/27/2012
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

❖ 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.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	N/A
❖ 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	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM ☒ DMEPA ☒ DMPP/PLT (DRISK) ☒ ODPD (DDMAC) ☒ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	 ☒ Not a (b)(2) ☒ 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
• 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 November 28, 2012 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• 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 1/25/2012
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 08/30/2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	CMC – 07/21/2011
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 3/27/2013
Division Director Summary Review *(indicate date for each review)*	☐ None 3/27/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 3/25/2013
PMR/PMC Development Templates *(indicate total number)*	☐ None 6
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Safety TL – 02/07/2013
• Clinical review(s) *(indicate date for each review)*	Efficacy: 03/25/2013 Safety: 01/09/2013
• 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)*	Addressed in Primary Clinical Efficacy Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None QT/IRT, Maternal Health, Pediatrics, DPV
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable 12/20/2012
❖ Risk Management • REMS Documents and Supporting Statement *(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 02/06/2013
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 11/16/2012

[6] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None 10/15/2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/18/2012
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None 09/21/2012
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 03/25/2013
• Supervisory Review(s) *(indicate date for each review)*	☐ None 03/20/2013
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 01/28/2013
❖ 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 10/24/2012 02/21/2013
❖ ECAC/CAC report/memo of meeting	☐ None 10/01/2012 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)*	☐ None 02/13/2013
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 11/19/2012
❖ 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 Biopharmaceutics – 11/19/2012

❖ 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)*	CMC primary review – 11/19/2012
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(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[7])*	Date completed: 03/20/2013 ☒ 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)

[7] 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

EXCLUSIVITY SUMMARY

NDA # 204063 SUPPL # HFD # 120

Trade Name Tecfidera

Generic Name dimethyl fumarate

Applicant Name Biogen Idec

Approval Date, If Known March 27, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Nicole L. Bradley, PharmD
Title: Regulatory Project Manager
Date: March 27, 2013

Name of Office/Division Director signing form: Russell G. Katz, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

NICOLE L BRADLEY
03/27/2013

RUSSELL G KATZ
03/27/2013

biogen idec

The services of any person debarred under Subsections A or B of Section 306 of the Federal Food, Drug and Cosmetic Act were not and would not be used in any capacity in connection with this application.

Jorge Guerra
SVP, Global Clinical Development Operations
Biogen Idec, Inc.

12/2/2012
Date

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, March 04, 2013 12:33 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 PMR revised milestone dates

Hi Tammy,

Reference is made to NDA 204063 and to your February 22, 2013, submission which provided acceptance of the Post-Marketing requirements (PMRs) and your proposed milestone dates.

We accept the milestone dates you provided for the following PMRs, as outlined below:

- A juvenile rat toxicology study. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of dimethyl fumarate on growth, reproductive development, and neurological and neurobehavioral development.

  Final Protocol Submission: 04/30/2014
  Study Completion: 01/31/2016
  Final Report Submission: 03/31/2016

- Deferred pediatric trial under PREA: A randomized, controlled, parallel group superiority trial to evaluate the pharmacokinetics of dimethyl fumarate, and the safety and efficacy of dimethyl fumarate compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

  Final Protocol Submission: 11/30/2016
  Study/Trial Completion: 10/31/2019
  Final Report Submission: 02/28/2020

- A large, long-term, prospective observational study in relapsing multiple sclerosis patients with the primary objective of determining the nature and incidence of serious infections including opportunistic infections, leiomyomata, malignancies including renal cell cancers, and other serious adverse events including serious renal and hepatic events and other medically significant events occurring with marketed use of Tecfidera. The study should include characterization of the finding of urinary ketones. A minimum of 5000 multiple sclerosis patients treated with Tecfidera should be enrolled and followed for a minimum of 5 years. Agency agreement with the protocol must be obtained prior to starting the study.

  Final Protocol Submission: 10/31/2013
  Study Completion: 10/30/2022
  Final Report Submission: 10/30/2023

We would like you to revise the milestone dates for the following PMRs, as outlined in red and strikeout below:

- Comprehensive in vitro receptor binding studies with dimethyl fumarate and with its metabolite monomethyl fumarate. This includes characterizing the affinity of dimethyl fumarate and monomethyl fumarate on dopamine, serotonin, GABA (gamma-amino-butyric-acid), opioid, NMDA, monoamine, sodium channel, calcium channel, and cannabinoid receptor sites, as well as the interaction of dimethyl fumarate and of monomethyl fumarate with nitric oxide synthase.

  Final Protocol Submission: 06/30/2013
  Study Completion: (b) (4) -08/30/2013
  Final Report Submission: (b) (4) -10/30/2013

- A nonclinical abuse potential assessment with a self-administration study using dimethyl fumarate in animals trained to discriminate the known drug of abuse from saline. The animals chosen must demonstrate similar

metabolism of dimethyl fumarate and monomethyl fumarate as observed in humans.

Final Protocol Submission: (b) (4) 10/30/2013
Study Completion: (b) (4)
Final Report Submission: (b) (4) 03/30/2014

- A nonclinical abuse potential assessment with a discrimination study using dimethyl fumarate in animals trained to discriminate the known drug of abuse from saline. The animals chosen must demonstrate similar metabolism of dimethyl fumarate and monomethyl fumarate as observed in humans.

Final Protocol Submission: (b) (4) -03/30/2014
Study Completion: (b) (4)
Final Report Submission: (b) (4) -08/30/2014

Please provide your acceptance of these revised milestone dates or your proprosed changes.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
03/04/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Thursday, February 14, 2013 1:29 PM
To: Tammy Phinney
Cc: Kimberly Richard O'Brien; Tammy Sarnelli; Bradley, Nicole
Subject: NDA 204063 FDA Proposed Label_February 14, 2013

Attachments: NDA 204063_FDA_PMRs_2013_0214.doc

Hi Tammy,

Reference is made to NDA 204063.

Please find attached the FDA proposed label. As discussed, we are prepared to have a brief teleconference with you at 3:15pm today to discuss our revisions.

Additionally, I have attached the Post-Marketing Requirements. Please provide the milestone dates.

NDA
_FDA_PMRs_2013_(

Thanks,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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

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/s/

NICOLE L BRADLEY
02/14/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Tuesday, February 05, 2013 8:46 AM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Carton and Container Labeling Comments_February 5, 2013

Hi Tammy,

Reference is made to NDA 204063. We also refer to your January 23, 2013, submission in which you provided responses to our January 15, 2013, carton and container labeling comments. We have reviewed this submission and have the following additional comment:

- The dosage form should utilize the same font as the active ingredient. Use a bold font for the dosage form 'delayed-release capsules' so that it matches the bold font for the active ingredient dimethyl fumarate.

Please provide your response by February 11, 2013.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
02/05/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, February 04, 2013 8:16 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 FDA Proposed Label_ February 4, 2013

Attachments: NDA 204063_FDA Proposed Label_2013_0204.doc

Hi Tammy,

Reference is made to NDA 204063. Please find attached the FDA proposed label.

NDA 204063_FDA
Proposed Label_...

We look forward to receiving your acceptance or revisions (in tracked changes) on Friday, February 8, 2013.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
02/04/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204063

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 New Drug Application (NDA) submitted February 24, 2012, received February 27, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dimethyl Fumerate Delayed-release Capsules, 120 mg, and 240 mg.

We also refer to your correspondence, dated and received October 24, 2012, requesting review of your proposed proprietary name, Tecfidera. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

Tecfidera will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 24, 2012 submission are altered prior to approval of the marketing application, the proprietary name 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 Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. 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

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/s/

LAURIE A KELLEY
01/17/2013

CAROL A HOLQUIST
01/17/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Tuesday, January 15, 2013 3:28 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Carton and Container Comments_January 15, 2013

Dear Tammy,

Reference is made to NDA 204063. We also refer to your December 7, 2012, submission in which you provided responses to our November 27, 2012, carton and container labeling comments. We have reviewed this submission and have the following additional comments:

A. General Comments for All Labels and Labeling

1. Use a bold font for the established name for increased prominence on all labels and labeling. As currently presented, the statement "Swallow capsule whole" on the container labels appears more prominent than the established name. While the "Swallow capsule whole" statement is important, the established name should be more prominent.

B. 14-day Sample Pack (Professional Sample), 30-day Sample Pack (Professional Sample), and 30-day (b) (4) (Retail)

1. Container Labels (120 mg and 240 mg)
   a. Decrease the font size of "Rx only" since it may take attention away from other important information on the label.

2. Carton Labeling
   a. Add a statement similar to "See back panel for dosage and administration instructions for use" on the principal display panel below the statement "Once the bottles are opened, use within 90 days."

C. Bottle Container Labels (120 mg and 240 mg: professional sample, retail, and no charge)

1. See recommendations B.1.a.

D. Bottle Carton Labeling (120 mg and 240 mg: professional sample, retail, and no charge)

1. See recommendation B.1.a.

2. Relocate the NDC from the colored bar on the top of the carton labeling to the same line of text as the net quantity X capsules. Revise the font to black similar to the presentation found on the container labels. As currently presented, the NDC appears highlighted and overly prominent.

Please provide your responses by January 23, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
01/16/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Tuesday, November 27, 2012 12:42 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Carton and Container Comments_November 27, 2012

Dear Tammy,

Reference is made to NDA 204063. We also refer to your October 10, 2012, submission which provided a response to our September 19, 2012, carton and container comments. We have reviewed your submission and have the following comments:

A. General Comments for All Labels and Labeling

1. We note that a placeholder for the NDC (XXXXX-XXX-XX) is present on the labels and labeling. We request that the actual number assigned to the label or labeling be submitted.

B. 14-day (b) (4) (Professional Sample)

1. Carton Labeling

a. The Agency does not consider (b) (4) to be drug samples; therefore, the use of the term (b) (4) on drug sample labeling is inappropriate and should not be used. Revise the statement (b) (4) to read "14-day Sample Pack" to comply with 21 CFR 203.38 (c) and 64 FR 67720 at 67741.

b. Revise the statement "SAMPLE" in all upper case to title case "Sample" for improved readability.

c. The statements "Regular Dose" and "Regular Dose Bottle" (b) (4) font next to the 240 mg strength are difficult to read against the (b) (4) (b) (4) color block. Revise the font color of the text or the color block for better contrast.

d. Increase the font size of the statement "Swallow capsule whole" on the principal display panel (PDP) for increased prominence.

e. Decrease the font size of the "Sample: Not for sale" statement and relocate it to the lower left corner, replacing the (b) (4) " statements. These two statements should be removed from the PDP since this information already appears elsewhere on the carton and is redundant.

f. In order to prevent confusion between the PDP and the back panel, remove all color blocking on the back panel and revise the package contents on the back panel to read similar to the side panel.

Package Contents:
One (b) (4) bottle containing 14 capsules of 120 mg each
One (b) (4) bottle containing 14 capsules of 240 mg each

Since the package contents will appear on the back panel, this information can be removed from the side panel.

2. Container Labels (120 mg and 240 mg)

a. See recommendation B.1.b and B.1.c.

b. The statements “Manufactured by...” and “Cambridge, MA...” on the principal display panel (PDP) appear prominent and detract from other important information on the label. Relocate these statements to the side panel. In order to accommodate these statements, remove the statement [redacted] since “Dosage: take one capsule by mouth twice daily” is already present on the side panel.

c. The net quantity statement is color blocked [redacted] for the 120 mg strength and [redacted] for the 240 mg strength, which increases the prominence of the net quantity statement. Relocate the net quantity statement to the upper right corner without any color block. Decrease the font size of the net quantity statement and the NDC number. In addition, relocate the ‘Rx only’ statement to the lower right corner and decrease the font size of this statement.

d. Relocate the statements “Take on days X to Y” to appear in the pale color block below the strength.

e. Relocate the statement “Swallow capsule whole” from the side panel to the PDP under the statement “Take on days X to Y."

f. Reduce the font size of the statement “Sample: Not for sale” since it is overly prominent on the side panel.

C. 30-day [redacted] (Professional Sample)

1. Carton Labeling
   a. See recommendations B.1.b to B.1.e.

   b. The Agency does not consider [redacted] to be drug samples; therefore, the use of the term [redacted] on drug sample labeling is inappropriate and should not be used. Revise the statement [redacted] to read “30-day Sample Pack” to comply with 21 CFR 203.38 (c) and 64 FR 67720 at 67741.

   c. In order to prevent confusion between the principal display panel and the back panel, remove all color blocking on the back panel and revise the package contents on the back panel to read
   Package Contents:
   One [redacted] bottle containing 14 capsules of 120 mg each
   One [redacted] bottle containing 46 capsules of 240 mg each

2. Container Labels (120 mg and 240 mg)
   a. See recommendation B.1.b, B.1.c, B.2.b to B.2.f.

D. 30-day [redacted] (Retail)

1. Carton Labeling
   a. See recommendations B.1.c, B.1.d, and C.1.c.

   b. The [redacted] statements should be removed from the PDP since this information already appears elsewhere on the carton.

