CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204063Orig1s000

<u>OTHER REVIEW(S)</u>

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: March 20, 2013

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 204-063 (BG-00012, dimethyl fumarate, TECFIDERA), labeling recommendations.

Recommendations for labeling are provided in this memo; the sponsor's proposed labeling was used as the base document. These labeling recommendations take into account those provided by Dr. Banks-Muckenfuss (*cf. Pharmacology/Toxicology NDA Review and Evaluation, NDA 204063, Melissa K. Banks-Muckenfuss, Ph.D., 1/28/2013*) and some, but not all, of the additional comments provided by the sponsor. Plasma exposure (AUC) margins were calculated using values in humans from repeat-dose studies (# 109HV103 and 109HV104): C_{max}: 2.24-2.4 μg/mL; AUC: 10-11.3 μg*hr/mL.

SPONSOR	RECOMMENDED
HIGHLIGHTS OF PRESCRIBING INFORMATION	
-----INDICATIONS AND USAGE-----	**-----INDICATIONS AND USAGE-----**
(b) (4)	TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis. (1)
	----USE IN SPECIFIC POPULATIONS-----
	Pregnancy: based on animal data, may cause fetal harm. (8.1)
	8 USE IN SPECIFIC POPULATIONS
	8.1 Pregnancy Pregnancy Category C There are no adequate and well-controlled studies in pregnant women. In animals, adverse effects on offspring survival, growth, sexual maturation, and neurobehavioral function were observed when dimethyl fumarate (DMF) was administered during pregnancy and lactation at clinical relevant doses. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In rats administered DMF orally (25, 100, 250 mg/kg/day) throughout organogenesis, embryofetal toxicity (reduced fetal body weight and delayed ossification) were observed at the highest dose tested. This dose also produced evidence of maternal toxicity (reduced body weight). Plasma exposure (AUC) for monomethyl fumarate (MMF), the major circulating metabolite, at the no-effect dose is approximately three times that in humans at the recommended human dose (RHD) of 480 mg/day. In rabbits administered DMF orally (25, 75, and 150 mg/kg/day) throughout organogenesis, embryolethality and decreased maternal body weight were observed at the highest dose tested. The plasma AUC for MMF at the no-effect dose is approximately 5 times that in humans at the RHD. Oral administration of DMF (25, 100, and 250 mg/kg/day) to rats throughout organogenesis and lactation resulted in increased lethality, persistent reductions in body weight, delayed sexual maturation (male and female pups), and reduced testicular weight in offspring at the highest dose tested. Neurobehavioral impairment was observed at all doses. A no-effect dose for developmental

(b) (4)	toxicity was not identified. The lowest dose tested was associated with plasma AUC for MMF lower than that in humans at the RHD. Pregnancy Registry *[No comment on PR wording; defer to clinical team.]*
	This section should be omitted.
8.3 Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRADENAME is administered to a nursing woman.	**8.3 Nursing Mothers** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TECFIDERA is administered to a nursing woman.
(b) (4)	**8.4 Pediatric Use** Safety and effectiveness in pediatric patients not been established.
12 CLINICAL PHARMACOLOGY	
(b) (4)	**12.1 Mechanism of Action** The mechanism by which dimethyl fumarate (DMF) exerts its therapeutic effect in multiple sclerosis is unknown. DMF and the metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist *in vitro*.
13 NONCLINICAL TOXICOLOGY	

(b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies of dimethyl fumarate (DMF) were conducted in mouse and rat. In mouse, oral administration of DMF (25, 75, 200 and 400 mg/kg/day) for up to two years resulted in an increase in nonglandular stomach (forestomach) and kidney tumors: squamous cell carcinomas and papillomas of the forestomach in males and females at 200 and 400 mg/kg/day; leiomyosarcomas of the forestomach at 400 mg/kg/day in males and females; renal tubular adenomas and carcinoma at 200 and 400 mg/kg/day in males; and renal tubule adenomas at 400 mg/kg/day in females. Plasma MMF exposure (AUC) at the highest dose not associated with tumors in mouse (75 mg/kg/day) was similar to that in humans at the recommended human dose (RHD) of 480 mg/day.

In rat, oral administration of DMF (25, 50, 100, and 150 mg/kg/day) for up to two years resulted in increases in squamous cell carcinomas and papillomas of the forestomach at all doses tested in males and females, and in testicular interstitial (Leydig) cell adenomas at 100 and 150 mg/kg/day. Plasma MMF AUC at the lowest dose tested was lower than that in humans at the RHD.

Mutagenesis
Dimethyl fumarate and monomethyl fumarate (MMF) were not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. DMF and MMF were clastogenic in the in vitro chromosomal aberration assay in human peripheral blood lymphocytes in the absence of metabolic activation. DMF was not clastogenic in the in vivo micronucleus assay in rat.

Impairment of Fertility
In male rat, oral administration of DMF (75, 250, and 375 mg/kg/day) prior to and throughout the mating period had no effect on fertility; however, increases in non-motile sperm were observed at the mid and high doses. The no-effect dose for adverse effects on sperm is similar to the recommended human dose (RHD) of 480 mg/day on a body surface area (mg/m^2) basis.

In female rat, oral administration of DMF (20, 100, and 250 mg/kg/day) prior to and during mating and continuing to gestation day 7 caused disruption of the estrus cycle and increases in embryolethality at the highest dose tested. The highest dose not associated with adverse effects (100 mg/kg/day) is

	twice the RHD on a mg/m^2 basis. Testicular toxicity (germinal epithelial degeneration, atrophy, hypospermia, and/or hyperplasia) was observed at clinically relevant doses in mouse, rat, and dog in subchronic and chronic oral toxicity studies of DMF, and in a chronic oral toxicity study of fumaric acid esters (including DMF) in rat.
(b) (4)	**13.2 Animal Toxicology and/or Pharmacology** Kidney toxicity was observed after repeated oral administration of dimethyl fumarate (DMF) in mouse, rat, dog, and monkey. Renal tubule epithelia regeneration, suggestive of tubule epithelial injury, was observed in all species. Renal tubular hyperplasia was observed in rats with dosing for up to two years. Cortical atrophy and interstitial fibrosis were observed in dog and monkey at doses above 5 mg/kg/day. In monkey, the highest dose tested (75 mg/kg/day) was associated with single cell necrosis and multifocal and diffuse interstitial fibrosis, indicating irreversible loss of renal tissue and function. In dog and monkey, the 5-mg/kg/day dose was associated with plasma MMF exposures less than or similar to that in humans at the recommended human dose (RHD). A dose-related increase in incidence and severity of retinal degeneration was observed in mouse following oral administration of DMF for up to two years at doses above 75 mg/kg/day, a dose associated with plasma MMF exposure (AUC) similar to that in humans at the RHD.

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/s/

LOIS M FREED
03/20/2013

PMR/PMC Development Template for TECFIDERA (dimethyl fumarate)

PMR # 2014-1

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

PMR/PMC Description: Deferred pediatric trial under PREA: A randomized, controlled, parallel group superiority trial in pediatric patients ages 10 through 17 years 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.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	11/30/2016
	Study/Clinical trial Completion Date:	10/31/2019
	Final Report Submission Date:	02/28/2020
	Other: _____	MM/DD/YYYY

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

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

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

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

The goal of this study is to evaluate the pharmacokinetics, safety, and efficacy of dimethyl fumarate in pediatric patients ages 10 to up to 17 compared to an appropriate control for treatment of relapsing forms of multiple sclerosis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☒ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

Deferred pediatric trial under PREA: A randomized, controlled, parallel group superiority trial in pediatric patients ages 10 through 17 years 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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

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

Agreed upon:

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

☐ Other

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

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

PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

PMR/PMC Development Template for TECFIDERA (dimethyl fumarate)
PMR # 2014-2

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

PMR/PMC Description: Receptor binding study for abuse potential assessment

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	6/30/12
	Study/Clinical trial Completion Date:	8/30/13
	Final Report Submission Date:	10/30/13
	Other:	MM/DD/YYYY

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

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

   The clinical data collected so far does not indicate major problems with respect to abuse potential.

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

   The NDA for dimethyl fumarate does not contain all of the information necessary for a complete evaluation of its abuse potential. The goal of this study is to provide information about the abuse potential of dimethyl fumarate. Although activation of the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2 or Nrf2) transcriptional pathway is not a pharmacological mechanism of action traditionally recognized to be associated with known drugs of abuse, comprehensive receptor binding studies with dimethyl fumarate would establish whether activity at receptor sites associated with abused drugs exists.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

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

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

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

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

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

A comprehensive in vitro receptor binding study 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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

_____

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

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

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

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(signature line for BLAs)

PMR/PMC Development Template for Tecfidera (dimethyl fumarate)
PMR # 2014-3

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

PMR/PMC Description: A nonclinical self-administration study to assess abuse potential using dimethyl fumarate in animals trained to discriminate the known drug of abuse from saline.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	10/30/2013
	Study/Clinical trial Completion Date:	02/28/2014
	Final Report Submission Date:	03/30/2014
	Other: _____	MM/DD/YYYY

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

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

   The clinical data collected so far does not indicate major problems with respect to abuse potential.

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

   The NDA for dimethyl fumarate does not contain all of the information necessary for a complete evaluation of its abuse potential. The goal of this study is to provide information about the abuse potential of dimethyl fumarate. The ability of dimethyl fumarate to produce self-administration is unknown. Among preclinical behavioral models used to evaluate the abuse potential of a drug, self-administration is often cited as the standard preclinical abuse potential assessment because of its face validity and predictive validity. Data from self-administration studies will provide information about the likelihood that dimethyl fumarate will function as a reinforcer and be abused.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

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

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

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

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

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

A nonclinical self-administration study to assess abuse potential 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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

_____

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

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

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

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(signature line for BLAs)

PMR/PMC Development Template for TECFIDERA (dimethyl fumarate)
PMR # 2014-4

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

PMR/PMC Description: A nonclinical discrimination study to assess abuse potential using dimethyl fumarate in animals trained to discriminate the known drug of abuse from saline.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	3/30/2014
	Study/Clinical trial Completion Date:	7/30/2014
	Final Report Submission Date:	8/30/2014
	Other: _____	MM/DD/YYYY

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

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

The clinical data collected so far does not indicate major problems with respect to abuse potential.

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

The NDA for dimethyl fumarate does not contain all of the information necessary for a complete evaluation of its abuse potential. The goal of this study is to provide information about the abuse potential of dimethyl fumarate. The similarity of dimethyl fumarate to other drugs of abuse as evaluated in the drug discrimination study is unknown. Among preclinical behavioral models used to evaluate the abuse potential of a drug, the discrimination study is often cited as one of the most important standard preclinical abuse potential evaluations because of its face validity and predictive validity. Data from discrimination studies will provide information about the similarity of dimethyl fumarate to other drugs of abuse and serve as a predictor of its potential for abuse

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

A nonclinical discrimination study to assess abuse potential 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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

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

Agreed upon:

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

☐ Other

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

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

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

_____
(signature line for BLAs)

PMR/PMC Development Template for Tecfidera (dimethyl fumarate)
PMR # 2014-5

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

PMR/PMC Description: Juvenile rat toxicology study to evaluate the effects of dimethyl fumarate on growth, reproductive development, and neurological and neurobehavioral development.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	04/30/2014
	Study/Clinical trial Completion Date:	01/31/2016
	Final Report Submission Date:	03/31/2016
	Other: _____	MM/DD/YYYY

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

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

   This product is ready for approval for use in adults and pediatric studies have not been conducted.

