

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204063Orig1s000**

**CHEMISTRY REVIEW(S)**

**MEMORANDUM**

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

**DATE:** 20 MAR 2013  
**FROM:** David J. Claffey, PhD  
**SUBJECT:** Approval recommendation for NDA 204063

On 20 MAR 2013 CDER Office of Compliance issued an overall acceptable recommendation for the manufacturing sites associated with this application. An approval recommendation for this application can now be made from a CMC perspective.

# ATTACHMENT

## OC Recommendation

### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

<b>Application:</b>	NDA 204063/000	<b>Sponsor:</b>	BIOGEN IDEC INC
<b>Org. Code:</b>	120		14 CAMBRIDGE CENTER
<b>Priority:</b>	1		CAMBRIDGE, MA 02142
<b>Stamp Date:</b>	27-FEB-2012	<b>Brand Name:</b>	dimethyl fumarate
<b>PDUFA Date:</b>	27-MAR-2013	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	dimethyl fumarate
<b>District Goal:</b>	26-JAN-2013	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
			001; CAPSULE, DELAYED ACTION; DIMETHYL FUMARATE; 120MG 002; CAPSULE, DELAYED ACTION; DIMETHYL FUMARATE; 240MG
<b>FDA Contacts:</b>	T. BOUIE	Project Manager	3017961649
	D. CLAFFEY	Review Chemist	3017961343
	M. HEIMANN	Team Leader	3017961678

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<b>Overall Recommendation:</b>	ACCEPTABLE	on 20-MAR-2013	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 08-MAR-2012	by EES_PROD		
	PENDING	on 08-MAR-2012	by EES_PROD		

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<b>Establishment:</b>		(b) (4)
<b>DMF No:</b>		<b>AADA:</b>
<b>Responsibilities:</b>		
<b>Profile:</b>		<b>OAI Status:</b> NONE
<b>Last Milestone:</b>	OC RECOMMENDATION	
<b>Milestone Date:</b>	20-MAR-2012	
<b>Decision:</b>	ACCEPTABLE	
<b>Reason:</b>	DISTRICT RECOMMENDATION	

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FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

<b>Establishment:</b>	(b) (4)	
<b>DMF No:</b>		<b>AADA:</b>
<b>Responsibilities:</b>		
<b>Profile:</b>		<b>OAI Status:</b> NONE
<b>Last Milestone:</b>	OC RECOMMENDATION	
<b>Milestone Date:</b>	11-MAR-2012	
<b>Decision:</b>	ACCEPTABLE	
<b>Reason:</b>	BASED ON PROFILE	
<hr/>		
<b>Establishment:</b>	(b) (4)	
<b>DMF No:</b>		
<b>Responsibilities:</b>		
<b>Profile:</b>		NONE
<b>Last Milestone:</b>	OC RECOMMENDATION	
<b>Milestone Date:</b>	11-MAR-2012	
<b>Decision:</b>	ACCEPTABLE	
<b>Reason:</b>	BASED ON PROFILE	
<hr/>		
<b>Establishment:</b>	(b) (4)	
<b>DMF No:</b>		<b>AADA:</b>
<b>Responsibilities:</b>		
<b>Profile:</b>		<b>OAI Status:</b> NONE
<b>Last Milestone:</b>	OC RECOMMENDATION	
<b>Milestone Date:</b>	11-MAR-2012	
<b>Decision:</b>	ACCEPTABLE	
<b>Reason:</b>	BASED ON PROFILE	
<hr/>		

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

Establishment: (b) (4)

DMF No: AADA:

Responsibilities: OAI Status: NONE

Profile:

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAR-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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Establishment: (b) (4)

DMF No: AADA:

Responsibilities: OAI Status: NONE

Profile:

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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Establishment: (b) (4)

DMF No: AADA:

Responsibilities: OAI Status: NONE

Profile:

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/  
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DAVID J CLAFFEY  
03/20/2013

RAMESH K SOOD  
03/21/2013

ONDQA Division Director's Memo

NDA 204-063, (b) (4) (dimethylfumarate delayed release capsules)

120 and 240 mg

Date: 13-FEB-2012

## Introduction

(b) (4) is a delayed-release capsule formulation to be marketed in two strengths – 120 and 240 mg. Both strengths were reviewed for adequacy as part of the current review. All excipients are commonly used in solid oral dosage forms. The two tablet strengths are qualitatively similar with (b) (4) exceptions: the 240 mg strength does not include (b) (4) (as is present in the lower dosage strength), and (b) (4) were used in the respective dosage strengths.