2. Container Label (120 mg and 240 mg)
   a. See recommendations B.1.c, B.2.b to B.2.e.

E. Bottle Container Labels (120 mg and 240 mg: retail and professional sample)

1. See recommendations B.1.b, B.2.b, and B.2.c.

F. Bottle Carton Labeling (120 mg and 240 mg: retail and professional sample)

1. See recommendation B.1.b

2. The net quantity statement is color blocked (b) (4) for the 120 mg strength and a (b) (4) for the 240 mg strength, which increases the prominence of the net quantity statement. Remove the color block and relocate the net quantity statement to the upper right corner of the PDP, away from the statement of strength. The 'Rx Only' statement can be relocated to the lower right corner and the "Biogen Idec" logo can be removed, since this appears on the back panel. In addition, the "Sample: Not for Sale" statement can be relocated to the lower left corner.

3. Relocate the statement "Swallow capsule whole" from the side panel to the PDP.

4. The NDC placeholder XXXXX-XXX-XX in black font for the 240 mg strength is difficult to read against the dark blue color block. Revise the font color of the text or the color block for better contrast.

Please provide your response by December 11, 2012.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
11/28/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Friday, November 16, 2012 9:36 AM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_November 16, 2012

Dear Tammy,

Reference is made to NDA 204063. We have the following questions:

Do you have access to samples that would allow for testing of fumarate hydratase (FH) activity in BG00012 patients 147-004 and 463-307, the patients who developed renal cell cancers?

In your response to our request for information about fumarate as an oncometabolite, you cited fumarate tissue levels in a paper by Pollard et al as the levels associated with FH deficiency. The fumarate levels cited were in uterine fibroid samples, in patients with recognized FH deficiency. You then made comparisons to plasma fumarate levels reported in the NDA trials. A potentially more useful comparison would be to tissue levels in patients with FH deficiency prior to development of tumors, since this would represent fumarate levels that lead to tumor development. Are you aware of tissue fumarate levels in patients with FH deficiency, prior to development of tumors?

Please provide your responses within two weeks.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
11/16/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204063

PROPRIETARY NAME REQUEST WITHDRAWN

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 New Drug Application (NDA) dated February 24, 2012, received February 27, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dimethyl Fumarate Capsules, 120 mg, and 240 mg.

We acknowledge receipt of your correspondence, dated and received October 24, 2012, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of October 24, 2012.

We note that you have proposed an alternate proprietary name in your submission dated August 29, 2012. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. 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

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/s/

LAURIE A KELLEY
10/29/2012

CAROL A HOLQUIST
10/29/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Tuesday, October 23, 2012 8:03 AM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_October 23, 2012

Hi Tammy,

Reference is made to NDA 204063. We request the following information:

1. Summary of inter-subject variability in PK parameters from all studies under fasted and fed conditions.
2. Summary of PK parameters for Study 109HV106. Include the mean, standard deviation, %CV, geometric mean ratio (GMR), and 90% CI of GMR.
3. Individual subject plasma PK profiles for Study C-1903 (food effect study). Include synoptic/spaghetti plots for each treatment.
4. Bioanalytical validation report for HPLC/UV assay. This assay was used in studies FAG-201-FG-PK-02-02 and FAG-201-FG-PK-03/04.

Please provide your responses by Thursday, October 25, 2012.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
10/23/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Wednesday, October 17, 2012 4:47 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_October 17, 2012

Importance: High

Attachments: Picture (Metafile)

Hi Tammy,

Reference is made to NDA 204063.

The clinical review team would like clarification on the table below, referred to as Table 14-62 in your submission on p. 620 of the study report for trial 109MS301. Please provide a response by COB October 24, 2012.

There are certain instances where reported values appear to be in error, and the review team is requesting that you verify that the numbers listed for the mean change from baseline for the 9HPT, PASAT-3 and the 25-Foot walk are correct. In addition, please confirm that the associated p values listed in the table below are correct. For example, in the 9HPT the placebo group had a change from baseline to 2 years of 5.20 seconds and the BG-12 BID group had a 5.25 second change. Your table below indicates that this difference represents a nominally significant change associated with a p value of 0.014, yet the BG-12 tid treatment group with a change of -0.37 represents a change associated with a p value of 0.0009. Is it correct, that the difference of 0.05 sec in the placebo and BG-12 bid group represents a change associated with the p value 0.014?

MSFC: Change of actual scores from baseline to 2 years- ITT population (trial 301)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in ITT population	408	410	416
Change from baseline to 2 years (Week 96) 25-Foot Walk (sec.)			
n	396	395	402
Mean	3.71	0.53	1.69
SD	23.809	12.809	14.885
Median	0.15	0.10	0.15
Min, Max	-62.4, 268.7	-113.4, 157.3	-87.3, 155.0
p-value (a)		0.1137	0.6891
9 HPT (sec.)			
n	396	395	402
Mean	5.20	5.25	-0.37
SD	60.549	56.132	14.079
Median	0.06	-0.30	-0.34
Min, Max	-158.8, 755.8	-193.7, 757.2	-179.9, 184.5
p-value (a)		0.0146	0.0009
PASAT 3 (# items)			
n	395	393	402
Mean	1.7	2.5	2.7
SD	7.75	6.46	7.31
Median	1.0	2.0	2.0
Min, Max	-43, 37	-22, 40	-20, 42
p-value (a)		0.0048	0.0122

Thank you,

Nicole

APPEARS THIS WAY ON ORIGINAL

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/s/

NICOLE L BRADLEY
10/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063

REVIEW EXTENSION – MAJOR AMENDMENT

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 New Drug Application (NDA) submitted on February 27, 2012, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dimethyl fumarate capsules 120 mg and 240 mg.

On October 5, 2012, we received your response to our October 2, 2012, information request. We consider your response a major amendment to this application because it provides information important for our evaluation of the carcinogenic potential of dimethyl fumarate. Our review of this information will have an impact on labeling as well as on the need for additional studies to address this concern. The receipt date of your October 5, 2012, submission is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 27, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 28, 2013.

If you have any questions, call Nicole 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

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/s/

RUSSELL G KATZ
10/17/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Thursday, October 04, 2012 8:58 AM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_October 4, 2012

Hi Tammy,

Reference is made to NDA 204063. We would like to add an additional comment pertaining to the carton and container labeling comments you received on September 19, 2012:

Revise the drug product dosage form designation on the label and labeling from "capsules" to "delayed release capsules" as it is a delayed release product.

Please confirm receipt of this request.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
10/04/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204-063

INFORMATION REQUEST

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 New Drug Application (NDA 204-063) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dimethyl fumarate.

We also refer to your June 27, 2012 submission, containing a 120-day Safety Update.

We are reviewing your submission and have the following comments and information requests.

Nonclinical

Your 120-Day Safety Update submission, dated June 27, 2012, provided a nonclinical safety update, which included expert reports prepared by (b) (4) . According to the information provided, (b) (4) re-examined the kidney sections from the 2-year carcinogenicity studies in mouse (P00012-05-03) and rat (P00012-04-11). The summary data tables indicate substantial changes in the renal histopathology findings, compared to the final study reports submitted in the original NDA submission. You will need to submit amended final study reports for the 2-year studies that include all information (including individual animal line listings) pertaining to (b) (4) re-examination. For both studies, you should provide summary tables specifying the original and revised kidney findings for each animal.

All nonclinical data should be submitted to Module 4, and not, as the 120-day nonclinical safety update was, to Module 5. We also ask that you specify if any additional nonclinical data have been placed in locations other than Modules 2 and 4 in the eCTD.

We request a prompt written response in order to continue our evaluation of your NDA.

Clinical

Our review of the literature identified publications that discuss deleterious effects of increased intracellular fumarate levels, and that label fumarate as an "oncometabolite", including

publications by Sudarshan *et al*. (Sudarshan S, Shanmugasundaram K, Naylor SL *et al*. PLoS ONE 6(6):e21037. doi:10:1371/journal.pone.0021037) and by Yang *et al*. (Yang M, Soga T, Pollard PJ, Adam J. Front. Oncol. **2**:85. doi:10.3389/fonc.2012. 00085). These publications describe germline loss of function mutations for fumarate hydratase that result in increased intracellular fumarate levels. Individuals with these mutations can develop skin and uterine leiomyomatosis, renal cysts, and renal cell cancers.

We request that you provide a discussion of the medical literature discussing deleterious effects of increased intracellular fumarate levels and its role as an oncometabolite. In addition we request that your discussion address the implications for dimethyl fumarate, with consideration of the nonclinical findings of increased renal cell cancers and of the renal cell cancers identified in the clinical trials database.

We also request an explanation of your rationale for not including renal monitoring recommendations in your proposed labeling for dimethyl fumarate. As you explain in your post marketing summary for Fumaderm, which includes dimethyl fumarate, you found that "Regular testing of urine for protein and blood serum for creatinine is recommended because of reports of very rare toxic effects of fumarates on renal proximal tubular cells."(ISS, p.8629). Please explain why renal monitoring is not necessary for dimethyl fumarate.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Nicole 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

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/s/

ERIC P BASTINGS on behalf of RUSSELL G KATZ
10/02/2012

Executive CAC
Date of Meeting: September 25, 2012

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair
Abigail Jacobs, Ph.D., OND-IO, Member
Paul Brown, Ph.D., OND IO, Member
Sushanta Chakder, Ph.D., DGIEP, Alternate Member
Lois Freed, Ph.D., DNP, Supervisor
Melissa Banks-Muckenfuss, Ph.D., DNP, Presenting Reviewer

Author of Draft: Melissa Banks-Muckenfuss

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 204063
Drug Name: BG-12 (dimethyl fumarate, DMF)
Sponsor: Biogen Idec, Inc.

Background information
BG-12 is an immunomodulator being developed for the treatment of multiple sclerosis. A GLP-compliant battery of genetic toxicology assays was conducted for DMF and MMF (a primary circulating metabolite); however, not all studies conducted were consistent with current ICH guidelines. DMF and MMF were positive only in *in vitro* chromosomal aberration assays in mammalian cells. The sponsor conducted 2-year carcinogenicity bioassays in rats and mice. Executive CAC concurrence was obtained for the doses used in the rat study (letter dated 10/6/04), but no agreement was reached for the doses used in the mouse study (see correspondence dated 6/15/05 and 8/9/05).

Rat Carcinogenicity Study
DMF was administered orally (by gavage) at doses of 0 (vehicle), 25 (LD), 50 (LMD), 100 (HMD), and 150 (HD) mg/kg (in 0.8% hydroxypropyl methylcellulose) in male and female Sprague-Dawley rats for up to 104 weeks. Dosing was suspended for HMD and HD males at weeks 82 and 80, respectively, and these groups were terminated early (weeks 88 and 86, respectively). A dose-related reduction in survival was observed for LMD, HMD, and HD males (17% to 13%, compared to 31% in controls) but not for females. Dose-related reductions in body weight were also observed at all doses in males (4-17%) and at the HMD and HD in females (8-12%). A dose-related exacerbation of chronic progressive nephropathy was observed; this was a common cause of death, especially in males. Target organs included nonglandular stomach, kidney, testes, parathyroid, and brain. The incidences of neoplasia(s) were significantly increased in nonglandular stomach and kidney in males and females and in testes.

Mouse Carcinogenicity Study
DMF was administered orally (by gavage) at doses of 0 (vehicle), 25 (LD), 75 (LMD), 200 (HMD) and 600/400 (HD) mg/kg (in 0.8% hydroxypropyl methylcellulose) in male

and female CD-1 mice for up to 104 weeks. The HD was reduced from 600 mg/kg to 400 mg/kg on day 9, after a dosing holiday on days 6 to 8 due to deaths occurring on days 5 to 8 (15 HDM and 13 HDF). Dosing was later suspended in all remaining HD males in week 72 and HD females in week 82. Survival was reduced at the HMD and HD; the HD males and females were terminated early, during week 101. Dose-related reductions in survival were observed (47%, 35%, 25%, and 13% [ss] in treated males, compared to 32% in controls; 36%, 38%, 32% and 13% [ss] in treated females, compared to 45% in controls). Average body weights were reduced at the HD before the dose reduction, secondary to markedly reduced food consumption, but were similar to controls afterward. Dose-related toxicity in the stomach and kidney was associated with drug-related mortality. Non-neoplasic changes were detected in a number of organs, including kidney (e.g., dose-dependent increases in nephropathy, especially males) and stomach (e.g., hyperplasia extending into the nonglandular submucosa and the serosa) at the HMD and/or HD. Significant increases in the incidence of neoplasms of the nonglandular stomach (i.e., adenomas, carcinomas, and leiomyosarcomas) and kidney (adenoma and/or carcinoma) were observed in both sexes.