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

   A juvenile rat toxicology study under PREA to identify the unexpected serious risk of adverse effects of dimethyl fumarate on postnatal growth and development. 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 must evaluate effects of dimethyl fumarate on growth, reproductive development, and neurological and neurobehavioral development.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

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

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

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

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

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

A 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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

_____

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

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

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

_____
(signature line for BLAs)

PMR/PMC Development Template for Tecfidera (dimethyl fumarate)
PMR # 2014-6

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

PMR/PMC Description: Postmarketing observational safety study in adult patients with relapsing multiple sclerosis patients

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	10/31/2013
	Study/Clinical trial Completion Date:	10/13/2022
	Final Report Submission Date:	10/30/2023
	Other: _____	MM/DD/YYYY

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

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

   This is appropriate for a PMR because a signal for the adverse events to be further evaluated was not identified in the clinical database.

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

   Several serious events are of potential concern based on the putative mechanism of action and based on findings in the nonclinical studies. These include serious infections including opportunistic infections, leiomyomata, malignancies including renal cell cancers, and other serious adverse events including serious renal and hepatic events. Additional long-term observation is needed, including in patients that may have been excluded from the clinical trials population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

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

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

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

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

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

A large, long-term, prospective observational study in adult patients with relapsing multiple sclerosis, 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 (dimethyl fumarate). The study should include characterization of the finding of urinary ketones. A minimum of 5000 multiple sclerosis patients treated with Tecfidera (dimethyl fumarate) should be enrolled and followed for a minimum of 5 years. The final protocol should reflect agency agreement and be submitted prior to starting the study.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

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

Agreed upon:

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

☐ Other

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

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

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

(signature line for BLAs)

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/s/

SALLY U YASUDA
03/07/2013

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

Final Label and Labeling Review

Date:	February 28, 2013
Reviewer:	Julie Neshiewat, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS, Team Leader Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Dimethyl Fumarate Delayed-release Capsules 120 mg, 240 mg
Application Type/Number:	NDA 204063
Applicant/sponsor:	Biogen Idec
OSE RCM #:	2012-530

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

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Dimethyl Fumarate Delayed-release Capsules received on February 7, 2013 and February 22, 2013 (Appendices A through E). DMEPA has reviewed previous versions of the container labels and carton labeling under OSE Review # 2012-530 dated September 17, 2012, November 26, 2012, January 15, 2013, and February 1, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the container labels and carton labeling received on February 7, 2013 and February 22, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2012-530 dated September 17, 2012, November 26, 2012, January 15, 2013, and February 1, 2013.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container labels and carton labeling show that the Applicant implemented DMEPA's previous recommendations. We have no additional recommendations at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

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

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/s/

JULIE V NESHIEWAT
02/28/2013

IRENE Z CHAN
02/28/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**TECFIDERA (dimethyl fumarate) delayed-release capsules, for oral use**
Applicant	Biogen Idec
Application/Supplement Number	NDA 204063
Type of Application	Original
Indication(s)	Treatment of patients with relapsing forms of multiple sclerosis
Established Pharmacologic Class[1]	none
Office/Division	ODE I/DNP
Division Project Manager	Nicole Bradley
Date FDA Received Application	February 27, 2012
Goal Date	March 27, 2013
Date PI Received by SEALD	February 26, 2013
SEALD Review Date	February 27, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information
[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

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

Comment:

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

Comment:

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

Comment: *In Dosage and Administration, each bullet should have a "(2)" at the end of the statement.*

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

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

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

Comment:

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The current wording states: "… do not include all of the information.."; the word "of" should be deleted.*

Product Title

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

Comment:

Initial U.S. Approval

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

Comment:

Boxed Warning

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

Comment:

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

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC)

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

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

Comment:

Contraindications

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

Comment:

N/A

24. Each contraindication is bulleted when there is more than one contraindication.
    Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

    Comment:

Patient Counseling Information Statement

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

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

- **"See 17 for PATIENT COUNSELING INFORMATION"**

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

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

Comment:

Revision Date

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

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
    Comment:

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

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
    Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
    Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.
    Comment:

Selected Requirements of Prescribing Information

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Section 13.1 is currently worded: "Carcinogenesies, Mutagenesis, and Impairment of Fertility"; the word "and" should be deleted.*

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

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *Most cross-references currently state "See" (should be lower-case: "see"; the only cross-reference that states "see" is under 6.1, reference to Clinical Studies) and all the numerical identifiers are not italicized. Also, sub-section 17.1 currently references "2"; it should reference "2.1" and sub-section 17.4 references "5" and it should reference "5.1".*

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

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

Comment:

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

Comment:

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

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES

Selected Requirements of Prescribing Information

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

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

    Comment:

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

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

    Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *The PI currently states: "See FDA-Approved Patient Labeling (Patient Information)"; this should read: "See FDA-approved patient labeling (Patient Information)" as stated above.*

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/s/

ELIZABETH A DONOHOE
02/27/2013

LAURIE B BURKE
02/27/2013

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

Final Label and Labeling Review

Date:	February 1, 2013
Reviewer:	Julie Neshiewat, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS, Team Leader Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Dimethyl Fumarate Delayed-release Capsules 120 mg, 240 mg
Application Type/Number:	NDA 204063
Applicant/sponsor:	Biogen Idec
OSE RCM #:	2012-530

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

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Dimethyl Fumarate Delayed-release Capsules received on January 24, 2013 (Appendices A through E). DMEPA has reviewed previous versions of the container labels and carton labeling under OSE Review # 2011-530 dated September 17, 2012, November 26, 2012, and January 15, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the container labels and carton labeling received on January 24, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2011-530 dated September 17, 2012, November 26, 2012, and January 15, 2013.

3 RESULTS

Review of the revised container labels and carton labeling determined that the Applicant did not implement all of our previous recommendations. We previously recommended that the established name be presented in bold font. The Applicant, however, only presented the active ingredient, dimethyl fumarate, in bold font and did not present the dosage form, delayed-release capsules, in bold font.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA recommends the following recommendations be implemented prior to approval of this application:

A. General Comments for All Labels and Labeling

1. 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 copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley at 301-796-5068.

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/s/

IRENE Z CHAN on behalf of JULIE V NESHIEWAT
02/05/2013

IRENE Z CHAN
02/05/2013

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

Final Label and Labeling Review

Date:	January 15, 2013
Reviewer:	Julie Neshiewat, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS, Team Leader Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Dimethyl Fumarate Delayed-release Capsules 120 mg, 240 mg
Application Type/Number:	NDA 204063
Applicant/sponsor:	Biogen Idec
OSE RCM #:	2012-530

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

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Dimethyl Fumarate Delayed-release Capsules received on December 7, 2012 (Appendices A through E). DMEPA has reviewed previous versions of the container labels and carton labeling under OSE Review # 2011-530 dated September 17, 2012 and November 26, 2012.

2 MATERIAL REVIEWED

DMEPA reviewed the container labels and carton labeling received on December 7, 2012. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2011-530 dated September 17, 2012 and November 26, 2012.

3 RESULTS

Review of the revised container labels and carton labeling determined that the Applicant implemented all of our previous recommendations. However, due to the revised placement of information, we identified additional changes that should be made to the container labels and carton labeling to clarify information and ensure that important information is prominent on the labels and labeling.

4 CONCLUSIONS AND RECOMMENDATIONS

We identified additional changes that should be made to the container labels and carton labeling to clarify information and ensure that important information is prominent on the labels and labeling.

DMEPA recommends the following recommendations be implemented prior to approval of this application:

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 Starter Pack (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 copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley at 301-796-5068.

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/s/

JULIE V NESHIEWAT
01/15/2013

KELLIE A TAYLOR on behalf of IRENE Z CHAN
01/15/2013

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

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

Memorandum

Date: January 14, 2013

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

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)

Subject: OPDP Comments on draft Prescribing Information (PI) for TRADENAME (dimethyl fumarate) capsules for oral use

NDA 204063

This consult is in response to DNP's request for OPDP's review of the proposed PI for dimethyl fumarate (FDA version last modified in the eroom 12/19/2012). We appreciate the opportunity to provide comments on the PI.

Please see attached PI with our comments incorporated therein.

If you have any questions, please contact Quynh-Van Tran, (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
01/14/2013

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Dec 20, 2012

To: Russell Katz, M.D., Director
Division of Neurology Products

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

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 204063**
Product name: Dimethyl Fumarate (BG00012) delayed release
Indication: Relapsing Multiple sclerosis
Dosages: 120, 240 mg [redacted] (b) (4) tablets
Sponsor: Biogen Idec

Materials reviewed: NDA is in EDR (Feb 27, 2012), IND 73061
Clin-Pharm review draft by Dr. JM Parepally

Table of Contents

I. Background

This memorandum responds to a consultation from the Division of Neurology Products regarding evaluation of abuse potential of Dimethyl fumarate (NDA 204-063).

Dimethyl fumarate (DMF or BG00012) was developed as an oral treatment for relapsing multiple sclerosis (MS). At a dose of 240 mg twice a day (BID), DMF is intended to [redacted] (b) (4)

The Sponsor performed 23 clinical studies with DMF, including studies for multiple sclerosis (MS, 6), psoriasis (4), rheumatoid arthritis (1) and healthy volunteers (12). A total of 2,665 subjects with MS were studied. Two pivotal Phase 3 studies were conducted to evaluate the efficacy and safety in the MS population (Trials 301 and 302).

II. Conclusions:

1. DMF has never been approved or marketed as a drug in U.S. As a CNS active new molecular entity (NME), the abuse potential of DMF needs to be fully characterized.

2. The submitted NDA lacked an abuse potential section and critical information necessary to evaluate the need for evaluation and scheduling of the drug.

3. CSS requested missing data in the 74 Day letter related to performing a complete assessment of the abuse potential of DMF and making a decision about whether the drug needs to be scheduled. However, the Sponsor did not provide all data that were requested by CSS.

4 Standard abuse liability assessments (both clinical and preclinical) were not been performed and characterization of the abuse potential of DMF is lacking.[1]

5 In addition, the dependence liability of DMF is unknown.

III. Recommendations:

1. As the sponsor has not assessed the abuse potential of dimethyl fumarate (DMF), a complete characterization of the abuse potential is recommended.