Executive CAC Recommendations and Conclusions:

Rat:

The Committee agreed that the study was acceptable, despite the presence of pinworms in many rats.

The Committee concurred that drug-related neoplasms were found in the following organs:

- Nonglandular Stomach – squamous cell carcinomas and papillomas in males and females at 25, 50, 100, and 150 mg/kg;
- Kidney – renal tubule adenomas in males and carcinomas in females at 150 mg/kg;
- Testes – interstitial cell adenoma in males at 100 and 150 mg/kg.

Mouse:

The Committee agreed that the study was acceptable, despite the presence of staph infections in many mice and lack of concurrence on the high dose selection by the exec-CAC.

The Committee concurred that drug-related neoplasms were found in the following organs:

- Nonglandular Stomach – squamous cell papillomas and carcinomas in males and females at 200 and 400 mg/kg, and leiomyosarcomas in males and females at 400 mg/kg;
- Kidney – renal tubule adenomas and carcinomas in males at 200 and 400 mg/kg and adenomas in females at 400 mg/kg.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DNP
/Lois Freed, DNP
/Melissa Banks-Muckenfuss, DNP
/Nicole Bradley, DNP
/ASeifried, OND-IO

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/s/

ADELE S SEIFRIED
10/01/2012

DAVID JACOBSON KRAM
10/01/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Thursday, September 27, 2012 3:53 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_September 27, 2012

Dear Tammy,

Reference is made to NDA 204063. We have the following information request:

Please provide a review of available abuse related data for Fumaderm (e.g., post-marketing reports, literature).

We request your response no later than October 11, 2012.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
09/27/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Wednesday, September 19, 2012 10:07 AM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Carton and Container Labeling_September 19, 2012

Hi Tammy,

Reference is made to NDA 204063. We also refer to your carton and container labeling submitted on February 27, 2012 and July 31, 2012. We have the following comments:

General Comments for All Labels and Labeling

1. Remove the (b) (4) graphic that appears next to 'Tradename' since it is distracting, may be misinterpreted as the (b) (4) and decreases the prominence of the proprietary name.

2. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and have a prominence commensurate with the prominence with which such proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).

3. Revise statements that appear in all upper case letters to title case to improve readability. For example, on the Retail 30-day (b) (4), revise the statement '30-DAY (b) (4)' from all upper case letters to title case '30-Day (b) (4).'

4. The unit designation, mg, immediately follows the numbers without a space, such as '120mg'. Insert a space between the number and unit designation to improve readability, such as '120 mg'.

5. The labels and labeling utilize (b) (4) in the background color scheme for both strengths that contributes to similarity between the two strengths. Remove the (b) (4) background color scheme to prevent product strength selection errors.

6. The '120 mg' statement in (b) (4) font appears faint against the (b) (4) background. Revise the font color of the strength or revise the (b) (4) background of the strength for better contrast and to improve readability of the information.

7. The Division of Professional Drug Promotion has determined that claims regarding (b) (4) on Panel B of the 30-day (b) (4) carton labeling, Panel C of the bottle carton labeling (b) (4), if included, require fair balance presentation. Delete these claims from the labeling or present adequate risk information in conjunction with these claims.

B. Retail 30-day (b) (4)

1. General Comments: The terms (b) (4) are utilized on the labels and labeling. It would be misleading to associate 120 mg as the (b) (4) and 240 mg as the (b) (4) since a patient may need to titrate down from 240 mg to 120 mg to reduce flushing and GI side effects. Remove these terms throughout the labels and labeling

2. Container Labels

a. On the 120 mg principal display panel, replace the statement '(b) (4)' to read 'Take on Days 1 to 7' similar to the instructions for use on the carton labeling. Which days the patient takes 120 mg is more useful information than indicating that the bottle contains a (b) (4).

b. On the 240 mg principal display panel, replace the statement '(b) (4)' to read 'Take on Days 8 to 30' similar to the instructions for use on the carton labeling. Which days the patient takes 240 mg is more useful information than indicating that the bottle contains a (b) (4).

c. On the 120 mg side panel, revise the statement [redacted] to read similar to the information found on the 240 mg side panel, 'Dosage: take one capsule by mouth twice a day. See package insert.' This will provide more meaningful information for the patient.

d. The use of [redacted] coloring on both the 120 mg and 240 mg strengths in the background color scheme contributes to similarity between the two labels. Remove the [redacted] background color. The [redacted] color may be retained for the proprietary name only.

e. Add a statement similar to 'Store in original container. Once opened, use the product within 90 days.' Since there is limited space on the principal display panel, this information can be placed on the side panel.

f. In order to keep information on the 120 mg label consistent with the 240 mg label, relocate the statements 'Store at 15-30°C/59-86°F. Protect from Light.' and 'Each capsule contains 120 mg dimethyl fumarate.' so they are in the same location on both labels.

g. Revise the storage statement to remove the hyphens and read 'Store at 15°C to 30°C (59°F to 86°F).'

h. The statement 'Rx only' appears overly prominent. Debold or change the font so that it does not detract from other important information on the labels.

3. Carton Labeling

a. The [redacted] color scheme used at the top and bottom of Panels A, C, and D is overly prominent and is the same color used for the 240 mg strength. In order to avoid confusion and minimize clutter, remove the color scheme.

b. Add a statement similar to 'Once the enclosed bottles are opened, the product must be used within 90 days.' to Panel C. This information is important and should appear with the statement 'Dispense in Original Package.' In order to accommodate this statement, remove [redacted] since this information already appears elsewhere on the carton.

c. Revise the statements 'Days 1-7' and 'Days 8-30' to read 'Days 1 to 7' and 'Days 8 to 30' for clarity.

d. On Panel A, add a statement similar to 'Swallow capsule whole and intact' beneath the Instructions for Use Box to help prevent wrong technique errors.

C. Professional Sample 30-day Sample Pack

1. General Comments: See Recommendation B.1

2. Container Labels

a. See Recommendations B.2.a to B.2.g

b. The statements '14 capsules' and 'Rx only' appear prominent. Debold or change the font color similar to the font for '46 capsules' on the 240 mg container label, so that it does not detract from other important information on the label.

c. Debold the statement 'Sample – not for sale'.

3. Carton Labeling:

a. See Recommendations B.3.a to B.3.d

b. On Panel A, replace the statement [redacted] with the statement 'Swallow capsule whole' to help prevent wrong technique errors.

D. Professional Sample 14-day Sample Pack

1. General Comments: See Recommendation B.1

2. Container Label: 240 mg

a. See Recommendation B.2.d, B.2.g, C.2.b, C.2.c

b. On the 240 mg principal display panel, replace the statement [redacted] to read 'Take on Days 8 to 14' similar to the instructions for use on the carton labeling. Which days the patient takes 240 mg is more useful information than indicating that the bottle contains a [redacted].

3. Carton Labeling

a. See Recommendation B.3.a

b. Add a statement similar to 'Once the enclosed bottles are opened, the product must be used within 90 days.' to Panel A. This information is important and should appear with the statement 'Dispense in Original Package.' In order to accommodate this statement, remove [redacted] since this information already appears elsewhere on the carton.

c. Revise the statements 'Days 1-7' and 'Days 8-14' to read 'Days 1 to 7' and 'Days 8 to 14' for clarity.

d. On Panel C, add a statement similar to 'Swallow capsule whole and intact' beneath the Instructions for Use Box to help prevent wrong technique errors.

E. Bottle Container Labels (retail and professional sample)

1. See recommendations B.2.d., B.2.e., and B.2.g.

2. Add statement similar to 'Swallow capsule whole' to the principal display panel to prevent wrong technique errors.

3. Debold then net quantity and 'Rx only' statements so they do not detract from other important information on the label.

F. Bottle Carton Labeling (retail and professional sample)

1. See recommendation B.2.g.

2. The colors [redacted] are used prominently throughout the carton labeling for both the 120 mg and 240 mg strengths. Improved differentiation is required in order to avoid selection errors and confusion. In order to avoid selection errors and confusion, remove the color scheme or revise the color scheme so that [redacted] is used only for the 120 mg strength and [redacted] is used only for the 240 mg strength.

3. Debold the net quantity statements.

4. Remove [redacted] from Panel A. This information already appears on the top panel.

5. Add a statement similar to 'Once the enclosed bottle is opened, the product must be used within 90 days.' to Panel A.

6. For the 120 mg professional sample and all the 240 mg carton labeling, add the statement 'Dispense in Original Package.'

Please address these comments and provide your responses as an amendment to NDA 204063.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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NICOLE L BRADLEY
09/19/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Wednesday, August 29, 2012 2:00 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_August 29, 2012

Dear Tammy,

Reference is made to NDA 204063. We have the following information request:

The protocol for trials 301 and 302 allowed for patients to reduce their dose to alleviate adverse events of flushing and GI disturbances. In addition, patients with laboratory abnormalities could interrupt their treatment for periods of time until resolution occurred. If lab values did not resolve some patients discontinued study medication. Please provide the following information about these patients:

The number of patients per trial and treatment arm that reduced their dose for at least 1 month during the trial. Please provide information stating whether certain patients reduced the dose multiple times during their participation in the trial, or whether they all only reduced the dose one time. Please provide information as to how many of these patients went on to increase the dose and continue the study medication and how many discontinued study medication after the dose reduction. If possible, provide this data in tabular form. Provide the number of patients that reduced the dose by reason for dose reduction. Please also provide the number of patients that had a dose interruption by reason for the dose reduction.

In addition, provide an analysis of the primary endpoint of the trials (301,302) on only the patients that had at least a 1 month dose reduction or interruption in study drug by treatment group and provide an analysis of the primary endpoint of the trial on only patients that did not have at least 1 month dose reduction or dose interruption of study drug by treatment group. Please provide the datasets used to conduct these analyses.

In addition, it appears that approximately 30% of patients had reduction of lymphocytes below the lower limits of normal in the pivotal trials (301,302) recorded as AEs. Please conduct an analysis on the primary endpoint for each trial looking only at the patients that had this reduction in lymphocytes by treatment and evaluate this per trial (not as a pooled analysis). In addition conduct an analysis on the primary endpoint for each trial for patients that did not have a reduction in lymphocytes below the lower level of normal by treatment group. Please provide the datasets used to conduct these analyses.

Please respond by COB September 14, 2012.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
08/29/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, August 27, 2012 3:52 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_August 27, 2012

Dear Tammy,

Reference is made to NDA 204063.

In your August 17, 2012, response to the information request on packaging configurations, you state in comment 2 that the (b) (4) 240 mg bottle configuration (b) (4)

However, this (b) (4) 240 mg bottle configuration is not included in comment 1 as a packaging configuration that you are seeking for approval. If you intend to distribute this packaging configuration, either as a commercial package or as a professional sample, then you must include it in your request for approval. Please clarify if you intend to seek approval for the (b) (4) 240 mg bottle configuration. If so, please submit pdf copies of the container label and carton labeling intended for the (b) (4) 240 mg replacement bottle.

Additionally, since dimethyl fumarate will be a prescription only product that can only be dispensed pursuant to a physician's prescription, clarify if the (b) (4) 240 mg bottle configuration will be labeled as a retail or professional sample packaging configuration. (b) (4)

We request a response by COB Thursday, August 30.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
08/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063

PROPRIETARY NAME REQUEST
UNACCEPTABLE

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 New Drug Application (NDA) dated February 24, 2012, received February 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dimethyl Fumarate Delayed-release Capsules, 120 mg and 240 mg.

We also refer to your correspondence, dated and received May 30, 2012, requesting review of your proposed proprietary name, (b) (4) We have completed our review of (b) (4) and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. 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

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/s/

LAURIE A KELLEY
08/24/2012

IRENE Z CHAN on behalf of CAROL A HOLQUIST
08/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063

METHODS VALIDATION
MATERIALS RECEIVED

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

Dear Nadine Cohen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dimethyl Fumarate Delayed Release Capsule, 120 mg and to our July 18, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 13, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
08/21/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Thursday, August 16, 2012 9:15 AM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_August 16, 2012

Tammy,

Reference is made to NDA 204063. We have the following information requests:

1) In your submission, you provided multiple sensitivity analyses for efficacy endpoints that excluded data from 3 sites that were not compliant with GCP guidelines. Please provide detailed information about the nature of the deficiencies for each noncompliant site and provide any reports that you have describing such details. If this information is provided in the NDA submission, please direct us to the location.

2) After review of your response on August 3, 2012, to our information request related to the MRI cohorts (sent July 25, 2012), we have the following additional information request:

We are aware that MRI data per the study schedules for trial 301 and 302 were obtained at baseline, month 6, year 1 and 2 for only patients in the MRI cohort. Please verify if screening MRIs were obtained for all enrolled patients to determine eligibility. If this was the case, as your protocols suggest, please provide the following MRI information based on the screening MRIs for the ITT group enrolled in trials 301 and 302:

Mean number of Gd enhancing lesions
Mean Gd enhancing lesion volume (and median)
Mean T2 hyperintense lesion volume (and median)
Mean T1 hypointense lesion volume (and median)
Percentage of patients with 0, 1-4, 5-8, >9 Gd enhancing lesions

Provide a summary table comparing this information in the MRI cohort to the ITT cohort and provide this information broken down by trial (301, 302).