2. The Sponsor should provide the following information as PMRs:

a. Comprehensive receptor binding studies with DMF and its main active metabolite mono-methyl fumarate (MMF). This would include characterization of the affinity of DMF and MMF to dopamine, serotonin, GABA (gamma aminobutyric-acid), opioid, NMDA, monoamine, sodium channel, calcium channel, and cannabinoid receptor sites and interaction with nitric oxide synthetase.

b. Preclinical drug discrimination and self-administration studies should be conducted to evaluate MMF in animals trained to discriminate the known drug of abuse from saline; the animals chosen need to demonstrate similar metabolism as by humans.

c. The Sponsor should analyze the adverse events, report any post-marketing data on abuse, misuse, overdose and diversion of DMF that becomes available. The Sponsor should evaluate any adverse events potentially related to abuse including suicidality and report this information to FDA as serious adverse events.

d. The Sponsor should submit an analysis of the abuse potential related adverse events reports of DMF including misuse, overdose, diversion and suicidality for all studies that had not been submitted, as requested by CSS. This should include some Phase 1 studies, MS studies, and the psoriasis study which were not integrated into safety data analysis.

[1] Draft Guidance for Industry -- Assessment of Abuse Potential of Drugs (Jan 2010). http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

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/s/

ALICJA LERNER
12/20/2012

MICHAEL KLEIN
12/20/2012

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: December 19, 2012

To: Nicole L. Bradley, Pharm.D.
Regulatory Project Manager
Division of Neurology Products (DNP)

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
Division of Consumer Drug Promotion (DCDP)

Subject: NDA 204063
DCDP Comments for draft PPI for dimethyl fumarate capsules, for oral use

DCDP has reviewed the proposed Patient Package Information (PPI) for dimethyl fumarate capsules, for oral use. We have reviewed DMPP's comments from 11/09/12 and agree with those changes and have one additional comment.

DCDP would like you to consider adding "or an infection" to the section, "Before taking and while you take TRADENAME, tell your healthcare provider if you have or have had:" We believe that would increase consumer comprehension of this risk information and reporting infections is not in any other section of the PPI. Adding this would also be consistent with the heading from the PI Section 5.1, "Lymphopenia and Risk of Infection."

Thank you for the opportunity to comment on the proposed PPI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
12/19/2012

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

Final Label and Labeling Review

Date:	November 26, 2012
Reviewer:	Julie Neshiewat, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS, Team Leader Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Dimethyl Fumarate Delayed-release Capsules 120 mg, 240 mg
Application Type/Number:	NDA 204063
Applicant/sponsor:	Biogen Idec
OSE RCM #:	2012-530

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1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Dimethyl Fumarate Delayed-release Capsules received on October 10, 2012 (Appendices A through E). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2011-530 dated September 17, 2012.

2 MATERIAL REVIEWED

DMEPA reviewed the container labels and carton labeling received on October 10, 2012. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2012-530 dated September 17, 2012.

3 RESULTS

Review of the revised container labels and carton labeling determined that not all of our previous recommendations were implemented by the Applicant. The Applicant noted in the cover letter that the use of the terms [redacted] (b) (4) were retained on the labels and labeling since these terms are only utilized for the 14-day Sample Pack (Professional Sample), the 30-day Sample Pack (Professional Sample), and the 30-day Starter Pack (Retail). The Applicant further stated that these terms would help patients to differentiate the titrated dose from the recommended dose in the kit. DMEPA determined that the terms [redacted] (b) (4) are acceptable to use on the labels and labeling for the sample and starter packs. We also identified additional changes that should be made to the container labels and carton labeling to clarify information and improve readability.

4 CONCLUSIONS AND RECOMMENDATIONS

We identified additional changes that should be made to the container labels and carton labeling to clarify information and improve readability.

DMEPA recommends the following recommendations be implemented prior to approval of this application:

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 [redacted] (b) (4) (Professional Sample)

1. Carton Labeling

a. The Agency does not consider [redacted] (b) (4) to be drug samples; therefore, the use of the term [redacted] (b) (4) on drug sample labeling is inappropriate and should not be used. Revise the statement [redacted] (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" in black font next to the 240 mg strength are difficult to read against the (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 (b) (4) since "Dosage: take one capsule by mouth twice daily" is already present on the side panel.

c. The net quantity statement is color blocked (b) (4) for the 120 mg strength and (b) (4) 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 (b) (4) 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 (b) (4) (Professional Sample)

1. Carton Labeling

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

b. 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 "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 (b) (4) bottle containing 14 capsules of 120 mg each
One (b) (4) 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 Starter Pack (Retail)

1. Carton Labeling

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

b. The (b) (4) 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 (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 (b) (4) 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 [redacted] (b) (4) font for the 240 mg strength is difficult to read against the [redacted] (b) (4) color block. Revise the font color of the text or the color block for better contrast.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley at 301-796-5068.

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/s/

JULIE V NESHIEWAT
11/26/2012

IRENE Z CHAN
11/26/2012

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

PATIENT LABELING REVIEW

Date:	**November 08, 2012**
To:	Russell Katz, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (dimethyl fumarate)
Dosage Form and Route:	Capsules for Oral Use
Application Type/Number:	NDA 204-063
Applicant:	Biogen Idec Inc.

1 INTRODUCTION

On February 24, 2012, Biogen IDEC submitted for the Agency's review a New Drug Application (NDA 204-063) for TRADENAME (dimethyl fumarate), indicated for the treatment of patients with relapsing forms of multiple sclerosis (b) (4) [redacted] On March 15, 2012, the Division of Neurology Products (DNP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (dimethyl fumarate). On November 07, 2012, DMPP met with DNP to discuss the proposed new one page PPI review format. DNP concurred with DMPP's proposed one page PPI review format.

This review is written in response to the March 15, 2012, request by DNP for DMPP to review the Applicant's proposed PPI for TRADENAME (dimethyl fumarate).

2 MATERIAL REVIEWED

- Draft TRADENAME (dimethyl fumarate) PPI received on February 27, 2012 and received by DMPP on October 15, 2012.
- Draft TRADENAME (dimethyl fumarate) Prescribing Information (PI) received on February 27, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on October 15, 2012.
- Approved AVONEX (interferon beta 1A) reference labeling dated February, 2012.

3 REVIEW METHODS

Review of new NDA and BLA Patient Package Insert and Medication Guide submissions will reflect changes to previous patient labeling practice. These changes are designed to decrease the length of patient information while maintaining consistency with the Regulations as specified in 21 CFR 208.20.

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved reference labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
11/08/2012

MELISSA I HULETT
11/09/2012

LASHAWN M GRIFFITHS
11/09/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 6, 2012

TO: Nicole Bradley, PharmD, Regulatory Health Project Manager
Heather Fitter M.D., Medical Officer
Division of Neurology Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204-063

APPLICANT: Biogen Idec

DRUG: Dimethyl Fumurate (BG00012)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard review
INDICATION: Treatment of patients with relapsing forms of multiple sclerosis
CONSULTATION REQUEST DATE: April 19, 2012
DIVISION ACTION GOAL DATE: December 20, 2012
PDUFA DATE: December 27, 2012

I. BACKGROUND:

The sponsor, Biogen Idec., has conducted studies in support of approval for the use of oral dimethyl fumarate as a novel treatment for relapsing forms of multiple sclerosis (MS).

Two pivotal studies (109-MS-301 and 109-MS-302) were submitted in support of the application. The studies submitted for the use of a delayed release dimethyl fumurate (DMF) capsule formulation [redacted] (b) (4). The product is intended for use in the treatment of patients with relapsing forms of multiple sclerosis (MS) [redacted] (b) (4). The recommended starting dose is 120 mg taken twice daily for seven days, followed by an increase to the target dose of 240 mg taken twice daily.

The sponsor submitted a new formulation for approval of BG00012 contained in a gelatin capsule. The exact mechanism of action by which DMF exerts its effect in MS is still unclear. Nevertheless, the effectiveness of fumaric acid esters may be attributed to its primary metabolite, monomethyl fumurate. The applicant submitted data primarily generated in foreign countries to support approval for the treatment of MS, a common neurological disease affecting over 1 million people worldwide. Fumaric esters (FAEs) may have both anti-inflammatory and neuroprotective effects.

Despite availability of other medications, more effective and better tolerated treatment options are needed for the population of medically intractable MS subjects. Dimethyl fumurate (BG00012) is not approved in the United States.

According to the applicant, BG00012 may provide an improved safety profile compared to other currently approved for the treatment of MS, may have a reduced frequency of relapse, and may delay physical disability when compared with other medications currently available for MS.

The two pivotal studies are summarized briefly below.

Protocol 109-MS-301 was a randomized, multicenter, double-blind, placebo-controlled, dose-comparison study. Approximately 1011 subjects with relapsing-remitting multiple sclerosis were randomized at approximately 140 sites around the world. Subjects were randomized into one of three groups in a 1:1:1 ratio.

The primary objective of Study 109-MS-301 entitled "A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-Comparison Study to Determine the Efficacy and Safety of BG000012 in Subjects With Relapsing-Remitting Multiple Sclerosis" was to determine whether BG00012, when compared with placebo, is effective in reducing the proportion of relapsing subjects at two years. The following assessments were performed to assess the efficacy of BG00012 by a composite of EDDS, MSFS, Visual Function Test, and MRI.

The secondary objectives were: 1) at one year to determine whether BG00012, when compared with placebo is effective in reducing the rate of clinical relapses and slowing the rate of progression of disability as measured by MSFC in each treatment, and 2) at two years to determine whether BG00012, when compared with placebo, is effective in reducing the progression of disease and attenuating the increase in T1 hypointense lesion volume on brain MRI scan.

Protocol 109-MS-302 was a randomized, multicenter, double-blind, placebo-controlled, dose-comparison study. Approximately 1232 subjects with relapsing-remitting multiple sclerosis were randomized at approximately 174 sites around the world. Subjects were randomized into one of four groups in a 1:1:1:1 ratio.

The primary objective of Study 109-MS-302 entitled "A Randomized, Multicenter, Double-Blind, Placebo-Controlled, and Active Reference (Glatiramer Acetate) Comparison Study to Determine the Efficacy and Safety of BG000012 in Subjects With Relapsing-Remitting Multiple Sclerosis" was to determine whether BG00012, when compared with placebo, is effective in reducing the proportion of relapsing subjects at two years. Assessments of relapse were determined by a composite of EDDS, MSFS, Visual Function Test, MRI and worsening of symptoms.

The secondary objectives were: 1) at one year to determine whether BG00012, when compared with placebo, is effective in reducing the rate of clinical relapses and slowing the rate of progression of disability as measured by MSFC in each treatment, and 2) at two years to determine whether BG00012, when compared with placebo is effective in reducing the progression of disease and attenuating the increase in T1 hypointense lesion volume on brain MRI scan.

The review division requested inspection of four foreign clinical investigators for the pivotal protocols Study 109-MS-301 and 109-MS-302 because data from the protocols are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects and had a treatment effect that was greater than average, 2) for Protocol 109-MS-302 60% of patients were enrolled from region 3 (Eastern Europe), and 3) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations.