Please provide your responses by EOB August 31, 2012.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
08/16/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Tuesday, August 14, 2012 12:18 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_August 14, 2012

Hi Tammy -

Reference is made to NDA 204063.

In your 7/30/12 response to our questions about positive urinary ketone test results that occurred more commonly among BG00012 patients in Pool A MS trials, you hypothesized that the finding might represent false positive results due to interference with the nitroprusside assay. Do you have quantitative serum ketone test results for any BG00012 patients in your clinical trials database?

To better assess the potential for renal toxicity with BG00012, we request additional lab data outlier analyses for the MS Pool A trials. The majority of the outlier criteria listed below come from cutoffs identified in the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Specifically, we request that you identify the percentage of patients with a normal result for the given analyte at baseline, and then had a lab result that met the listed outlier criteria.

Analyte	Outlier criteria
Creatinine (increased)	>1 - 1.5 x baseline; >ULN - 1.5 x ULN
	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN
	> 3.0 x baseline; >3.0 - 6.0 x ULN
	>6.0 x ULN
Sodium (increased)	>ULN - 150 mmol/L
	>150 - 155 mmol/L
	>155 - 160 mmol/L
Sodium (decreased)	<LLN - 130 mmol/L
	<130 - 120 mmol/L
	<120 mmol/L
Calcium (increased)	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L
	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L
	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L
	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L
Calcium (decreased)	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L
	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L

	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L
	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L
Potassium (increased)	>ULN - 5.5 mmol/L
	>5.5 - 6.0 mmol/L
	>6.0 - 7.0 mmol/L
	>7.0 mmol/L
Potassium (decreased)	<LLN - 3.0 mmol/L
	<3.0 - 2.5 mmol/L
	<2.5 mmol/L
Bicarbonate (increased)	>ULN-32 mmol/L
	>32mmol/L-34mmol/L
	>34mmol/L
Bicarbonate (decreased)	<LLN-15 mmol/L
	<15mmol/L-13mmol/L
	<13mmol/L
Chloride (increased)	>ULN - 115 mmol/L
	>115 - 118 mmol/L
	>118 mmol/L
Chloride (decreased)	<LLN-91 mmol/L
	<91mmol/L-88mmol/L
	<88mmol/L

In addition to the above analyses, we ask that you identify the percentage of patients, by treatment, in the Pool A MS studies with an anion gap >12meq.

In trial 109MS032, Subject 017-405 experienced a non-serious AE of Renal Tubular Acidosis. Please provide a narrative for this event. The narrative should provide information about how the diagnosis was made, any relevant diagnostic test results, likely etiology, and a listing of all urinalysis, electrolyte, BUN, and creatinine results collected during the trial (i.e., screening, baseline, on treatment, and post treatment).

Please submit your responses to these requests within 2 weeks.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
08/14/2012

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, August 13, 2012 3:03 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_August 13, 2012

Reference is made to NDA 204063 and to your submission dated August 8, 2012, providing a response to our August 3, 2012, information request.

We have the following additional questions:

1) Clarify which packaging configurations (commercial and physician's sample) you are seeking for approval (not just the packaging configurations that you plan to market at product launch)

2) Provide a rationale for removing any packaging configuration that was originally submitted for approval. Below is a list of the original packaging configurations submitted for approval.

- 30-day (b) (4) (14-count bottle of 120 mg capsules and 46-count bottle of 240 mg capsules, packaged in the same carton): commercial and physician's sample
- 120 mg capsules
  - 14-count bottle: commercial and physician's sample
- (b) (4)
- 240 mg capsules
  - 14-count bottle: commercial and physician's sample
- (b) (4)

Please respond by EOB Monday, August 20th.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
08/13/2012

Toure, Hamet

From: Toure, Hamet
Sent: Friday, August 03, 2012 9:19 AM
To: Tammy Sarnelli
Cc: Toure, Hamet; Bradley, Nicole
Subject: 204063_Information request

Dear Ms. Sarnelli,

We refer to NDA 204063. We have the following information request:

1) [redacted] (b) (4)

2) Provide a list of all packaging configurations that will be available if the product is approved (include commercial and physician's sample)

3) Provide a rationale for proposing a [redacted] (b) (4) when a 30-day starter kit will be available [redacted] (b) (4) [redacted] (b) (4)

Please provide your response by Wednesday, August 8, 2012.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

HAMET M TOURE
08/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063 **INFORMATION REQUEST**

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

Dear MS. Cohen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dimethyl fumarate capsules.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. (a) Provide updated drug product stability data.
   (b) Provide stability data used to support delay in processing of the bulk (b) (4) .
   (c) The calculation of expiration period for a drug product is typically calculated from the time drug substance is mixed with excipient in the drug product manufacturing. Provide confirmation on the start time for the calculation of the drug product expiry period.
   (d) Provide a list of differences between the drug product registration batches and the primary validation batches and supportive stability lots (formulation, manufacture, container closure system etc.).
   (e) Propose and justify an expiry period for the 240 mg strength product.

2. Provide justification for the proposed drug produc (b) (4) acceptance criterion for the 240 mg strength as it differs from that of the 120 mg strength and appears to exceed the calculated acceptable (b) (4) limit.

3. Provide any additional in-process capsule fill-weight controls put in place as a result of observations during the recent FDA inspection.

4. We request that an acceptance range for median particle size (b) (4) be added to the drug substance specification.

5. Include an appropriate peak resolution acceptance criterion in the system suitability tests for the drug substance impurity methods.

6. We recommend that you commit to placing one drug substance production batch *from each manufacturing site* on stability per year, if manufactured.

7. Provide clarification on the drug substance storage conditions. The proposed (b) (4) retest period appears to be for storage at 25ºC/60%RH, however the postapproval stability protocol requires storing samples at 30ºC/65%RH. As (b) (4) levels in the latter condition tended to reach the (b) (4) specified limit at 60 months, provide the results of a statistical analysis to show that (b) (4) levels will not exceed (b) (4) within a 95% confidence limit.

8. In order to evaluate the proposed dissolution acceptance criteria, provide dissolution profile data (individual, mean, SD, figures) for the pivotal clinical batches and the primary stability/registration batches. For the stability batches, provide the dissolution profile data at release and upon storage during the stability study.

(b) (4)

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
07/27/2012

From:	Bradley, Nicole
To:	Tammy Sarnelli
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_July 25, 2012
Date:	Wednesday, July 25, 2012 6:46:58 PM

Hi Tammy,

Reference is made to NDA 204063. We have the following information request:

> In order to adequately compare the MRI cohort to the ITT group, the review team would like the following information about the baseline scans of the ITT group. Provide this information in tabular form by treatment group, total ITT and by individual trial (301 and 302). If this information is within the NDA submission, please direct the reviewer to where this information can be found. Provide the following **baseline** values for the ITT group: the mean number of Gd enhancing lesions, the mean Gd enhancing lesion volume (and median), the mean T2 hyperintense lesion volume (and median), the mean T1 hypointense lesion volume (and median), the percentage of patients with 0, 1-4, 5-8, >9 Gd enhancing lesions. Providing a summary table in addition, comparing this information in the MRI cohort, non MRI cohort and ITT would be useful, if possible. This information should be broken down by study trial, for example, the ITT group from 301 should be described separately from the ITT group from 302 in terms of the above information. In addition, if you provide the summary table, include values for the MRI cohort and non MRI cohort by trial (301 or 302), do not group these values.
>
> Please provide the baseline information for the MRI cohorts (by trial 301 or 302), % breakdown of race, mean height, mean weight, mean BMI, % with MS diagnosis by McDonald criterion 1, percentage < 40 years of age, percentage with an EDSS less than or equal to 2.
>
> Please refer to Figure 14, page 96 of the Summary of clinical efficacy. This figure includes information for the pooled MRI cohort (trials 301,302) and pooled non MRI cohort and demonstrates a difference in the ARR at 2 years in these two groups. Please provide more specific information about your analysis and findings of the ARR in the MRI cohort as compared to the non MRI cohort in the individual pivotal trials (301,302). Please provide the analysis for the ARR as described in your submission (conducted as specified for the primary endpoint in 302 in the SAP), for the adjusted rate, unadjusted rate and subject rate for these subgroups.

Please provide this information by COB August 3, 2012.

Thanks
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
07/25/2012

From:	Bradley, Nicole
To:	Tammy Sarnelli
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_July 20, 2012
Date:	Friday, July 20, 2012 2:37:04 PM

Hi Tammy,

Reference is made to NDA 204063. We have the following information request:

- Please identify the location within the NDA of the electronic datasets for the 2-year carcinogenicity bioassays in rat and mouse (studies p00012-04-11 and p00012-05-03).

Please respond no later than Wednesday July 25th.

Thanks
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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NICOLE L BRADLEY
07/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063

REQUEST FOR METHODS VALIDATION MATERIALS

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

Dear Nadine Cohen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dimethyl Fumarate Delayed Release Capsule, 120 mg.

We will be performing methods validation studies on Dimethyl Fumarate Delayed Release Capsule, 120 mg as described in NDA 204063.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Assay, content uniformity and impurity determination for Dimethyl Fumarate Delayed Release Capsule, 120 mg HPLC.

LIST OF REQUESTED MATERIALS

100	Dimethyl Fumarate Delayed Release Capsules, 120 mg
2 g	Dimethyl Fumarate reference standard
[redacted]	(b) (4)

LIST OF REQUESTED EQUIPMENT

1	LiChrosorb Rp-18, 100 Å, 10 µm, 250 mm x 4.6 mm column
1	C18 8 mm x 4 mm column precolumn and holder
25	1.2 µm glass microfiber membrane

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael Trehy
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael Trehy, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/18/2012

From:	Bradley, Nicole
To:	Tammy Sarnelli
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_July 6, 2012
Date:	Friday, July 06, 2012 9:45:25 AM

Hi Tammy,

Reference is made to NDA 204063. We have the following information request:

In the ISS for dimethyl fumarate, you included as Appendix 3 an executive summary of the review of the safety profile for Fumaderm. We request additional information from your post marketing safety database for Fumaderm. Specifically, we request the following:

- the total number of unique post marketing reports for Fumaderm
- a listing of that provides the number of each adverse event reported
- a listing that provides the number of each serious adverse event reported
- the actual reports for all serious liver events
- the actual reports all serious renal events
- the actual reports for all malignancies

In the ISS, you clearly demonstrated that patients exposed to dimethyl fumarate test positive for urinary ketones, but provided little discussion of this finding. Please provide an explanation as to why dimethyl fumarate exposed patients are testing positive for urinary ketones. In addition, please discuss the potential implications of this finding in general, and in patients with diabetes mellitus or other relevant underlying metabolic conditions.

Please provide your responses to these requests in 3 weeks.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
07/06/2012

From:	Bradley, Nicole
To:	"Tammy Sarnelli"
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_June 7, 2012
Date:	Thursday, June 07, 2012 11:41:49 AM

Hello Tammy,

Reference is made to NDA 204063. We have the following request for additional information:

In the ISS, you summarized information for Subject 237-301, a 29-year-old female with RRMS, and an SAE of chronic hepatitis. We request additional information for this patient. Specifically, we ask that you identify any risk factors for NASH such as diabetes, obesity, and hypertriglyceridemia. Provide a description of the evaluation of potential nondrug causes of liver injury including recent hepatitis A, B, C, D, and E serology, other underlying viral disease (CMV, EBV), and other causes of hepatitis (autoimmune, metabolic, genetic, etc.). Please also provide any available supplemental information, including consultation reports, imaging studies, and special studies.

In the ISS, you summarized information for Subject 505-303, a 45 year old female with RRMS and an SAE of cholestatic hepatitis.

You mentioned in the narrative that this subject had follow up with hepatology. Provide all available information from this follow up consult.

In the ISS, you summarized information for Subject 364-302, a 26-year-old female with RRMS, and an SAE of rhabdomyolysis. This event was attributed to “excessive muscular activity”. Provide a description of the muscular activity that was believed to be the cause of rhabdomyolysis in this patient.

Please provide your response by June 22, 2012.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
06/07/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063

PROPRIETARY NAME REQUEST
UNACCEPTABLE

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 New Drug Application (NDA) dated February 24, 2012, received February 27, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for dimethyl fumarate delayed-release capsules, 120 mg and 240 mg.

We also refer to your correspondence, dated and received February 29, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of (b) (4) and have concluded that this name is unacceptable for the following reasons:

(b) (4)

2. (b) (4) is vulnerable to name confusion that could lead to medication errors with a pending proposed proprietary name due to orthographic and phonetic similarity.

We note that you have proposed an alternate proprietary name in your submission dated February 29, 2012. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review within 14 days of this letter. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. 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

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/s/

CAROL A HOLQUIST
05/25/2012

From:	Bradley, Nicole
To:	"Tammy Sarnelli"
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_May 11, 2012
Date:	Friday, May 11, 2012 1:34:30 PM

Hello Tammy,

Reference is made to NDA 204063. Please also refer to our information requests dated April 11, 2012 and May 4, 2012, regarding the 24-hour ECGs collected during Study 109-HV-101. We note your responses dated May 2, 2012 and May 9, 2012, respectively.

In your May 9, 2012 response, you established that you do indeed possess these ECGs. We request that you measure the intervals on these ECGs, and provide analyses of these intervals. Specifically, we request mean change from baseline and outlier analyses similar to those performed for the other time points evaluated in this trial.

Please provide your response by June 1, 2012.

Thank you
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
05/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063

FILING COMMUNICATION

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 New Drug Application (NDA) dated February 24, 2012, received February 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for dimethyl fumarate.

We also refer to your additional submissions dated February 29, 2012, and April 13, 2012.

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 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 27, 2012.

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, midcycle, 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 November 30, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

CHEMISTRY, MANUFACTURING AND CONTROLS

1. You state in Module 3.2.S.1.3 that dimethyl fumarate is classified as BCS classification I. Provide data to support this classification or identify the location of the data in the NDA submission.

2. We will review the data provided to support your proposal to exclude testing for (b) (4) in the bulk drug substance. In the interim, we request that you provide the analytical method and supporting validation data, for review.

3. (b) (4)

4. With regard to formulation development [Module 3.2.P.2.1] provide a tabular summary of all drug product batches used in Phase 1, 2, and 3 clinical studies (including clinical pharmacology and bioequivalence studies, and stability studies. Identify the specific studies in which each batch was used. If any of the clinical or stability batches differed from the proposed commercial product, the qualitative and quantitative formulation should be provided.

5. With respect to the manufacturing process and manufacturing process development; provide data to support the proven acceptable ranges (PARs) given in Module 3.2.P.2.3 and the in-process controls given in Module 3.2.P.3.3.

6. Revise the drug product dissolution test to include all equipment, instrument parameters, and solution preparations necessary for quantitation of the dissolution results by HPLC.

7. Revise the container closure information in Module 3.2.P.7 to include the details of the proposed commercial HDPE bottle packaging configurations (i.e., capsule strength, capsule count, and bottle size).

Drug Product Stability

8. Provide details regarding the HDPE bottle configurations (i.e., bottle size and tablet count) studied for the 120 mg primary validation batches (Batch Numbers 27664, 27665 and 27666) and the 240 mg primary validation batches (Batch Numbers 56060, 556061, and 56062).

9. Provide headspace and surface area information to justify the HDPE bottle bracketing approach used in the stability protocols for Batches 47823, 47824, 47825, 54164, 54165, and 54166.

10. You have provided graphical presentations of regression analyses for (b) (4) in 120 mg capsules in Module 3.2.P.81. Provide details of the statistical

analyses performed, including batches analyzed, whether data from batches were pooled and statistical output.

CLINICAL PHARMACOLOGY

11. Provide all datasets, programs and outputs for your analyses which were reported in Tables 6 and 7 in Section 2.2.3 (Study 109MS101) of the Summary of Clinical Pharmacology Studies, using the following instructions:
    - Submit all datasets used for the analyses as SAS transport files (*.xpt)
    - Provide a description of each data item in a Define.pdf file
    - Submit codes and output listings as ASCII text files with the (*txt) file extension.

CONTROLLED SUBSTANCE STAFF

12. The data related to abuse potential could not be located in the NDA. Provide the location (with links) of the standard studies.

    According to 21 CFR § 314.50 (5) (vii), the abuse potential section of an NDA includes a proposal for scheduling and all scientific data that form the basis of the proposal. The abuse potential assessment of a drug includes primary data, data analysis and a discussion of the following areas:
    - Chemistry (including the chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)
    - Pharmacokinetics and pharmacodynamics (including all data on receptor binding for DMT and its main active metabolite monomethylfumarate)
    - Primary data from abuse potential studies in animals and humans
    - Adverse events (AEs) related to abuse potential from clinical studies
    - Information and data related to abuse potential in the integrated summaries of safety and efficacy (ISS and ISE)
    - Information related to overdose
    - Prospective assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies
    - Epidemiological data related to abuse.

13. Provide the following information and data related to abuse potential from all clinical studies, including raw data and adverse events coded with the most recent MedDRA terminology, that includes:
    - Table of pooled Adverse Events related to abuse potential that summarizes all studies submitted, broken down by population, MS patients, non-MS patients, and healthy volunteers
    - For MedDRA coding of AEs, provide your coding convention, as MedDRA SOC terms may not capture unusual signs and symptoms that may be related to abuse liability if verbatim terms were used.

14. Provide descriptions and details of all reports in all clinical studies, including narratives, of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for, and related to drug withdrawal and withdrawal symptoms, and any other indication of dependence.

15. Provide case narratives of patients in clinical trials who are discontinued from studies for lack of compliance with study medication or procedures, or who discontinue participation without returning the study medication.

16. Provide tabulation of patients who were discontinued from the study, or dropped out for reasons related to potential abuse and diversion, including narratives describing reasons and follow-up information.

17. Provide all post-marketing safety reports of AEs related to potential abuse.

18. Due to the appearance of suicidality risk for this drug, prospective assessments of suicidality in ongoing clinical trials (where possible) and all planned clinical trials should be included. The details of abuse potential evaluation are described in the FDA draft Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

CLINICAL

Safety

19. In the ISS, you summarized information for Subject 237-301, a 29-year-old female with RRMS, and an SAE of chronic hepatitis. We request additional information for this patient. Specifically, we ask that you identify any risk factors for non-alcoholic steatohepatitis such as diabetes, obesity, and hypertriglyceridemia. Provide a description of the evaluation of potential nondrug causes of liver injury including recent hepatitis A, B, C, D, and E serology, other underlying viral disease (CMV, EBV), and other causes of hepatitis (autoimmune, metabolic, genetic, etc.). Also provide any available supplemental information, including consultation reports, imaging studies, and special studies.

20. With regard to Subject 505-303, a 45 year old female with RRMS and an SAE of cholestatic hepatitis, you mentioned in the narrative that this subject had follow-up with hepatology. Please provide all available information from this follow-up consult.

21. In the ISS, you summarized information for Subject 364-302, a 26-year-old female with RRMS, and an SAE of rhabdomyolysis. This event was attributed to “excessive muscular activity”. Provide a description of the muscular activity that was believed to be the cause of rhabdomyolysis in this patient.

Efficacy

22. Certain patients have reasons listed for discontinuation of treatment in the clinical study reports (trials 301 and 302: Module 5.3.5.1.16 in Table 1) such as consent withdrawn, other, MS relapse, treatment suspected to be ineffective or wanted to start alternate treatment. In an attempt to group the patients together that stopped treatment due to perceived lack of efficacy or actual lack of efficacy, we request the following information on patients from trials 301 and 302 in tabular form:

    Patient ID, study assignment, treatment assignment, days on treatment, days in study, EDSS at baseline, number of relapses recorded for that particular patient during the time on treatment, rescue treatment given, for all patients that:
    - Withdrew consent due to suspicion of lack of effect
    - Discontinued because of MS relapse
    - Discontinued to obtain rescue medication due to suspected lack of effect of study treatment

23. We are aware that many study sites enrolled variable numbers of patients and that many sites enrolled too few patients to make meaningful conclusions about treatment effects per site. With this in mind, we would still like to review the treatment effect per site to determine how consistent this effect was between sites. Provide the treatment effect per site for the primary endpoint in the two pivotal studies, 301 and 302.

MATERNAL HEALTH

24. Provide the pregnancy narratives in a single list with hyperlinks to each narrative or a single document with all the narratives.

LABELING

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

- In the Highlights section under Adverse Reactions, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact Biogen Idec at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**"
- The section headings and subheadings in the Table of Contents must match the headings and subheadings in the Full Prescribing Information (FPI)
- The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.1)*]
- FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use [see your Section 17.5 as submitted]) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval

- Patient Counseling Information must reference FDA-approved patient labeling, including the type of patient labeling, and use the statement "See FDA-approved patient labeling (Patient Information)" at the beginning of Section 17.

We request that you resubmit labeling (as PDF and WORD files) that addresses these issues by May 25, 2012. 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). 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 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 for pediatric patients ages birth to < 10 years of age. 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 deferral of pediatric studies for pediatric patients 10 to 17 years of age. However, we note that your pediatric plan did not contain the timeline for completion of studies as required under the law. Within 30 days of the date of this letter, please submit the dates for the (1) protocol submission, (2) study completion, and (3) submission of study reports. Dates should include the month, day, and year. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Neurology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

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

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/s/

RUSSELL G KATZ
05/08/2012

From:	Bradley, Nicole
To:	"Tammy Sarnelli"
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_May 8, 2012
Date:	Tuesday, May 08, 2012 2:00:31 PM

Hello Tammy,

Reference is made to NDA 204063. We have the following Information Request:

In your ISS for dimethyl fumarate, you note that in MS pool A trials and Psoriasis pool C trials there were no subjects who experienced elevations in ALT or AST ≥3 × ULN concurrent with an elevated total bilirubin >2 × ULN. We were unable to find specific reference from you for a similar analysis of the remaining subjects in the development program. Were there any patients in any of the clinical trials that you submitted as part of the dimethy fumarate NDA who experienced elevations in ALT or AST ≥3 × ULN concurrent with an elevated total bilirubin >2 × ULN? If so, provide the study numbers and subject ID numbers for these patients.

Please provide a response by May 15, 2012.

Thank you
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
05/08/2012

From:	Bradley, Nicole
To:	"Tammy Sarnelli"
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_May 4, 2012
Date:	Friday, May 04, 2012 11:52:30 AM

Hello Tammy,

Reference is made to NDA 204063. Please also refer to our April 11, 2012 e-mail communication requesting additional information for Study 109-HV-101 and to your May 2, 2012 submission providing a response to this information request.

In your response you wrote the following:

> "The investigator evaluated each paper ECG and the data captured on the case report form was an assessment of whether the ECG was "Normal", "Abnormal, not adverse event" or "Abnormal, adverse event". Based on these assessments, no shifts to "abnormal, adverse event" were reported at any time point in Study 109HV101 (Table 14-3.10). No quantitative or qualitative data were collected at the 24-hour timepoint and thus no additional analysis can be performed."

From your answer, we understand that you did not measure the intervals on the 24-hour ECGs when you analyzed the data from 109-HV-101. Do you, or does the investigator, have the ECGs from the 24-hour measurement? If not, explain what was done with these ECGs.

Please provide a response by May 9, 2012.

Thank you
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

From: Tammy Sarnelli [mailto:tammy.sarnelli@biogenidec.com]
Sent: Thursday, April 12, 2012 4:19 PM
To: Bradley, Nicole
Subject: RE: NDA 204063 Information Request_April 11, 2012

Hello Nicole:

I have discussed this request with my colleagues and we will provide a response on or before May 2, 2012.

Kind regards

Tammy

From: Bradley, Nicole [mailto:Nicole.Bradley@fda.hhs.gov]
Sent: Wednesday, April 11, 2012 4:37 PM
To: Tammy Sarnelli
Cc: Bradley, Nicole
Subject: NDA 204063 Information Request_April 11, 2012

Hello Tammy,

Reference is made to NDA 204063. We have the following information request:

Your analysis of the thorough QT study (Study 109-HV-101) included ECG samples only up to 8 hours. Therefore, the effect of BG00012 on the QT interval at later time points can not be evaluated. We note, however, that the you collected a safety ECG at 24 hours. Please provide an analysis including the 24 hour time point to consider information about any delayed effects of BG00012 administration on the QT interval. Please provide this analysis by May 2, 2012. Please confirm by COB on April 12, 2012 that you will provide this analysis.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
05/04/2012

From:	Bradley, Nicole
To:	"Tammy Sarnelli"; "paula.sandler@biogenidec.com"
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_April 18, 2012
Date:	Wednesday, April 18, 2012 6:42:29 PM

Hello Tammy and Paula,

We request assistance with the ISS MS safety datasets for NDA 204063 (BG00012).

In trying to open some of the ISS Multiple-sclerosis analysis safety datasets for BG00012, we have encountered difficulties. The Division safety reviewers use JMP version 9 software for dataset analyses. While some data sets opened without difficulty (ex. ADAE, ADEX), there are several data sets that we have been unable to open (ex. ADLB02, ADLB04).

We contacted our internal consultants about this issue. Our consultants found no inherent issues with your datasets. They felt the difficulty opening the datasets may be related to the limitations of JMP v.9 and possibly the dataset size. Our consultants suggested that we request resubmission of the datasets in files that are smaller in size.