II. RESULTS (by protocol/site):

Name of CI, Site # and Location	Protocol and # of subjects	Inspection Dates	Final Classification
Hanka Hertmanowska, M.D. Specjalistyzny Gabinet Neurologizny Osrodek Badan Klinicznych Os Pogodone 22 62-064 Plewiska/Pozanania Poland Sit# 514	Protocol 109-MS-301 Number of subjects: 26	7/23-26/2012	Pending (Preliminary classification NAI)

Name of CI, Site # and Location	Protocol and # of subjects	Inspection Dates	Final Classification
Dragana Obradovic, M.D. Military Medical Academy Neurology Department Crnotravska 17 Belgrade, 11000 Serbia Site# 413	Protocol 109-MS-301 Number of subjects: 24	9/17-21/2012	Pending (Preliminary classification VAI)
Eva Hardova, M.D. Neurologica klinika Fakultni Poliklinik Karlovo namesti 32 Budova A. 4 Praha 2 128 08 Praha 2 Czech Republic Site# 451	Protocol 109-MS-302 Number of subjects: 27	8/13-17/2012	Pending (Preliminary classification NAI)
Tomasz Zielinski, M.D Diagnomed-Clinical Research Sp-zo.o Vice President, Consultant of Neurology UI. Lesnego Potoku 40-414 Katowice Poland Site# 516	Protocol 109-MS-302 Number of Subjects: 45	7/30-8/3/2012	Pending (preliminary classification VAI)
Biogen Idec 14 Cambridge, MA 02142 Sites # 451 and 514	Protocols 109-MS-301 and 302 Number of subjects: 53	6/20-27/2012	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. **An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.**

1. **Hanka Hertmanowska, M.D.**
   62-064 Plewiska/Pozanania
   Poland

   a. What Was Inspected: This inspection was performed as a data audit for NDA 204-063. For Protocol 109-MS-301 at this site, a total of 29 subjects were screened, and three subjects were reported as screen failures. Twenty six (26) subjects were randomized, and 23 subjects completed the study. Review of the Informed Consent Documents, for 13 subjects verified that subjects signed informed consent prior to enrollment.

The medical records/source data for 13 subjects enrolled were reviewed in depth including drug accountability records, inclusion/exclusion criteria, vital signs, laboratory results, and adverse events. Source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events.

b. General observations/commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Hertmanowska. The medical records reviewed were found to be in order, organized and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data generated in support of the clinical efficacy and safety at Dr. Hertmanowska's site are considered reliable and acceptable in support of the pending application.

2. **Dragana Obradovic, M.D.**
Belgrade, Serbia 11000

a. What Was Inspected: This inspection was performed as a data audit for Protocol 109-MS-301: At this site, a total of 28 were screened, and four subjects were reported as screen failures. Twenty four (24) subjects were randomized into the study, and 18 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for 11 subjects were reviewed including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents for 11 subjects were compared to data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site. There were no known limitations to the inspection.

b. General Observations/Commentary: At the conclusion of the inspection, a 3 item Form FDA 483 was issued to Dr. Obradovic. Our investigation found minor protocol deviations and a discrepancy in the actual count of returned capsules for only one subject. The source documents regarding the Independent Neurology Evaluation Committee (INEC) confirmations of relapses were missing/misfiled for Subjects 413-302 and 413-306. Therefore, we cannot confirm the relapses for these subjects based on our inspectional findings. The clinical investigator was able to locate the confirmations of relapse for the following subjects 413-307, 413-309, 413-318, and 413-323. For Subjects 413-313 and 413-324, there were discrepancies between the visit dates listed in the Subject Enrollment Log when compared to the actual dates that subjects were seen for study at certain visits. The clinical investigator agreed with the inspectional findings in a letter dated October 2, 2012, in which he promised to take appropriate steps to remedy the situation. OSI finds his response adequate and acceptable.

The medical records reviewed were verifiable based on the information available at the site. With the exceptions of the INEC confirmation of relapses noted above, the records reviewed were found to be organized and the data verifiable. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events. The study appears to have been conducted adequately, and the data generated by this site may be used to support the pending application.

c. Assessment of Data Integrity: Although regulatory deviations were noted, the findings are unlikely to affect integrity of the data because the violations appear to be isolated and not systemic in nature. However, it should be noted that OSI cannot confirm relapses for Subjects 413-302 and 413-306 based on our inspectional findings. The data from Dr. Obradovic's site are considered reliable and appear acceptable in support of the pending application.

3. **Tomasz Zielinski, M.D.**
40-414 Katowice, Poland

a. What Was Inspected: This inspection was performed as a data audit for Protocol 109-MS-302. At this site, a total 53 subjects were screened, and eight subjects were reported as screen failures. Forty-five subjects were randomized into the study, and 39 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 26 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events

b. General Observations/Commentary: At the conclusion of the inspection, a 1 item Form FDA 483 was issued to Dr. Zielinski. Our investigation noted failure to adhere to the protocol investigational plan. The deviations included but were not limited to the following:

- Failure to re-consent two subjects when relapse or progression occurred during the study with a specific informed consent written for relapse and progression cases or a confirmed INEC relapse during the subsequent visits. Note that all subjects were initially consented with the study approved Informed consent.
- Protocol required assessments for primary efficacy endpoints (EDDS, MSFS, Visual Function Test, ECGs and MRI) were conducted outside the recommended visit window in about 32 visits or 7.75 % of the time. For example, Subject 516-414 assessment was out of window 24 days for Visit 12, and Subject 516-435 assessment was out of window 15 days for Visit 15. These two subjects were the farthest out from the required window.

- Additional minor protocol deviations were noted such as failure to retest abnormal laboratory values. For example, Subject 516-418 had a result of urine Beta-2 microglobulin at Visit 6 of 0.61mg/L which is greater than the acceptable range of <0.300mg/L.

The clinical investigator agreed with the inspectional findings in a letter dated August 16, 2012, in which he acknowledged that the audit was a learning experience and promised to take appropriate steps to remedy the situation in regards to protocol adherence and to ensure subjects safety in his future studies. OSI finds his response adequate at this time, and we expect that these actions will be implemented.

The medical records reviewed were found to be in order with the exception of the deviations noted above. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: Although regulatory deviations were noted, the findings are unlikely to affect integrity of the data because the violations appear to be isolated incidences and not systemic in nature. The data from Dr. Zielinski's site are considered reliable and may be used in support of the pending application.

4. **Eva Hardova, M.D.**
128 08 Praha 2, Czech Republic

a. What was Inspected: This inspection was performed as a data audit for NDA 204-063 Study Protocol I09-MS-302: At this site, a total of 27 subjects were screened, and 27 subjects were randomized into the study. Twenty subjects completed the study, and seven subjects withdrew early from the study and the reason(s) were documented. Five subjects withdrew from the study due to side effects (not known at this time, but were reported), one subject decided to get pregnant after Visit 19, and one subject transferred to another site. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents were compared to case report forms and data listings, to include primary efficacy endpoint and adverse events.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Hardova. The FDA investigator discussed with the clinical investigator the missing entries regarding the recordkeeping log for MRI scans. However, documents available at the site confirmed the scans were in fact performed according to the protocol required plan. The clinical investigator stated that she will address the issues with MRI team. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data generated in support of the clinical efficacy and safety at Dr. Hardova's site are considered reliable and appear acceptable in support of the pending application.

5. **Biogen Idec**
   14 Cambridge, MA 02142

a. What was Inspected: This sponsor inspection of Biogen Idec. was issued to review the conduct of the clinical studies performed in support of NDA 204-063 for dimethyl fumarate (BG00012), in accordance with the Sponsor/Monitor/Contract Research Organization Compliance Program. The inspectional assignment requested evaluation of the sponsor's oversight of Protocol 109-MS-301, focused on clinical investigator Hanka Hertmanowska, M.D. (Poland) and of Protocol 109-MS-302, focused on clinical investigator Eva Hardova, M.D. (Czech Republic).

Biogen Idec conducted the studies and submitted data in support of the application NDA 204-063 for the marketing of dimethyl fumarate as a novel treatment for the relapsing forms of multiple sclerosis (MS).

During the inspection the following were reviewed: Company history and officers responsibilities, Sponsor's obligations, monitoring plan, training program, site monitoring, manufacturing/design operation, selection of clinical investigators, quality control and assurance practices, (including identification of systemic errors and issues of significant and /or persistent noncompliance), and evaluation of suspected scientific misconduct on the part of the clinical investigators. In addition, protocol development and site specific documents associated with the clinical investigators noted above were reviewed. The inspection also focused on selected clinical trials activities to determine whether adequate controls such as written procedures and policies, training, monitoring, auditing were in place and whether appropriate activities were properly carried out and in compliance with FDA regulations. The clinical trial activities reviewed included: study monitoring procedures, drug accountability, CRO information, regulatory documents such as 1572's, signed agreements, data review reports, protocol adherence, sponsor adequate oversight of clinical sites, monitoring reports, e-CRFs, transfer of data to the sponsor, methods of data collection and retention, and reporting of adverse events. The investigation found no discrepancies.

b. General Observations/Commentary: At the conclusion of the inspection, no regulatory violations were noted and no Form FDA 483 was issued to Biogen Idec. The FDA investigation found that the sponsor adhered to their SOP's regarding proper monitoring of their clinical investigators. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The sponsor monitoring procedures for the above two sites appear to have been conducted adequately and the data submitted may be used in support of the respective indication. In general, the sponsor appears to have fulfilled their regulatory obligations for the two sites identified above. Therefore, data generated from the two sites in support of the requested indication are considered reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four clinical investigator sites and the sponsor were inspected in support of this application. The inspection of Drs. Hertmanowska, Hardova and the sponsor revealed no regulatory violations, and the pending classification for these inspections is No Action Indicated (NAI). The pending classification for the inspection of Drs. Obradovic and Zielinski is Voluntary Action Indicated (VAI). While regulatory violations were identified during the inspections of Drs. Obradovic and Zielinski, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect of the violations on overall data integrity to be significant. Overall, the data submitted from these four sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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11/09/2012

SUSAN D THOMPSON
11/16/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
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M E M O R A N D U M

Date:	October 31, 2012
From:	Nadia Hejazi, M.D., Medical Officer Pediatric and Maternal Health Staff (PMHS)
Through:	Hari Cheryl Sachs, M.D., Team Leader Lynne Yao, MD, Acting Associate Director Pediatric and Maternal Health Staff Office of New Drugs
NDA:	204063
Sponsor:	Biogen Idec, Inc.
Drug:	Dimethyl fumarate
Approved indications:	None
Proposed indication:	Treatment of relapsing remitting multiple sclerosis (RRMS).
Proposed pediatric indication:	Same
Dosage form:	Capsule
Proposed dosage form and dosing regimen:	120 mg and 240 mg twice daily

Route of administration: Oral

PeRC Date: November 28, 2012

Consult Question: The Division of Neurology has requested PMHS assistance with PeRC review preparation, and for input on the pediatric section of the labeling.

Dimethyl Fumarate is a fumaric acid ester that is being evaluated for the treatment of multiple sclerosis (MS). The exact mechanism of action of dimethyl fumarate in not completely understood, but laboratory studies suggest a mechanism through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, which is the primary cellular defense system for responding to a variety of potentially toxic stimuli through up-regulation of antioxidant response genes. [1& 2]

PMHS worked with DNP in preparing paperwork for the review of the pediatric plan by the Pediatric Review Committee (PeRC) which will take place on November 28, 2012.

The Division plans to waive the required studies under PREA in pediatric patients birth to less than 10 years of age because studies are impossible or highly impractical, and to defer studies in patients 10 years to 17 years of age because the product is ready for approval in adults, and because studies designed to evaluate the product safety profile are still ongoing. Given the potential vulnerability of the pediatric population, PMHS agrees with the deferral in pediatric age group 10 to 17 years of age. A partial waiver less than 10 years of age is based on the epidemiology of MS and is consistent with the PREA requirements outlined in the Sept 2012 approval of Aubagio (teriflunomide).

PMHS has also participated in the initial labeling meetings for dimethyl fumarate and provided comments for the Pediatric Use Section 8.4.

[1] 1.9.2 Request for Deferral of Pediatric Studies
[2] Jiang L et al. Genetic dissection of systemic autoimmune disease in Nrf2-deficient mice. 2004 physiol Genomics 18;261-272

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/s/

NADIA S HEJAZI
10/31/2012

HARI C SACHS
11/05/2012

LYNNE P YAO
11/08/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	October 29, 2012
Reviewer:	Andrew Fine, Pharm.D., Safety Evaluator Division of Pharmacovigilance I
Team Leader:	Cindy Kortepeter, Pharm.D. Division of Pharmacovigilance I
Deputy Division Director:	Min Chen, R.Ph., M.S., Deputy Director Division of Pharmacovigilance I
Product Name:	Dimethyl Fumarate
Subject:	Adverse Events of Misuse and Abuse
NDA Number:	204063
Applicant/Sponsor:	Biogen Idec
OSE RCM #:	2012-2309

TABLE OF CONTENTS

1 INTRODUCTION

This review evaluates adverse event reports related to abuse, misuse, overdose, psychiatric events, suicidal behavior, and deaths associated with dimethyl fumarate. Dimethyl fumarate is not an approved drug in the United States, but it is currently under review by the Division of Neurology Products (DNP) for the treatment of multiple sclerosis. Dimethyl fumarate (Fumaderm) has been approved for the treatment of psoriasis in Germany since 1994. Resultantly, CSS requested DPV to review foreign adverse event databases for misuse and abuse events associated with this NME. This review examines adverse events for dimethyl fumarate from the World Health Organization (WHO) Vigibase Database system and the FDA Adverse Event Reporting System (FAERS). More than 80 countries participate in the WHO program, with the majority of countries from Europe and North America.[1] See Appendix A for more information on the WHO Vigibase Database.

Dimethyl fumarate is a fumaric acid ester (FAE) historically used as a fungicide and desiccant when shipping sofas.[2] The use of FAEs dates back to 1959 for the treatment of psoriasis, while clinical studies in the 1990s demonstrated its clinical efficacy. Dimethyl fumarate has also been shown to have beneficial effects in preclinical models of neuroinflammation, neurodegeneration, and toxic oxidative stress, which may benefit MS patients.[3] Additionally, FAEs may affect immune responses by shifting dendritic-cell differentiation, suppressing proinflammatory-cytokine production, or directly inhibiting proinflammatory pathways.

[1] Lindquist M. Vigibase, the WHO global ICSR database system: basic facts. Drug Info Journal; 42: 409-19.
[2] Ropper AH. The "poison chair" treatment for psoriasis. N Engl J Med; 367: 1149-50.
[3] Gold RF, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med; 367: 1098-1107.

2 METHODS AND MATERIALS

The WHO Vigibase Database and FAERS were searched with the strategies described in Table 1 and Table 2 below.

Table 1. WHO Vigibase Search Strategy*	
Date of search	October 24, 2012
Time period of search	All Dates
Product Terms	Dimethyl fumarate, fumarate disodium, fumaric acid
MedDRA Search Terms	None

* See Appendix A for description of the WHO Vigibase database.

Table 2. FAERS Search Strategy*	
Date of search	October 25, 2012
Time period of search	All Dates
Product Terms	Dimethyl fumarate, fumaric acid
MedDRA Search Terms	None

* See Appendix A for description of the FAERS database.

All reported adverse events from all retrieved cases were organized by System Organ Class (SOC) and preferred term (PT) and reviewed to identify relevant terms indicating abuse or misuse using a list of adverse event terms provided by CSS (see Appendix B).

3 RESULTS

The WHO Vigibase search retrieved 68 reports for dimethyl fumarate and related FAEs. After reviewing the SOC and PT list for all reported adverse events in these 68 cases, depressed mood (n=1) and memory impairment (n=1) matched the adverse events list of abuse and misuse terms provided by CSS. No additional terms identified matched events on the CSS list. Complete case description, including narrative summaries are not available for cases retrieved from the WHO Vigibase. Therefore, it is unknown if these highlighted adverse events were temporally related to dimethyl fumarate, or to another suspect product in the report.

The FAERS query retrieved 2 cases for dimethyl fumarate, and neither case reported events related to misuse and abuse.

4 DISCUSSION

This review evaluated foreign adverse event databases for reports of abuse and misuse associated with dimethyl fumarate. The WHO Vigibase database and FAERS database were queried for all individual case safety reports for dimethyl fumarate and two events of interest (depressed mood and memory impairment) were captured. The inability to access and review the clinical narratives of these cases prevents an accurate assessment of dimethyl fumarate temporal and/or causal relationship. Additionally, underlying limitations in these spontaneously reported adverse events, which include missing data, underreporting, and possible duplicate cases make an assessment of dimethyl fumarate's abuse potential from this data source challenging. Notwithstanding these limitations, a large or disproportionate number of terms suggestive of abuse was not seen in Vigibase. Finally, based on dimethyl fumarate's pharmacologic effect on the immune system and possible anti-oxidant effect, abuse and misuse of this drug appears unlikely.

5 CONCLUSION/RECOMMENDATION

Based on adverse event data from the WHO Vigibase Database, dimethyl fumarate does not appear to have abuse or misuse potential.

6 APPENDICES

APPEARS THIS WAY ON ORIGINAL

6.1 APPENDIX A. DATABASE DESCRIPTION

WHO Vigibase Database

The WHO global individual case safety report (ICSR) database system, VigiBase, contains more than 3,800,000 spontaneously reported Individual Case Safety Reports (ICSRs) contributed by the national centers (as of March 2007). VigiBase is used directly by the national centers and is accessed indirectly by other regulatory bodies, the pharmaceutical industry, and academia through data requests to the UMC. The top 15 contributors to Vigibase (2000-2005) are: United States, United Kingdom, Canada, Germany, Australia, Thailand, Netherlands, Spain, France, New Zealand, Sweden, Italy, Switzerland, Ireland, and Cuba.

Vigibase is a relational database management system (RDMS) that uses the WHO Drug Dictionary (WHO-DD) and the Medical Dictionary for Regulatory Affairs (MedDRA). Like other passive surveillance systems, Vigibase is subject to underreporting and missing data. Also Vigibase is dependent on the contributing centers for timeliness, completeness, and quality of the adverse event reports.

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.2 APPENDIX B. ADVERSE EVENT TERMS SUGGESTIVE OF ABUSE POTENTIAL

The following list of terms provides a general guide of terms suggestive of abuse potential. This list has been compiled based on our experience to date and is not intended to be inclusive of all possible abuse related MedDRA terms.

Terms suggestive of abuse potential:

- *EUPHORIA-RELATED TERMS:*

Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high*, high* feeling, laughter. (* Exclude terms that clearly are not related or relevant such as "high blood pressure," etc.)

Elevated mood: mood elevate, elation.

Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.

Feeling of relaxation: Feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

Dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts.

Hallucination (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

Inappropriate affect: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laugher, inappropriate mood elevation.

- *SUBJECTIVE RESPONSE TERMS INDICATIVE OF IMPAIRED ATTENTION, COGNITION, MOOD, AND PSYCHOMOTOR EVENTS WHICH ARE OFTEN ASSOCIATED WITH DRUGS OF ABUSE):*

Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor.

Mood disorders and disturbances (mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

- *DISSOCIATIVE/PSYCHOTIC* (TERMS OFTEN ASSOCIATED PCP, AND KETAMINE):
Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia

Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity.

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/s/

ANDREW FINE
10/29/2012

CINDY M KORTEPETER
10/29/2012

MIN CHU CHEN
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Pediatric and Maternal Health Staff Review

Date: October 19, 2012 **Date Consulted:** March 1, 2012

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S Tassinari, PhD, DABT
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne Yao, M.D., Acting OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Neurology Products (DNP)

Drug: TRADENAME (dimethyl fumarate/DMP) capsules/NDA 204063

Subject: Labeling Revisions – Pregnancy, Nursing Mothers

Applicant: Biogen Idec, Inc.

- **Materials Reviewed:** Dimethyl fumarate labeling, submitted February 24, 2012.

Consult Question: "We request your participation in the NDA planning meetings and our review of this original NDA."

INTRODUCTION

On February 24, 2012, Biogen Idec, Inc., submitted a New Drug Application for dimethyl fumarate/DMF (tradename not yet established) NDA 203085 for the treatment of relapsing multiple sclerosis (MS).

The Division of Neurology Products (DNP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the pregnancy and nursing mothers information in the dimethyl fumarate labeling.

This review provides suggested revisions and re-ordering of existing information related to pregnancy and nursing mothers dimethyl fumarate labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Dimethyl fumarate is a fumarate ester drug product formulation containing the active ingredient dimethyl fumarate (DMF). The proposed indication of dimethyl fumarate is for the treatment of patients with relapsing multiple sclerosis. The mechanism by which dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood. It is believed that dimethyl fumarate reduces inflammatory responses in both peripheral and central cells which may promote cytoprotection of central nervous system.

DISCUSSION AND CONCLUSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy and lactation. A further goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective tool for communication to clinicians.

The PMHS-MHT discussed labeling recommendations with the review team during a labeling meeting on October 10, 2012. The following PMHS- MHT recommendations reflect the discussions with the Division at that meeting.

The applicant has also proposed to establish a pregnancy registry as part of their post-marketing safety surveillance plan to further evaluate the safety profile of the drug product. The PMHS-MHT recommends the Division accept this proposal. Additionally, PMHS recommends that the protocol be submitted for Agency review prior to initiation of the registry. The PMHS-MHT would be happy to review the protocol and provide comment. PMHS-MHT also recommends the Division ask the applicant to include a plan for regular submission of the data collected by the pregnancy registry for Agency review.

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling recommendations (label excerpts) appear below. The animal data section below in 8.1 may receive further edits from nonclinical. **Appendix A** of this review provides a tracked-changes version of labeling that highlights the recommended PMHS-MHT revisions.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

(b) (4)

Reviewer comments: As noted in the Label Review Tool from SEALD, information about the pregnancy registry should not be in the highlights of prescribing information section.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with dimethyl fumarate in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 6 and 7 times the recommended human dose (RHD) and have revealed no evidence of impaired fertility or teratogenicity due to dimethyl fumarate. Dimethyl fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to TRADENAME during pregnancy. Encourage patients to enroll by calling 1-800-456-2255.