We ask that you resubmit the following ISS Multiple-sclerosis analysis safety datasets:
ADLB01, ADLB02, ADLB03, ADLB04, ADLB05, ADLBS, ADLBVI01, ADLBVI02, ADLBVI03, ADLBVI04, ADLBVI05, and ADLBVI06

We request that when you resubmit these datasets, you limit the file size to 400MB or less per dataset.

We ask that you submit these datasets within 1 week. If this deadline is not reasonable, we ask for an estimate of when you would be able to submit these datasets.

Thank you,

Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
04/18/2012

From:	Bradley, Nicole
To:	"Tammy Sarnelli"
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_April 11, 2012
Date:	Wednesday, April 11, 2012 4:36:49 PM

Hello Tammy,

Reference is made to NDA 204063. We have the following information request:

Your analysis of the thorough QT study (Study 109-HV-101) included ECG samples only up to 8 hours. Therefore, the effect of BG00012 on the QT interval at later time points can not be evaluated. We note, however, that you collected a safety ECG at 24 hours. Please provide an analysis including the 24 hour time point to consider information about any delayed effects of BG00012 administration on the QT interval. Please provide this analysis by May 2, 2012. Please confirm by COB on April 12, 2012 that you will provide this analysis.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
04/11/2012

From:	Bradley, Nicole
To:	"Tammy Sarnelli"
Cc:	Bradley, Nicole
Subject:	NDA 204063 Information Request_April 10, 2012
Date:	Tuesday, April 10, 2012 4:27:44 PM
Importance:	High

Dear Tammy,

Reference is made to NDA 204063.

The clinical review team is having difficulty locating the Integrated Summary of Effectiveness (ISE) in your application for NDA 204063. It does not appear to be located following the subheading for the ISE in Section 5.3.5.3. Please direct us to the location of the ISE in your application.

Please respond by 10am April 11, 2012.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
04/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063

NDA ACKNOWLEDGMENT

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

Dear Dr. Cohen:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: dimethyl fumarate (BG00012)

Date of Application: February 24, 2012

Date of Receipt: February 27, 2012

Our Reference Number: NDA 204063

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 27, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 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 NDA 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. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, please 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

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/s/

NICOLE L BRADLEY
03/01/2012

From:	Bradley, Nicole
To:	"Tammy Sarnelli"
Cc:	Bradley, Nicole
Subject:	NDA 204063 - CMC Information Request #1
Date:	Wednesday, February 29, 2012 9:35:47 AM

Good Morning Tammy,

Reference is made to NDA 204063. We have the following request:

Please submit a revised 356h form that includes all drug master files (DMFs) that are referenced in the application.

Thank you,
Nicole

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

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
02/29/2012
Sent at request of M. Heimann

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 73061

MEETING MINUTES

Biogen Idec
Attention: Nadine O. 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 BG00012.

We also refer to the meeting between representatives of your firm and the FDA on January 25, 2012. The purpose of the Type B Pre-NDA meeting was to discuss and reach agreement on the format and content of the BG00012 marketing application for the treatment of patients with relapsing multiple sclerosis.

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:	**Type B**
Meeting Category:	**Pre-NDA**
Meeting Date and Time:	January 25, 2012 10:00 AM EST
Meeting Location:	FDA White Oak Campus, Building 22, Rm. 1311
Application Number:	IND 73061
Product Name:	BG00012
Indication:	Multiple Sclerosis
Sponsor/Applicant Name:	Biogen Idec
Meeting Chair:	Russell G. Katz, MD
Meeting Recorder:	Nicole L. Bradley, PharmD

FDA ATTENDEES

Division of Neurology Products
Russell G. Katz, MD, Director
Eric Bastings, MD, Deputy Director
Billy Dunn, MD, Team Leader
Heather Fitter, MD, Clinical Reviewer
John Marler, MD, Clinical Reviewer
Sally Yasuda, PharmD, MS, Safety Team Leader
Gerard A. Boehm, MD, MPH, Safety Reviewer (via teleconference)
LCDR Hamet Toure, PharmD, MPH, Regulatory Project Manager
Nicole Bradley, PharmD, Regulatory Project Manager

Division of Clinical Pharmacology I
Angela Men, PhD, Clinical Pharmacology Team Leader
Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer

Division of Biometrics I
Sharon Yan, PhD, Biostatistics Reviewer

Division of Medication Error, Prevention, and Analysis
Julie Neshiewat, PharmD, Safety Evaluator

SPONSOR ATTENDEES

Biogen Idec
Carmen Bozic, MD, Senior Vice President, Safety and Benefit-Risk
Christina Casteris, Associate Director, Statistical Programming
Kate Dawson, MD, Senior Director, Clinical Development, Neurology
Lynn DiFinizio, Senior Director, Statistical Programming
Mary Geissler, MPH, Associate Director, Regulatory Affairs
Ivan Nestorov, PhD, Director, Clinical Pharmacology & Pharmacometrics
Mark Novas, MD, Director, Safety and Benefit-Risk
Gilmore O'Neill, MD, Vice President, Clinical Development, Neurology
Suezanne Parker, PhD, Director, Preclinical Safety
Kartik Ragupathi, MS, Principal Biostatistician
Paula Sandler, PhD, Vice President, Regulatory Affairs
Tammy Sarnelli, Director, Regulatory Affairs
Alpna Seth, Vice President, Program Management

1.0 BACKGROUND

In a letter dated October 26, 2011, Biogen Idec requested a Type B, Pre-NDA meeting to discuss and reach agreement on the format and content of the BG00012 marketing application for the treatment of patients with relapsing multiple sclerosis.

2.0 DISCUSSION

2.1 Format and Content of the Marketing Application

Question 1:
Does the Agency concur that the two Phase 3 studies (Study 301 and Study 302) are adequate to establish BG00012 safety and effectiveness for the treatment of multiple sclerosis?

FDA Preliminary Response to Question 1:

Safety:
It is not possible to determine the adequacy of the safety data for BG00012 based on the information in the briefing packet. Safety data from studies 301 and 302 will be an important part of the application, but the Division will assess the safety of BG00012 using all available safety data and the ultimate answer to this question will be a matter of review.

Efficacy:
On face, it appears that studies to evaluate efficacy in MS may be adequate, but the ultimate answer to this question will be a matter of review.

Biometrics:
On face, the two studies appear to demonstrate a beneficial effect on the primary efficacy endpoint of annualized relapse rate, based on summary results provided in the package. The ultimate answer to this question will be a matter of review.

Meeting Discussion:
No meeting discussion.

Question 2:
Does the Agency concur with the proposed provision of CRFs and safety narratives in the NDA?

FDA Preliminary Response to Question 2:

Safety:
Yes, the Division agrees with your proposed criteria for selecting the CRFs and narratives to be submitted with the NDA. When you discussed in your briefing document the narratives and CRFs to be submitted, it was in the context of the pivotal trials. The

Division expects that you will provide CRFs and narratives for all clinical trials that are included in the application. See additional comments below.

Meeting Discussion:
No meeting discussion.

Question 3:
Does the Agency concur with the proposed presentation of electronic data, which include datasets for key studies?

FDA Preliminary Response to Question 3:

Safety:
Yes. Your briefing document suggests that you will provide safety datasets only for the pivotal Phase 3 data and table 15 suggests that you will only provide CSRs for other studies. The Division expects that you will provide safety datasets for all clinical trials that are included in the application.

Efficacy:
Please also provide electronic datasets for the phase 2 dose finding study in MS (C-1900).

Clinical Pharmacology:
We concur with your proposed dataset format for the clinical pharmacology studies to be submitted in the NDA submission. In addition, please provide the population PK model code in the submission.

Biometrics:
The proposed presentation of data appears to be acceptable. Additional documentation is recommended if variables cannot be explained clearly by the label in the dataset.

Meeting Discussion:

Safety:
The Sponsor explained that they intended only to submit electronic datasets with safety data for the pivotal trials. They stated that the datasets they intended to submit included over 99% of the person time exposure to DMF. The Division noted that the expectation was to receive electronic datasets with safety data from all trials in the application, including Phase 1 trials. The Sponsor then explained that they do not have datasets for all Phase 1 trials (this application was taken over from another sponsor and Biogen does not have all of the datasets). The Sponsor proposed submitting listings for those Phase 1 trials where they do not have electronic datasets. In addition, the Sponsor committed to submitting the electronic datasets for Phase 1 trials that are available. The Sponsor

requested and FDA agreed that if these Phase 1 datasets were not available at the time of filing, they would be submitted as soon as possible.

Efficacy:
The Sponsor wanted to understand how the Division planned to use the Phase 2 datasets and what information they should include when they sent them. They also asked if a SAS data file with data define information would be adequate. The Division stated that during the NDA review cycle, there may be inconsistencies or questions that arise in the Phase 3 trial data that may require looking more closely at the Phase 2 data. An example of the kind of data that the Division may want to have a closer look at is information about MRI variables since Phase 2 trials often include more frequent MRI measurements than the Phase 3 trials. The Division would also want all other efficacy measures included in the datasets that were measured during the Phase 2 trial. The Division agreed that SAS datasets would be acceptable.

Biometrics:
A review guide for datasets was requested and the Sponsor agreed to provide one.

Question 4:
Does the Agency concur with the proposed approach to integrate efficacy data?

FDA Preliminary Response to Question 4*:*

Efficacy:
No, we do not agree with your proposed approach to the ISE. Although you may pool the data from the two similar studies and do analyses of interest, our primary focus for the ISE is to provide a data driven discussion of the comparison of efficacy findings in the individual studies, with a focus on how the studies support each other to provide sufficient evidence of effectiveness of your product. You should delineate any important differences between the studies and discuss how these differences may have affected results. In addition, the ISE would be an adequate location to evaluate the effect of patients that transitioned to rescue medication and provide a more in-depth analysis of how this affects overall results seen at 2 years. You should refer to clinical pharmacology data to provide a justification for the dose and frequency of dosing chosen for marketing and how the efficacy results support your proposed dosing schedule. You should describe any limitations of the efficacy studies, and how these limitations are addressed. You should describe any important statistical issues that may have affected the results.

Biometrics:
An important part of the ISE should be to compare and contrast the designs and results of the studies that you plan to submit (see clinical comments above). Differences of particular interest include the patient populations, demographic characteristics, outcome

determinations, availability and use of rescue medication, drop-out rates, and differences in the centers that participated.

Meeting Discussion:
The Sponsor agreed to follow the suggestions in reference to the ISE and ISS.

Question 5:
Does the Agency concur with the proposed approach to integrate safety data?

FDA Preliminary Response to Question 5:
The Division agrees with the proposed data pools for the safety data analyses as described in the briefing document. On page 57 of your briefing document, you state the following, "Phase 1 studies, including the single dose pharmacokinetic study in MS subjects (Study 109MS101), will not be pooled for integrated analysis, as the design, objectives, and/or populations in these studies were significantly different (e.g., single-dose design, conducted in healthy volunteers, etc.) from the Phase 2 and 3 studies." We agree that data for Phase 1 studies should not be pooled with data from Phase 2/3 studies for safety analyses, however, the Division expects that the safety data from Phase 1 studies be summarized and discussed as a separate grouping in your submission.

Meeting Discussion:
Please see meeting discussion that follows question 4.

Question 6:
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?

FDA Preliminary Response to Question 6:
On face this approach is acceptable. A final determination will be made once the NDA is submitted and the Division has met with the Pediatric Review Committee (PeRC).

Meeting Discussion:
There was discussion of the recent meeting involving pediatric neurologists and industry, in which both the Division and the Sponsor participated, on the approach to pediatric multiple sclerosis trials. The Division encouraged the sponsor to consider the issues discussed at the meeting in their pediatric proposals to the Division. Issues of particular relevance included the appropriate age range in which to study pediatric multiple sclerosis, the feasibility of conducting a pediatric multiple sclerosis trial in terms of the number of patients available to participate, and an appropriate choice of a meaningful clinical outcome.

2.2 Process for Review

Question 7:
For our planning purposes, we would like to ask if the Agency anticipates providing a Day 74 letter to Biogen Idec.

FDA Preliminary Response to Question 7:
This will be determined at the filing meeting after initial review of your NDA submission.

Meeting Discussion:
No meeting discussion.

Question 8:
Does the Agency anticipate convening an Advisory Committee to discuss BG00012?

FDA Preliminary Response to Question 8:
A final determination will be made as soon as possible after receipt of the NDA submission and you will be notified if our intention is to hold an Advisory Committee meeting. At this time, there are no issues that suggest the need for Advisory Committee input but it is possible that this may change after an initial review of your formal submission.

Meeting Discussion:
In response to an enquiry from the Sponsor, the Division clarified that at this time there are no apparent issues that are expected to prompt a change after initial review of the formal submission. The Division stated that the need for an Advisory Committee meeting can be determined at any point in the review process and that such a decision is always made as early as possible. If such a decision is made at any point, the Division stated that it would immediately inform the Sponsor so that appropriate planning could begin.