Reviewer comment: The second sentence in the Risk Summary will be revised as needed by the Division pharm/tox reviewer.

Animal Data

No malformations were observed at any dose of dimethyl fumarate in rats or rabbits. Administration of dimethyl fumarate at daily oral doses of 25, 100, and 250 mg/kg/day to pregnant rats during the period of organogenesis resulted in reductions in maternal body weight at 2 times the RHD on a mg/m^2 basis, and reductions in fetal weight and ossification (metatarsals and hindlimb phalanges) at 6 times the RHD on a mg/m^2 basis. The lower fetal weight and ossification findings were considered secondary to maternal toxicity.

Administration of dimethyl fumarate at daily oral doses of 25, 75, and 150 mg/kg/day to pregnant rabbits during organogenesis had no effect on embryo-fetal development and resulted in reductions in maternal body weight at doses 4 times the RHD and increased abortion at 7 times the RHD on a mg/m^2 basis.

Administration of dimethyl fumarate at daily oral doses of 25, 100, and 250 mg/kg/day to rats during pregnancy and lactation resulted in lower body weights in the F1 offspring, and delays in sexual maturation in F1 males at 6 times the RHD on a mg/m^2 basis. There were no effects on fertility in the F1 offspring. The lower offspring body weight was considered secondary to maternal toxicity.

Reviewer comment: The Animal Data section is under review by the Division pharm/tox reviewer and PMHS-MHT has no further comment on this data section.

(b) (4)

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRADENAME is administered to a nursing woman.

Reviewer comment: PMHS-MHT agrees with the applicant's proposed language for section 8.3 and did not make any changes to this section.

17 PATIENT COUNSELING INFORMATION

17.3 Pregnancy and Pregnancy Registry

Instruct patients that if they are pregnant or plan to become pregnant while taking TRADENAME they should inform their physician.

Encourage patients to enroll in the TRADENAME Pregnancy Registry if they become pregnant while taking TRADENAME. Advise patients to call 1-800-456-2255 for more information *[see Use in Specific Populations (8.1)]*.

Reviewer comment: PMHS-MHT agrees with the proposed language in this section that was proposed by the applicant and with the addition of the pregnancy registry paragraph added by SEALD.

APPENDIX A – annotated labeling with PMHS-MHT edits.

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

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/s/

CARRIE M CERESA
10/19/2012

MELISSA S TASSINARI
10/19/2012

LYNNE P YAO
10/22/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 19, 2012

TO: Russell G. Katz, M.D.
Director, Division of Neuropharmacology Products
Office of New Drugs

FROM: Michael F. Skelly, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 204-063, BG00012 (Dimethyl Fumarate) Capsules, Sponsored by Biogen Idec, Inc.

At the request of DNP, the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections for the following bioequivalence study:

Study Number: 109HV107
Study Title: "A Randomized, Two-Period Crossover Study in Healthy Volunteers to Establish the Bioequivalence of BG00012 Given as a Single Capsule and Given as Two Capsules"

The audits included thorough examinations of study records, facilities, and equipment, and interviews and discussions with the firms' management and staff.

Clinical Site: Prism Clinical Research
St. Paul, MN

Clinical portions of the study were audited at Prism Clinical Research in St. Paul, MN by ORA Investigator Sharon L. Matson. Following the inspection (July 30 to August 6, 2012), Form FDA 483 was issued. At the time of this review, OSI has not received the firm's response to the Form FDA 483 observations (Attachment 1). Our evaluation of the Form FDA 483 observations follows:

1. **There are no records to show pharmacokinetic samples were processed and stored according to protocol requirements.**

Methyl hydrogen fumarate (MHF), the putative active metabolite of dimethyl fumarate, is susceptible to hydrolysis or covalent reaction with sulfhydryl moieties. Therefore, proper sample processing and storage are essential to accurate measurement of MHF concentrations. Records at Prism did not confirm proper handling of samples. Although (b) (4) (below) was able to measure concentrations of MHF in post-dosing samples, it is not assured that these are the actual MHF concentrations achieved in the body.

This DBGCLPC reviewer recommends that the OCP reviewer evaluate the impact of the lack of sample handling records on the bioequivalence assessments.

2. **Records covering preparation of pharmacokinetic sample tubes were not complete.**

Prism was instructed to collect blood samples in chilled tubes containing sodium fluoride and heparin. The records of addition of sodium fluoride (an inhibitor of plasma and monocyte esterase, and presumptive preservative for MHF) were not complete. Although (b) (4) (below) was able to measure concentrations of MHF in post-dosing samples, it is not assured that these are the actual MHF concentrations achieved in the body.

This DBGCLPC reviewer recommends that the OCP reviewer evaluate the impact of the lack of sample handling records on the bioequivalence assessments.

3. **Not all records that accompany shipment of pharmacokinetic samples to the analytical lab were checked against source records before shipment as required by the firm's SOPs.**

Prism failed to confirm the records accompanying samples to the bioanalytical lab against original records of sample collection and handling. Although FDA cannot enforce most requirements of local SOPs, the three observations on Form FDA 483 suggest that Prism has been casual in record-keeping and procedural controls. At the close of the inspection, Prism management indicated that corrections would be implemented for future studies.

Analytical Site: [redacted] (b) (4)

Analytical portions of the study were audited at [redacted] (b) (4) [redacted] (b) (4) (conducted [redacted] (b) (4) by ORA Investigator Michael Serrano and OSI Scientist Michael Skelly). Following the inspection [redacted] (b) (4), no objectionable conditions were observed and Form FDA 483 was not issued.

Conclusion:

Following the above inspections, the DBGLPC reviewer recommends that the clinical and bioanalytical portions of study 109HV107 be accepted for agency review, subject to evaluations by the OCP reviewer of MHF stability in plasma samples without detailed records of handling and preservation.

Final Classifications:

VAI: **Prism Research, St. Paul, MN**
FEI 3006318259

NAI: [redacted] (b) (4)

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Dejernett/Skelly/CF
DNP/Katz/Bradley
OCP/DCPI/Parepally
MIN-DO/HFR-CE850/Matson
[redacted] (b) (4)/HFR-CE350/Serrano
Draft: MFS 9/18/12
Edit: XC 9/18/12
DSI: 6331; O:\BE\EIRCOVER\204063.bio.dmf.doc
FACTS: 1405280

ATTACHMENT 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

(b) (4)

[redacted]

FORM FDA 483 (9/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS Page 1 of 1

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/s/

MICHAEL F SKELLY
09/21/2012

SAM H HAIDAR
09/21/2012

WILLIAM H TAYLOR
09/21/2012

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

Label, Labeling and Packaging Review

Date:	September 17, 2012
Reviewer:	Julie Neshiewat, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Dimethyl Fumarate Delayed-release Capsules 120 mg, 240 mg
Application Type/Number:	NDA 204063
Applicant/Sponsor:	Biogen Idec
OSE RCM #:	2012-542

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

Contents

1 INTRODUCTION

This review evaluates the proposed container labels, carton labeling, and insert labeling for Dimethyl Fumarate, NDA 204063, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Dimethyl fumarate is a New Molecular Entity (NME).

An Information Request (IR) was sent to the Applicant on March 20, 2012 regarding their rationale for marketing specific packaging configurations. The Applicant stated that (b) (4) bottle (b) (4) pack configurations are being proposed so that physicians and patients have the option to choose the configuration which best suits their needs given the varying dexterity level in Multiple Sclerosis (MS) patients. The Applicant also stated that the 240 mg (b) (4) configurations will be distributed to patients in instances of replacing lost or damaged product.

On July 31, 2012, the Applicant proposed an additional packaging configuration of 14-day sample pack as a professional sample (b) (4) (b) (4)

An IR was sent to the Applicant on August 13, 2012 to clarify which packaging configurations they are seeking for approval, to clarify which packaging configurations they plan to market at product launch, to provide a rationale for proposing a 14-day sample pack, and to provide a rationale for removing any packaging configuration that was originally submitted for approval. The Applicant responded that they are seeking approval for the 14-day sample kit (professional sample), 30-day starter kit (retail), 30-day sample kit (professional sample), 120 mg 14-count bottle (retail), and 240 mg 60-count bottle (retail). The Applicant clarified that they expect to move toward using the 14-day sample pack vs. the 30-day sample pack once insurance coverage is more normalized. (b) (4) (b) (4)

An IR was sent to the Applicant on August 27, 2012 to clarify discrepancies between the packaging configurations they are seeking for approval and the packaging configurations they intend to remove. The Applicant clarified that they are still seeking approval for the 120 mg 14-count bottle (retail), 240 mg 14-count bottle (professional sample), 240 14-count bottle (retail) in addition to the packaging configurations stated in the previous IR. The Applicant also stated that these packaging configurations will only be dispensed pursuant to a physician's prescription.

The proposed proprietary name, (b) (4), was reviewed under separate cover in OSE Review # 2012-542 and was found unacceptable. The proposed proprietary name, (b) (4), was reviewed under separate cover in OSE Review # 2012-1263 and was found unacceptable. The proposed proprietary name, (b) (4) is being reviewed under separate cover in Ose Review # 2012-2025.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 15, 2012 insert labeling submission.

- Active Ingredient: Dimethyl Fumarate

- Indication of Use: Treatment of patients with relapsing Multiple Sclerosis (MS) (b) (4)
- Route of Administration: Oral
- Dosage Form: Delayed-release Capsules
- Strength: 120 mg, 240 mg
- Dose and Frequency: 120 mg by mouth twice daily for 7 days, then 240 mg by mouth twice daily; temporary dose reduction to 120 mg twice daily may reduce occurrence of flushing and gastrointestinal (GI) side effects – within 1 month, the recommended dose of 240 mg twice daily should be resumed
- How Supplied:
  - 14-day sample pack (14-count bottle of 120 mg capsules and 14-count bottle of 240 mg capsules, packaged in the same carton): professional sample
  - 30-day starter pack (14-count bottle of 120 mg capsules and 46-count bottle of 240 mg capsules, packaged in the same carton): retail
  - 30-day sample pack (14-count bottle of 120 mg capsules and 46-count bottle of 240 mg capsules, packaged in the same carton): professional sample
  - 120 mg capsules
    - 14-count bottle: retail and professional sample
  - 240 mg capsules
    - 14-count bottle: retail and professional sample
    - 60-count bottle: retail
- Storage: Store at 15°C to 30°C (59°F to 86 °F). Protect capsules from light; Once opened, discard bottles after 90 days
- Container and Closure Systems: HDPE bottles sealed with an aluminum foil induction seal and white polypropylene (b) (4) (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Professional sample 14-day Sample Pack Labels and Labeling submitted July 31, 2012 (Appendix B)
- Retail 30-day Starter Pack Labels and Labeling submitted February 27, 2012 (Appendix C)
- Professional sample 30-day Sample Pack Labels and Labeling submitted February 27, 2012 (Appendix D)

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

- Bottle Container Labels submitted February 27, 2012 (Appendix E)
- Bottle Carton Labeling submitted February 27, 2012 (Appendix F)
- Insert Labeling submitted May 15, 2012 (No image)

The Division of Professional Drug Promotion (DPDP) was consulted on June 1, 2012 to determine if the following claims found on the carton labeling are considered promotional: [redacted] (b) (4)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

A. Container Labels and Carton Labeling

1. The colors [redacted] (b) (4) 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.
2. The CMC reviewer indicated that this delayed-release capsule should not be opened and sprinkled on food [redacted] (b) (4). The container labels and carton labeling need a statement instructing patients to swallow the capsule whole.
3. The insert labeling states that the bottle configurations should be discarded within 90 days of opening. This information is important and should appear on the bottle container label and bottle carton labeling.
4. DPDP determined that the claims "[redacted] (b) (4) [redacted]" are considered promotional and require fair balance presentation.

B. Capsules

Section 16 of the Full Prescribing Information states that the 120 mg capsules will be green and white and the 240 mg capsules will be green. Having similar colored capsules for different strengths may cause confusion. This information was discussed with the CMC reviewer, who indicated that additional stability studies, and possibly compatibility and photo stability studies would be needed to change the color of the capsules. Based on this information, DMEPA will monitor for post marketing errors that could be caused by the similar appearance of the two capsule strengths.

C. Insert Labeling

The insert labeling states [redacted] (b) (4) [redacted] (b) (4) [redacted] We discussed this information with the Medical Officer who verified that the 120 mg twice a day dose was not studied in terms of efficacy and that phase 2 trials of a 120 mg three times a day dose failed to support efficacy. This information will need to be appropriately addressed in the labeling.

4 CONCLUSIONS

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

5 RECOMMENDATIONS

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

5.1 RECOMMENDATIONS TO THE DIVISION

Insert Labeling

A. We recommend adding a statement similar to '**Swallow capsule whole and intact.** Do not crush, chew, or sprinkle capsule contents on food' to Section 2 Dosage and Administration and Section 17 Patient Counseling to help prevent wrong technique errors.

B. Any packaging configurations that the Applicant intends to market commercially should appear in Section 16 How Supplied.

C. The terms [redacted] (b) (4) are utilized in the Patient Information section. It would be misleading to associate 120 mg as [redacted] (b) (4) dose and 240 mg as the [redacted] (b) (4) since a patient may need to titrate down from 240 mg to 120 mg to reduce flushing and GI side effects. We recommend these terms be removed throughout the labeling.

D. Section 2 Dosage and Administration states tha [redacted] (b) (4) The Medical Officer verified that the 120 mg twice a day dose was not studied in terms of efficacy and that phase 2 trials of a 120 mg three times a day dose failed to support efficacy. We recommend that information stating that the lower dose of 120 mg is not efficacious should be conveyed to ensure that patients are not maintained on the lower dose for longer than one month.

5.2 RECOMMENDATIONS TO THE APPLICANT

A. General Comments for All Labels and Labeling

1. Remove the [redacted] (b) (4) graphic that appears next to 'Tradename' since it is distracting, may be misinterpreted [redacted] (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 Starter Pack, revise the statement '30-DAY STARTER PACK' from all upper case letters to title case '30-Day Starter Pack.'

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) (b) (4) background. Revise the font color of the strength or revise the 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) and (b) (4) on Panel B of the 30-day starter pack carton labeling, Panel C of the bottle carton labeling, (b) (4) are promotional and, 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 Starter Pack

1. General Comments: The terms (b) (4) are utilized on the labels and labeling. It would be misleading to associate 120 mg as (b) (4) dose and 240 mg as (b) (4) dose (b) (4) 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 (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 23-day supply.

   c. On the 120 mg side panel, revise the statement (b) (4) 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 (b) (4) coloring on both the 120 mg and 240 mg strengths in the background color scheme contributes to similarity between the two labels.

Remove the (b) (4) background color. The (b) (4) 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 (b) (4) 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 (b) (4) 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 'Sample – Not for Sale' 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] (b) (4) 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 [redacted] (b) (4)
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] (b) (4) 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] (b) (4) 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] (b) (4) is used only for the 120 mg strength and [redacted] (b) (4) is used only for the 240 mg strength.
3. Debold the net quantity statements.
4. Remove [redacted] (b) (4) 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.’

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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

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/s/

JULIE V NESHIEWAT
09/17/2012

IRENE Z CHAN
09/17/2012

KELLIE A TAYLOR
09/18/2012

CAROL A HOLQUIST
09/18/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 6, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Nicole Bradley, DNP

Subject: QT-IRT Consult to NDA204063

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated June 6, 2012 regarding sponsor's respond to FDA request on NDA 204063. The QT-IRT received and reviewed the following materials:

- Your consult
- Sponsor's Response

QT-IRT Comments for DNP

We have reviewed the responses to our comments and have determined that the Sponsor has adequately addressed QT-IRT's previous concerns.

BACKGROUND

The study report for TQT Study 109HV101 was reviewed by the QT-IRT on August 29, 2007. NDA 204063 is currently under review for the treatment of Multiple Sclerosis. On May 11, 2012 an information request was sent to the Sponsor regarding 24-hour ECG data for Study 109HV101. The Sponsors submitted their response on June 1, 2012:

- As requested, data from the paper ECG tracings taken at the 24-hour time point in Study 109HV101 were analyzed. The mean change from baseline (analysis of central tendency) and outlier analyses were performed for this time point. These analyses were similar to those performed on the digital Holter ECG data from the other time points.

- The adjusted mean (95% CI) for the BG00012 240 mg and 360 mg are -0.82 (2.86), and -1.07 (2.61) msec respectively. Both groups showed a mean change of less than 5 msec, and the upper limits of both one-sided 95% CIs were less than 10 msec. Moxifloxacin showed a mean of 5.68 msec and upper limit of the one-sided 95% CI of 9.36 msec.

- No subjects in any group had a post-dose QTc value exceeding 450 msec or above that was not present at baseline (Table 4). No subjects in either BG00012 group, and 1 subject each in the placebo and Moxifloxacin groups had a change from baseline QTc between 30-60 msec (Table 5). No subject in any group had a change from baseline QTc > 60 msec. Corresponding results based on uncorrected QT intervals are shown in Table 6 and Table 7.

Thank you for requesting our input into the development of this product under NDA204063. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

QIANYU DANG
09/06/2012

KEVIN M KRUDYS
09/06/2012

NORMAN L STOCKBRIDGE
09/06/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 17, 2012

TO: Director, Investigations Branch
Minneapolis District Office (MIN-DO)
250 Marquette Avenue, Suite 600
Minneapolis, MN 55401

Director, Investigations Branch
(b) (4)

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority User Fee NDA, Pre-Approval Data Validation Inspection** Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 204-063
DRUG: Dimethyl fumarate (BG00012) Capsules
SPONSOR: Biogen Idec Inc.

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. **A DBGC, OSI scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspections.** The **inspections should be completed before August 20, 2012.**

Study Number: 109HV107
Study Title: A Randomized, Two-Period Crossover Study in Healthy Volunteers to Establish the Bioequivalence of BG00012 Given as a Single Capsule and Given as Two Capsules

Clinical Site: Prism Clinical Research
1000 Westgate Drive, Suite 149
St. Paul, MN 55114
(FEI not found)

Clinical Investigator: Mark A. Matson, M.D.
TEL: 651-641-2900
FAX: 651-641-2901

Please have the records of all study subjects audited. The subject records in the ANDA submission should be compared to the original documents at the sites. **The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined.** The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings.

Please check the batch numbers of the test and reference products used in these studies with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63[1]. The site conducting the above study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please refer to CDER's guidance document "Handling & Retention of BA and BE Testing Samples" that clarifies the requirements for reserve samples.

---

[1] Please see the Final Rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) (http://www fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265 htm) and CDER's guidance document "Handling and Retention of BA and BE Testing Samples" (http://www fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf) for more details.

Collect enough of the original containers of reserve samples of the test and reference products used in the study, to meet the "5x quantity" specified in 21 CFR 320.38(c). Mail the collected reserve samples to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Custom house Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101

Also, obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letter head, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected and ship them to DPA under current program directives. Please see the IOM and/or contact your district for assistance with the Sample Collection Report.

Analytical Site: (b) (4)

Methodology: LC/MS-MS

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. **The SOP(s) for repeat assays and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content. **Please verify and confirm the**

security of electronic records generated for the study at (b) (4)**.**

Following the identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: Arindam Dasgupta, Ph.D.
(301) 796-3326

CC:
CDER OSI PM TRACK
OSI/DBGC/Taylor/Haidar/Skelly/Dasgupta/Dejernett/CF
(b) (4)
MIN-DO/HFR-CE850/Bigham/Matson
MIN-DO/MIB/MIL-WI/Richard-Math
OND/ODEI/DNP/Bradley/Katz
CDER/OCP/DCPI/Parepally
Draft: AD 07/17/2012
Edit:
OSI: BE6331; O:\BE\assigns\bio204063add.doc
FACTS: 1405280

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/s/

ARINDAM DASGUPTA
07/17/2012

SAM H HAIDAR
07/18/2012

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

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

Memorandum

Date: June 14, 2012

To: Julie Villanueva Neshiewat, PharmD
Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

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

Sharon Watson, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Meeta Patel, PharmD
Regulatory Review Officer
DCDP

Mathilda Fienkeng, PharmD
Team Leader, Acting
DPDP

Subject: DPDP's comment for NDA 204063
BG00012 (Dimethyl Fumarate) delayed release capsules

Background

This consult is in response to DMEPA's June 1, 2012, request for DPDP's review on carton and container labeling for BG00012 (Dimethyl Fumarate) delayed release capsules. This consult provides comments on the following carton container labeling for the 30-day starter pack carton.

(b) (4)

Consult Response:

DPDP has reviewed the proposed carton container labeling for the 30-day starter pack carton and offers the following comments.

The 30-day starter pack carton has the following claims (bolded emphasis original; italicized emphasis added):

(b) (4)

These claims are considered promotional and require fair balance presentation. We recommend deleting them on the proposed carton container labeling or presenting adequate risk information in conjunction with these claims.

Thank you for the opportunity to comment on the proposed carton container labeling for the 30-day starter pack carton. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185 or Quynh-Van.Tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
06/14/2012

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

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

Application: NDA 204063

Application Type: New NDA

Name of Drug: dimethyl fumarate delayed release capsule

Applicant: Biogen Idec.