Question 9:
To ensure that responses to requests are provided quickly and effectively, would it be useful to the Agency to schedule meetings with us during the review cycle?

FDA Preliminary Response to Question 9:
We do not anticipate a need to schedule a meeting during the review cycle, but if this need arises, we will make this request.

Meeting Discussion:
No meeting discussion.

Question 10:

Biogen Idec plans to provide a rationale for priority review for this product based on the safety and efficacy of the product, its convenience as an oral product appropriate for a wide range of MS subjects, and unmet need in this disease area. Does the Agency concur that the product should be considered for priority review?

FDA Preliminary Response to Question 10:
At this point, we do not anticipate designating your application for priority review, however, a final decision on review status will be made following receipt of your application.

Meeting Discussion:
The Sponsor asked for clarification from the Division regarding this anticipated designation. The Division stated that this product does not appear to address an unmet medical need as there are other products with apparently similar clinical profiles, both injectable and oral, currently on the market for this patient population.

3.0 ADDITIONAL COMMENTS

SAFETY
Based on the information included in your briefing document, we agree with your list of AEs of special interest. We ask that you add skin reactions to your list of AEs of special interest. The Division expects you will include in your application thorough discussions of the AEs of special interest. For several events you note characteristics such as early onset, resolution, or improvement over time, etc. We request that your summaries of these events include the analyses that support these conclusions. For any of the special events where you find increases in risk among dimethyl fumarate treated patients, we ask that you analyze available data to look for co-factors that predict increased risk. Examples of such co-factors include demographic factors, dose, duration of exposure, concomitant medications, comorbid disease, severity of underlying disease, etc.

We request that discussion of malignancy cases with dimethyl fumarate include the following information:

- We request a table of all known cases of malignancy (or pre-malignant conditions) that have occurred in subjects who participated in studies of dimethyl fumarate. The table should include the study, subject number, event Preferred Term, cumulative dose of dimethyl fumarate received at the time of the event, latency from first dose of dimethyl fumarate to malignancy diagnosis, subject's age at the time of diagnosis, subject's country of origin, subject's sex, duration of follow-up for that subject, and a link to the narrative.

- We request tables with the number of reported malignancies, number of subjects, incidence proportions, subject-years of exposure, and incidence rates for cases of malignancy in completed and ongoing trials for placebo-treated and dimethyl fumarate treated subjects. We also request presentation of these analyses stratified by duration of

subject follow-up (less than 1 year, 1 to less than 2 years, 2 to less than 3 years, and more than 3 years). For each subject group, we request the median cumulative dose, the cumulative dose range, and the median duration of treatment exposure.

To assist in our evaluation of the dimethyl fumarate study data, we request that you provide a list of the inclusion and exclusion criteria for each of the dimethyl fumarate studies, including those introduced as part of protocol amendments.

Please include in your submission an index listing all submitted narratives with links to the narratives.

For narratives, please use a common template that is easy to review. Narrative summaries should provide a common synthesis of all available clinical data and an informed discussion of the case. Narrative summaries should allow a better understanding of what the patient experienced. The following items should be included:

- Patient age and gender
- 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 the available clinical data
- For events without a definitive diagnosis, a list of differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

If more than one event is contained in a single narrative, then there should be a line listing at minimum for each event. It is preferable, however, to have separate narratives, especially if events in an individual are separated by 6 months or more.

Adverse Event Datasets
For each of the Phase 1 and Phase 2-3 study pools, we request that the submitted datasets contain verbatim terms and MedDRA coding with all levels of the MedDRA hierarchy.

Meeting Discussion:
No meeting discussion.

CLINICAL PHARMACOLOGY

- Since you presented no relevant information pertinent to the formulations used in the clinical studies, your rationale for establishing a bridge between the formulation used in your clinical studies and the proposed commercial formulation is unclear. Without appropriate bridging data and discussion, significant differences between the two formulations may be an NDA filing issue.

- No details were provided in the current submission regarding in vitro metabolic characterization and screening for DDI potential using human biomaterial or cell lines. Therefore, the adequacy (or completeness) of these investigations cannot be considered at this point and will be a review issue at the NDA stage. Please refer to the Agency's DDI Guidance for Industry for further recommendations.

- For studies in specific populations: We noted that you proposed studies for hepatic and renal impairment with an adaptive, two-stage, reduced study design in your end-of-phase 2 submission. However, in the current submission, you state that such studies are not necessary.

    - You should provide convincing scientific justification to support a lack of significant impact by hepatic impairment on the major metabolic pathways (via esterases and the downstream TCA cycle) for BG00012 with regard to PK, PD, and safety. Your proposal for not conducting a renal impairment study, based on results of the mass-balance study, seems reasonable. Again, please provide convincing scientific justification in the NDA submission for not conducting such a study.
    - You should include hepatic and renal function in population PK analyses to examine their impact on BG00012 disposition if such data are available.

- You should clarify whether the food effect study was conducted using the highest strength of the proposed commercial formulation. If not, you should provide justification on why the food effect study with a lower strength capsule formulation is adequate in the NDA submission.

- If dose-dumping is a likely concern as a result of interaction between gastro-resistant (b) (4) and alcohol in the stomach, you should address this concern by first conducting an in vitro dissolution study in alcoholic media (if not done).

- An outline of the summary section of the human Clinical Pharmacology and Biopharmaceutic Studies is provided. We request that you provide such a summary section as a review aid for the Clinical Pharmacology reviewer. At the time of NDA submission, you can use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it separately to the Agency as a review aid. This summary section should be submitted electronically with appropriate hyperlinks to the relevant supporting data (document provided below).

Meeting Discussion:

The Sponsor elected to clarify the additional clinical pharmacology comments pertaining to the formulations, population PK analysis, and location of the Clinical Pharmacology and Biopharmaceutic Studies Review Aid in the NDA, as summarized below. The Division acknowledged these clarifications.

- There are two commercial strengths of capsule formulations, 120 mg and 240 mg. The clinical formulation is identical to the commercial formulation of 120 mg strength. For the highest 240 mg strength, the Sponsor stated that evaluation has been performed to show bioequivalence and provide bridging data.
- Per previous IND submissions, the PK data were collected via intensive PK sampling in a subset of 48 MS patients so no sparse PK samples were collected in the Phase 3 trials. No sparse PK samples were collected in Phase 2 trials, either. Therefore, no population PK analysis will be conducted for examining the potential impact of organ dysfunction.
- The Sponsor proposed to place the Review Aid in Module 1 of the NDA submission. The Division advised the Sponsor to submit the Review Aid in Module 2.7.2, along with the Summary of Clinical Pharmacology Studies, containing sufficient hyperlinks to the supporting data. The Sponsor agreed to do this.

PROJECT MANAGEMENT

At the time of your NDA submission, please submit a table listing all investigators by country. Please provide in this table the address and contact information for each investigator, the investigator's number, center number, study ID, as well as the number of subjects at each center.

Please provide links to the following sections in the cover letter of your NDA submission:

- Integrated Summary of Safety (ISS)
- Drug Abuse Liability Assessment Summary
- Risk Management plan
- Labeling
- Regulatory history
- Pediatric plan
- Clinical Pharmacology and Biopharmaceutics Review Aid
- Carcinogenicity studies
- QT study

Meeting Discussion:

The Sponsor stated they will not be including a Risk Management plan section within the NDA and the Division agreed.

3.1 ADDITIONAL MEETING DISCUSSION

Clinical

The Division asked the Sponsor what their plan was for the presentation and handling of the Copaxone data in trial 302 in their submission with regard to possible provision of any comparisons or conclusions based on this data. The Sponsor stated that they planned to provide data and make efficacy comparisons to the other treatment arms in the study, but did not intend to reach definitive conclusions regarding the study drug and Copaxone . The Sponsor discussed the measures they took to ensure a decrease in the bias introduced by the unblinded treatment and FDA stated that measures to control this issue are often problematic and may lead to uninterpretable results. The Division asked if the Copaxone arm was included due to EMA requirements and the Sponsor stated that this was the reason.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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/s/

ERIC P BASTINGS on behalf of RUSSELL G KATZ
02/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 73,061

MEETING MINUTES

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 BG000012 (Dimethyl Fumarate).

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2011. The purpose of the meeting was to discuss topics pertaining to the development of BG00012 (Dimethyl Fumarate) delayed release capsules and registration plans for the submission of a New Drug Application.

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 me at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, OTR/L
CDR, USPHS, Regulatory Health Project Manager
Branch VII, Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: CMC

Meeting Date and Time: July 21, 2011; 2:00 – 3:00 p.m. EST
Meeting Location: FDA White Oak Campus

Application Number: IND 73,061
Product Name: BG000012 (Dimethyl Fumarate)
Indication: Multiple Sclerosis
Sponsor/Applicant Name: Biogen Idec

Meeting Chair: Ramesh Sood, Ph.D.
Meeting Recorder: Teshara G. Bouie

FDA ATTENDEES

Office of New Drug Quality Assessment
Ramesh Sood, Ph.D., Branch Chief
Martha Heimann, Ph.D., CMC Lead
Houda Mahayni, Ph.D., Biopharmaceutics Reviewer
Lyudmila Soldatova, Ph.D., Chemistry Reviewer
Teshara G. Bouie, Regulatory Health Project Manager

SPONSOR ATTENDEES

Ann Dodds-Frerichs, Senior Director, Regulatory Affairs CMC
David Goldman, Director, Small Molecule Development
William F. Kiesman, Director, Chemical Process Research and Development
Rajesh Manchanda, Senior Director, CMC Team Leader
Joseph Molon, Director, Quality Control
Kenneth Oh, Director, Regulatory Affairs CMC
Michael Szulc, Principal Scientist, Analytical Development
Nicholas M. Themeles, Senior Manager, Regulatory Affairs CMC
Juan Torres, Senior Vice President, Global Quality

1.0 BACKGROUND

IND 73,061 proposed indication is for the treatment of multiple sclerosis. On April 25, 2011, the sponsor submitted a type C meeting request to discuss topics pertaining to the development of BG00012 (Dimethyl Fumarate) delayed release capsules and registration plans for the submission of a New Drug Application. Background materials were received June 20, 2011. Preliminary meeting responses were sent to the sponsor on July 19, 2011.

2. DISCUSSION

Drug Substance:

1. [redacted] (b) (4), used in the synthesis of the dimethyl fumarate drug substance, is tested and released as per compendial requirements. Biogen Idec has fully characterized the starting material, [redacted] (b) (4) with additional tests beyond the compendial requirements. Does the Agency agree with our approach for characterization [redacted] (b) (4) as the starting material for the synthesis of dimethyl fumarate?

   FDA Preliminary Response: *Yes, the* [redacted] (b) (4) *can be considered as a starting material for the synthesis of dimethyl fumarate based on the rationale and characterization data you have provided.*

   Meeting Discussion: No further discussion at the meeting.

2. Drug substance and drug product manufacturing processes have been validated which included evaluation of robustness of each unit operations. Due to the robustness of each operating step, normal operating ranges adequately provide consistent product quality attributes and therefore, no critical process parameters have been identified that would adversely affect product quality attributes. Does the Agency concur that the process when operated within normal operating ranges does not require any critical process parameters?

   FDA Preliminary Response: *Provide the drug substance and drug product process development information in the NDA. The development report should include the rationale for the determination that there are no critical process parameters along with the data to support the proposed normal operating ranges. The information submitted will be a matter of the review.*

   Meeting Discussion:
   Sponsor asked more details on the response. FDA has clarified that sponsor should provide a list of both studied and not studied potential critical process parameters, and to justify their impact on the drug substance quality attributes.

3. The drug substance synthesis utilizes [redacted] (b) (4) and hence, the potential exists of generating [redacted] (b) (4) Biogen Idec has conducted extensive studies including kinetic modeling to predict the potential formation [redacted] (b) (4) in the process and spiking experiments to show that the process removes any [redacted] (b) (4) that may be formed and thus,

the removal of any (b) (4) formed is controlled in-process. Additionally, we have not observed any (b) (4) in the drug substance batches tested to date. Therefore, we do not plan to include (b) (4) in the release specification for the drug substance. Does the Agency agree that (b) (4) does not need to be included in the release specifications?

FDA Preliminary Response: *The threshold for toxicological concern (TTC) (b) (4) for a total daily dose of (b) (4) is too close to the LOD (b) (4) of the detection method (b) (4). We recommend that you continue monitoring the level (b) (4) in the first ten commercial batches. Based on the results from these batches you may submit a supplement to delete the test from the specification.*

Meeting Discussion:
Sponsor informed that two batches produced at (b) (4) scale and one batch produced at (b) (4) scale are the commercial scale batches. Sponsor was advised to provide the justification for not including the test and limits for (b) (4) in the drug substance specifications, additional supportive data from other batches that were not included in the briefing package if any. Sponsor was told that it will be the review matter to take a final decision.