Submission Date: February 24, 2012

Receipt Date: February 27, 2012

1.0 Regulatory History and Applicant's Main Proposals

- This new drug application provides for the use of dimethyl fumarate for the treatment of patients with relapsing multiple sclerosis (b) (4)
- Dimethyl fumarate is classified as a new molecular entity

2.0 Review of the Prescribing Information (PI)

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

3.0 Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 25, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

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

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

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

Comment:

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

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

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

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

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

Comment:

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title

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

Comment:

Initial U.S. Approval

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

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

    Comment:

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

    Comment:

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

    Comment:

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

    Comment:

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

    Comment:

Recent Major Changes (RMC)

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

    Comment:

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

    Comment:

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

    Comment:

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

    Comment:

Indications and Usage

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

    Comment:

Dosage Forms and Strengths

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

Comment:

Contraindications

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

Comment:

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

Comment:

Adverse Reactions

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

Comment: *Statement not bolded*

Patient Counseling Information Statement

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

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

- **"See 17 for PATIENT COUNSELING INFORMATION"**

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

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

Comment:

Revision Date

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

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

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

Comment:

NO

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

    Comment: *Section 8.6 and 8.7 heading/subheadings in the TOC do not match the headings/subheadings in the FPI*

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

    Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

    Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

    Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

    Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

    Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **"FULL PRESCRIBING INFORMATION".**

    Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

    Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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

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

Comment:

NO 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Currently, the Sponsor includes Patient Labeling in Section 17. Will request Sponsor to remove Section 17.5 and append to FPI*

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *Entire cross-reference statement is not in italics (only the headings are in italics)*

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

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

Comment:

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

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

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

Comment:

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

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

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Includes patient labeling in Section 17. Will request sponsor to remove Section 17.5 and append to FPI*

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/s/

NICOLE L BRADLEY
05/07/2012

ROBBIN M NIGHSWANDER
05/11/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 204063 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: dimethyl fumarate Dosage Form: capsule Strengths: 120, 240 mg		
Applicant: Biogen Idec Inc. Agent for Applicant (if applicable):		
Date of Application: February 24, 2012 Date of Receipt: February 27, 2012 Date clock started after UN:		
PDUFA Goal Date: December 27, 2012	Action Goal Date (if different): December 27, 2012	
Filing Date: April 27, 2012	Date of Filing Meeting: April 11, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of patients with relapsing multiple sclerosi (b) (4) [redacted]		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 73061, (b) (4)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			Standard Review
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

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

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

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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

Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* 03/01/12 For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	**X**			

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)?	X			

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Date(s): Meeting Date: August 30, 2006 **Meeting minutes sent: September 26, 2006** ***If yes, distribute minutes before filing meeting***				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Meeting Date: January 25, 2012 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** Clinical (MS301, 302) submitted on 10/27/2006. FDA response: 12/11/2006 Carcinogenicity SPA submitted on August 20, 2004 (IND (b) (4) FDA response: October 6, 2004 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 11, 2012

BLA/NDA/Supp #: NDA 204063

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: dimethyl fumarate

DOSAGE FORM/STRENGTH: Capsule / 120, 240 mg

APPLICANT: Biogen Idec Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Multiple Sclerosis

BACKGROUND:

- This new drug application provides for the use of dimethyl fumarate for the treatment of patients with relapsing multiple sclerosis (b) (4)
- Dimethyl fumarate is classified as a new molecular entity

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nicole Bradley	Y
	CPMS/TL:	Robbin Nighswander	N
Cross-Discipline Team Leader (CDTL)	Billy Dunn		Y
Clinical	Reviewer:	Heather Fitter	Y
	TL:	Billy Dunn	Y

Clinical Pharmacology	Reviewer:	Jagan Parepally	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Xiang Ling	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Melissa Banks-Muckenfuss	Y
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:	Atiar Rahman	N
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	David Claffey	Y
	TL:	Martha Heimann	Y
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Jenny Qin	Y
	TL:	Lori Gorski	
OSE/DMEPA (proprietary name)	Reviewer:	Julie Neshiewat	Y
	TL:	Irene Chan	
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Antoine El Hage	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer: PM:	Alicja Lerner Sandy Saltz, Corinne Moody	Y
	TL:	Michael Klein	N
Other reviewers	Sharon Watson (OPDP) Nadia Hejazi (Peds) Shawna Hutchins (patient labeling) Joo-Yeon Lee (Pharmacometrics)		Y Y Y Y
Other attendees	Robert Temple (Signatory Authority) Eric Bastings, Deputy Director, DNP Russell G. Katz, Director, DNP Courtney Suggs (Peds)		Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: o Statistics: define.PDF hyperlinking not working o Safety: Several files in ISS not opening	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO ☐ To be determined Reason: ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues***
• Abuse Liability/Potential **Comments**: No pre-clinical or clinical data for CNS submitted in NDA. The status of CNS studies will be requested in 74 day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed? BE study site	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: Submitted by ONDQA on March 8, 2012	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Dr. Robert Temple

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

Stamp Date: February 27, 2012
RTF/Filing Date (day 60): April 27, 2012
74 Day letter goal date: May 11, 2012

Review completion goal date according to GRMP:
Primary reviews: November 1, 2012
Secondary reviews: November 8, 2012
Complete CDTL: November 15, 2012
Division Director Review: December 6, 2012
OD Review: December 26, 2012

PDUFA Action Goal Date (10 month): December 27, 2012

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).

☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Regulatory Project Manager Date

Chief, Project Management Staff Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(3) 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) 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, and.

(3) 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) 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, or

(3) 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 OND ADRA or OND IO.

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

/s/

NICOLE L BRADLEY
05/07/2012

ROBBIN M NIGHSWANDER
05/11/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 30, 2012

TO: Director, Investigations Branch
Minneapolis District Office (MIN-DO)
250 Marquette Avenue, Suite 600
Minneapolis, MN 55401

Director, Investigations Branch
(b) (4)

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority User Fee NDA, Pre-Approval Data Validation Inspection** Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 204-063
DRUG: Dimethyl fumarate (BG00012) Capsules
SPONSOR: Biogen Idec Inc.

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. **A DBGC, OSI scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspections. The inspections should be completed before August 20, 2012.**

Study Number: 109HV107
Study Title: A Randomized, Two-Period Crossover Study in Healthy Volunteers to Establish the Bioequivalence of BG00012 Given as a Single Capsule and Given as Two Capsules

Clinical Site: Prism Clinical Research
1000 Westgate Drive, Suite 149
St. Paul, MN 55114
(FEI not found)

Clinical Investigator: Mark A. Matson, M.D.
TEL: 651-641-2900
FAX: 651-641-2901

Please have the records of all study subjects audited. The subject records in the ANDA submission should be compared to the original documents at the sites. **The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined.** The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings.

Please check the batch numbers of the test and reference products used in these studies with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63[1]. The site conducting the above study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please refer to CDER's guidance document "Handling & Retention of BA and BE Testing Samples" that clarifies the requirements for reserve samples.

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[1] Please see the Final Rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) (http://www fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265 htm) and CDER's guidance document "Handling and Retention of BA and BE Testing Samples" (http://www fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf) for more details.

Collect enough of the original containers of reserve samples of the test and reference products used in the study, to meet the "5x quantity" specified in 21 CFR 320.38(c). Mail the collected reserve samples to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Custom house Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101

Also, obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letter head, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected and ship them to DPA under current program directives. Please see the IOM and/or contact your district for assistance with the Sample Collection Report.

Analytical Site: (b) (4)

Methodology: LC/MS-MS

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. **The SOP(s) for repeat assays and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should

be examined for their content. **Please verify and confirm the security of electronic records generated for the study at** [redacted] (b) (4)

Following the identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: Arindam Dasgupta, Ph.D.
(301) 796-3326

CC:
CDER OSI PM TRACK
OSI/DBGC/ Taylor/Haidar/Skelly/Dasgupta/Dejernett/CF
[redacted] (b) (4)
MIN-DO/HFR-CE850/Bigham/Matson
MIN-DO/MIB/MIL-WI/Richard-Math
OND/ODEI/DNP/Bradley/Katz
CDER/OCP/DCPI/Parepally
Draft: AD 04/30/2012
Edit: MFS 4/30/2012
OSI: BE6331; O:\BE\assigns\bio204063.doc
FACTS: 1405280

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/s/

ARINDAM DASGUPTA
05/02/2012

SAM H HAIDAR
05/03/2012

DSI CONSULT: Request for Clinical Inspections

Date: April 19, 2012

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Antoine El Hage, PhD, Clinical Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Heather Fitter, MD, Clinical Reviewer, DNP
Billy Dunn, MD, Team Leader, DNP
Eric Bastings, MD, Deputy Director, DNP
Russell Katz, MD, Director, DNP

From: Nicole Bradley, PharmD, Regulatory Project Manager, DNP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 204063
Applicant/ Applicant contact information (to include phone/email):

Nadine D. Cohen, PhD
Senior Vice President, Regulatory Affairs
Biogen Idec
14 Cambridge Center
Cambridge, MA 02142
Tel: 617-679-3783
Fax: 617-679-4459
E-mail: Nadine.cohen@biogenidec.com

Drug Proprietary Name: dimethyl fumarate
NME or Original BLA (Yes/No): NME
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication: For the treatment of patients with relapsing multiple sclerosis (b) (4)

PDUFA: December 27, 2012
Action Goal Date: December 20, 2012
Inspection Summary Goal Date: TBD

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site: 514 **Name:** Hanka Hertmanowska **Address:** Specjalistyczny Gabinet Neurologiczny Osrodek Badan Klinicznych Os.Pogodne 22 62-064 Plewiska k/Poznania Poland **Phone:** +48616101710 **Fax:** +48618675576 **Email:** hertmanowska@wp.pl	109-MS-301	26	Multiple Sclerosis
Site: 413 **Name:** Dragana Obradovic **Address:** Military Medical Academy Neurology Department Crnotravska 17 Belgrade 11000 Serbia **Phone:** +381638008083 **Fax:** +381113670785 **Email:** sobradovic@ikomline.net	109-MS-301	24	Multiple Sclerosis

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site: 516 **Name:** Tomasz Zielinski **Address:** Diagnomed-Clinical Research Sp. zo.o. Vice President, Consultant of Neurology Ul. Lesnego Potoku 49 40-414 Katowice Poland **Phone:** +48322557340 **Fax:** +48322564604 **Email:** tzielinski@op.pl	109-MS-302	45	Multiple Sclerosis
Site: 451 **Name:** Eva Hardova **Address:** Centrum pro deyelinizacni onemocneni Assistant Professor, Head of Multiple Sclerosis Center Karlovo namesti 32 Budova A, 4.patro 128 08 Praha 2 Czech Republic **Phone:** +420224966515 **Fax:** +420224917907 **Email:** ehavr@lf1.cuni.cz	109-MS-302	27	Multiple Sclerosis

III. Site Selection/Rationale

Sites were chosen based on:

- Highest enrollers with greatest treatment effect
- 109-MS-302 – 60% of patients were enrolled from region 3 (Eastern Europe)

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

  *See*** at end of consult template for DSI's thoughts on things to consider in your decision making process*

Domestic Inspections: - Not Applicable

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
_X_ Other (specify): New Molecular Entity

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

Should you require any additional information, please contact Nicole Bradley, PharmD, Regulatory Project Manager at *301-796-1930* or Heather Fitter, MD, Medical Reviewer at 301-796-3984.

Concurrence: (as needed)

___Billy Dunn, MD____ Medical Team Leader
__Heather Fitter, MD__ Medical Reviewer
Russell G. Katz, MD__ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

NICOLE L BRADLEY
04/25/2012

RUSSELL G KATZ
05/02/2012