Drug Product:

4. As described above, development of the drug product has utilized size 0 gelatin capsules of different colors (b) (4) for the clinical, validation and registration lots. Extensive studies have been performed to show compatibility and stability of the drug product in these different colored capsules. Biogen Idec has also conducted comparability studies to demonstrate the equivalence of the different colored capsules.
Does the Agency concur that we do not need to conduct any additional studies to show the equivalence of the drug products with different colored capsule shells?

   FDA Preliminary Response: *Yes, provided you show similarity of dissolution profiles using an acceptable dissolution method.*

   Meeting Discussion: No further discussion at the meeting.

5. The dissolution procedure was developed as per USP <711> for delayed release dosage forms. The dissolution profile data from our drug product demonstrated that the proposed dissolution procedure is appropriate for the different strengths of the drug product. Does the Agency agree that the dissolution procedure as developed and used for the testing of our drug product is suitable?

   FDA Preliminary Response: *FDA needs to review the dissolution method development report before a decision is made about the suitability of the dissolution method. Please note the proposed specification in the intestinal pH media of Q = (b) (4) is not justifiable as more than (b) (4) of the drug is released after 10 minutes.*

   Meeting Discussion:

The sponsor was advised to submit a Request for Feedback on their full dissolution method development report. The request should be submitted as an amendment to the IND. The report should include information supporting the selection of the proposed dissolution methodology, including choice of apparatus, media, and rotation speed. The Agency will provide feedback on the dissolution method development report within 4 weeks. However, feedback on the dissolution specifications will take place during the NDA review. The sponsor was referred to SUPAC-MR and Dissolution guidances for further details.

6. Phase III studies have been conducted with the 120 mg strength of the drug product. An additional strength, 240 mg is being developed with similar composition to the 120 mg. Biogen Idec plans to conduct characterization testing with the two strengths to show that they are comparable. Does the Agency agree that the proposed equivalency protocol to show comparability between the two strengths of the drug product, 240 mg and 120 mg is sufficient?

   FDA Preliminary Response:
   Yes, the Agency agrees if you plan to conduct the proposed bioequivalence study comparing 2x120 mg dimethyl fumarate capsules vs. 1x240 mg dimethyl fumarate capsule. However, based on the limited stability data provided for 240 mg strengths capsules, the expiry may be limited according to the scope of data provided. You should provide at least 12-month stability data to have commercially viable expiry.

   Meeting Discussion:
   Sponsor confirmed that they plan to conduct the bioequivalence study for 2x120 mg and 1x240 mg dimethyl fumarate capsule . Regarding the expiry for 240 mg capsules, the 3-month data are acceptable for filing of NDA. Additional 3-month data will be provided during the review cycle to have total 6-month data. However, the extrapolation of the 6-month data is not possible because the requirements of the ICH guidance Q1A should be fulfilled first, and then the extrapolation according to ICH guidance Q1E is considered. Sponsor was told that the extention of the expiry for 240 mg capsules is possible post-approval in the Annual Report when updated stability data will be available.

7. Drug product manufacturing processes have been validated which included evaluation of robustness of each unit operations. Due to the robustness of each operating step, normal operating ranges adequately provide consistent product quality attributes and therefore, no critical process parameters (CPPs) have been identified that would adversely affect product quality attributes. Does the Agency concur that the process when operated within normal operating ranges does not require any CPPs?

   FDA Preliminary Response: *You have stated that all potential critical parameters were evaluated over ranges that may be expected to occur in the manufacturing process. Provide all pharmaceutical development data that supports the acceptable quality of the drug product. It will be a matter of the review to evaluate the potential critical process parameters.*

   Meeting Discussion:

Sponsor asked more details on the response. FDA has clarified that sponsor should provide a list of both studied and not studied potential critical process parameters, and to justify their impact on the drug product quality attributes.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

The Sponsor will amendment the IND with a Request for Feedback on their full dissolution method development report.

5.0 ATTACHMENTS AND HANDOUTS

None.

_____

{See appended electronic signature page}

Teshara G. Bouie
Regulatory Health Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

TESHARA G BOUIE
08/26/2011

RAMESH K SOOD
08/26/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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) file for BG00012.

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on August 30, 2006. The purpose of the meeting was to discuss the continued development of BG00012.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 30, 2006

TIME: 3:00 – 4:30 PM

LOCATION: White Oak, Building 22, Rm. 1309

APPLICATION: PIND 73,061, BG00012

TYPE OF MEETING: B: End of Phase 2

MEETING CHAIR: Dr. Russell Katz

FDA Attendees
Russell Katz
Kun Jin
Eric Bastings
Janeth Rouzer-Kammeyer
Paul Roney
Ta-Chen Wu
James Reese

Biogen Idec Attendees
Nadine Cohen
Tammy Sarnelli
Katherine Dawson
Michael Panzara
Frances Lynn
Lisa Beebe
Chris TenHoor
Khandan Baradaran
Sophia Lee
Minhua Yang
Janet Clarke
Ratna Lingamaneni
Jason Brauner
Carmen Bozic
Kah Lay Goh

The questions discussed below were submitted as part of the EoP2 package dated July 24, 2006. The Sponsor's questions are presented below in italics, followed by the preliminary FDA response (conveyed to the sponsor by e-mail just prior to the meeting), and then a summary of the discussion from the meeting.

Pharmacology/toxicology:

1) Does the Agency concur that the preclinical plan is sufficient to support Phase 3 clinical studies and registration of BG00012 (Section 5)?

FDA Response:
With the following exception, your nonclinical program appears to be acceptable for supporting Phase 3 clinical studies and registration of BG00012:
In Table 5-2 on page 34 of the briefing package, you state that the Pre- and Post-Natal Development Toxicity Study will be conducted using rabbits. We recommend that this study be conducted using rats.

Meeting Discussion
The Sponsor asked if they could begin their Phase 3 clinical trial prior to submitting the 12 month repeat dose toxicity study in monkeys. The monkey study will be submitted within three months of the initiation of the clinical trial. The Sponsor has already submitted a nine month repeat dose toxicity study in dogs.
The Division stated that this approach is acceptable.

Clinical pharmacology:

2) Does the Agency concur that the clinical pharmacology plan is sufficient to support Phase 3 clinical studies and registration of BG00012 (Section 6)?

FDA Response:
1. We recommend that you conduct additional screening for drug interaction potential involving CYP2C8 or P-glycoprotein inhibition by BG00012. Though not a prerequisite before the initiation of Phase 3 clinical trials, you should consider conducting studies or providing justifications for not conducting such investigation to eventually support an NDA application.

2. Your proposal for PK studies in subjects with hepatic or renal impairment seems reasonable. However, we recommend that you initiate the planned human mass-balance study at an earliest time, so that the results obtained will not only help in assessing the need for studies in patients with hepatic or renal impairment, but will also help guide the proper design for such studies.

3. You should provide more details of the (b) (4) formulation and the rationale for (b) (4) coating. If dose-dumping (or degradation in acidic pH) is a likely concern, then we recommend that you investigate the potential dose-dumping effect as a result of interaction between the MR formulations and alcohol. This should be discussed in the future with the Agency.

4. We also recommend you include a population PK program and collect sparse samples (in proposed Phase 3 trials) that may help detect the potential drug-drug interaction with concomitant medications and/or other factors, e.g., body weight, age, etc, that contribute to the variability. This will also help explore the exposure-response relationships for efficacy and safety, which is an important aspect of development program. Please be aware that it will be important to have adequate support for safety and efficacy across the range of patients

who would be in the indicated population (e.g., the range in body weight). We will be happy to review the protocol when submitted.

Clinical:

3) Are the Phase 3 study designs appropriate to support registration of BG00012 in relapsing forms of MS? (Section 1)? Specifically:

a. Is the patient population described in the clinical development plan appropriate? (Section 8.2)?

FDA response:
You are excluding patients with progressive-relapsing MS, yet your indication is for "relapsing forms of MS". The indication for the population as defined in the study protocols would likely be "relapsing-remitting MS".

Meeting Discussion
The sponsor stated that he is excluding patients with slow progressive MS and that historically, patients with a substantial number of relapses would be included. FDA stated that excluding people with secondary progressive (non relapsing) MS is acceptable, but that the definition of "relapsing forms of MS" includes progressive-relapsing.

b. Does the Agency concur that the primary endpoint of proportion relapsing is appropriate to support registration? (Section 8.6)?

FDA response:
According to your proposed analysis plan, your endpoint is actually time to first relapse (survival curve distribution). That endpoint will not give adequate information regarding the maintenance of efficacy in the second year of treatment. You should instead analyze an endpoint that will not be sensitive to only shifting the time of occurrence of relapses (e.g., the proportion of patients relapsing or relapse-free). You should also carefully design your studies to address the issue of maintenance of efficacy in the second year (see also below).

Meeting Discussion
These are actually two separate issues.
1. The proportion of patients who are relapse free is an acceptable endpoint. However, the time to event is problematic. Your approach to imputation should be explained.
2. You should provide sufficient data to support chronic treatment in MS. We will need to see consistent efficacy for two years. Your design gives little data for year two in the case of an early dropout. Your expected dropout rate of 25% makes this a problem. The Agency is open to other designs intended to provide more data from the second year. An interim analysis at 18 months may not be needed.

c. Is the selection of dose appropriate for the Phase 3 studies? (Section 8.4)?

FDA response:
We agree that tolerability issues appear to limit the maximum dose to be tested to 240 mg t.i.d. You should however consider testing intermediate doses in the Phase 3 study, e.g. 240 mg b.i.d.

or 120 mg t.i.d.. Such a dose might improve patient compliance and/or minimize dropouts from adverse effects during the study.

We note that you hypothesize that BG00012 at 240mg t.i.d. might develop the efficacy effect over a period of several months, and that your phase 2 study was limited to 6 months of assessment. You have no data that a dose less than 240 mg t.i.d. might provide equivalent efficacy in the longer period (i.e., longer than 6 months) and have lesser adverse effects. For a chronic disease such as MS, the longer term efficacy is more important than small differences in the rapidity of effect.

In addition, if the lower dose was observed to be less efficacious in an adequate and well controlled study, this evidence of dose superiority could strengthen the totality of evidence supporting marketing of your product.

Meeting Discussion
Biogen Idec indicated that the 240 mg t.i.d. group has shown continued efficacy, and proposed that dose as the best choice.

d. Does the Agency concur that if a superiority analysis of the primary endpoint at the specified alpha level after an average of 18 months and after all subjects have had a minimum of 1 year of treatment demonstrates statistical significance, then the blinded portion of the Phase 3 trials could be terminated and these data would be sufficient to file the NDA (Section 8.5)?

FDA response:
No. Considering the potentially large number of patient dropouts or early escapes, it is difficult to predict how many patients will have data approaching 2 years of treatment if the studies, as currently proposed, were carried out without early termination. In the event of early termination as proposed, it is likely that a very limited number of patients would reach that 2 year timepoint. You may have only a fraction of patients left to analyze sustained efficacy and safety during the second year of treatment, in particular in the last 6 months. Early termination of the trial may provide inadequate evidence of efficacy during the second year.

As discussed above, we are concerned about having insufficient information on the maintenance of efficacy in the second year of treatment. This concern applies to the studies as proposed, with or without early termination. It will be necessary for you to supply adequate evidence of efficacy during the second year of treatment. We are also interested in getting sufficient 2-year safety data, to adequately assess the risk of delayed infectious, neoplastic, and cardiac adverse events.

We are also concerned about your plan to offer a switch to open-label study drug for patients who have a relapse during the study. Given the intended therapeutic equipoise, the drug proposed for patients relapsing during the study should be one of the approved MS drugs, and not your investigational drug, for which efficacy and safety have not been established.

In order to improve the retention of patients in the trial and maintenance of study treatment, we suggest that you modify your proposed active comparator study by transforming it into an add-on trial, where a combination of your study drug and copaxone could be compared to copaxone and placebo. This trial design may have improved likelihood to provide adequate second year safety and efficacy data.

e. Assuming the Phase 3 trials terminate at 18 months, does the Agency concur that the overall patient safety database is adequate for registration? (Section 8.7)?

FDA response:
No. We are concerned that the safety database will be inadequate due to expected dropout of patients due to relapse or adverse events. As discussed above, we are concerned about obtaining sufficient long-term safety data in the second year of treatment, to obtain adequate information on possible delayed infectious and neoplastic toxicities, and have an adequate assessment of the cardiac risk in the MS population.

4) Is the overall clinical development plan for BG00012 adequate to support registration of BG00012 for relapsing forms of MS? (Section 8)?

FDA response:
See above.

5) Does the Agency concur that a pediatric waiver is appropriate for BG00012? (Section 8.8)?

FDA response:
Yes.

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/s/

Russell Katz

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