The recommended starting dose of (b) (4) is 120 mg, twice daily and taken for the first seven days, followed by a daily dose of 240 mg, twice daily and thereafter. (b) (4) can be taken with or without food.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation from the Office of Compliance has not yet been issued.

*All CMC review issues have been resolved, and ONDQA recommends approval of this NDA pending the receipt of an overall acceptable recommendation from the Office of Compliance.*

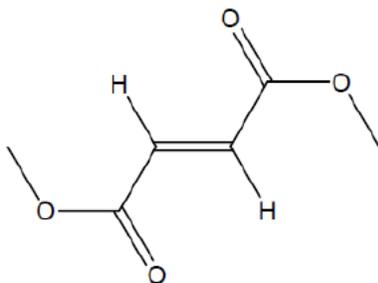
## Administrative

The original submission of this 505(b)(1) NDA was received on 27-FEB-2012 from Biogen Idec, Inc. Six (6) CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (19-NOV-2012, Dr. D. Claffey), Biopharmaceutics Review (19-NOV-2012, Dr. E. Chikhale), and the Biopharmaceutics Review Addendum (12-FEB-2013).

The NDA is supported by thirteen (13) drug master files (DMFs). All DMFs were assessed for adequacy in the chemistry review.

## Drug Substance (dimethyl fumarate)

Chemical Name: Dimethyl (E)-butenedioate



MW = 144.1 g/mol

C<sub>6</sub>H<sub>8</sub>O<sub>4</sub>

Dimethyl fumarate is an achiral trans-butene diester and is a new molecular entity. It has limited aqueous solubility (3-4 mg/ml) but possesses higher solubility in methanol (ca. 30 mg/ml). (b) (4)

Dimethyl fumarate is non-hygroscopic

(b) (4)

Dimethyl fumarate is relatively stable; no extraordinary storage precautions are required. The proposed re-test period (b) (4) when stored in the recommended container closure system under the proposed storage conditions (b) (4) is granted.

## Drug Product (dimethyl fumarate delayed release capsules)

The drug product is supplied in two strengths, 120 mg and 240 mg, in Size-0 hard-gelatin capsules (b) (4). The 120 mg strength has a white body with green (b) (4) printed with "BG-12 120 mg". The 240 mg strength has a green body (b) (4) printed with "BG-12 240 mg". The capsules will be packaged in HDPE bottles. (b) (4)

The drug product formulation was designed to prevent release of the drug substance in the stomach while allowing a rapid release in the intestine. The formulation consists (b) (4) a size-0 hard gelatin capsule. Although both strengths share the same capsule size, they differ quantitatively and in some more minor respects, qualitatively. Additional and specific formulation details can be located in the 19-NOV-2012 Chemistry Review by Dr. D. Claffey.

(b) (4)

The Applicant proposed a (b) (4) expiry for this product when stored in the commercial packaging at ≤30°C. Based on the stability data provided and in accordance with ICH Q1E, the Agency grants an actual expiry of 18 months for the 120 mg strength, and 9 months for the 240 mg strength. Due to the discrepancy between the proposed and granted expiration dating periods,

***I concur with the primary reviewer that appropriate confirmatory language regarding expiration dating is needed in the action letter (see page 7 of the Chemistry Review).***

***I also concur with the Chemistry review team's recommendation of approval pending an overall "Acceptable" recommendation from the Office of Compliance.***

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/s/  
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SARAH P MIKSINSKI  
02/13/2013

Initial Quality Assessment  
Branch I  
Division of New Drug Quality Assessment I

**OND Division:** Division of Neurology Products  
**NDA:** 204-063  
**Applicant:** Biogen Idec Inc.  
**Stamp Date:** 27-Feb-2012  
**PDUFA Date:**  
**Trademark:** (b) (4) is proposed  
**Established Name:** Dimethyl fumarate [USAN 2005]  
**Dosage Form:** Capsule, delayed release  
**Route of Administration:** Oral  
**Indication:** Treatment of relapsing forms of multiple sclerosis  
**CMC Lead:** Martha R. Heimann, Ph.D.

	Yes	No
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

## Summary and Critical Issues:

### *Summary*

Dimethyl fumarate (BG00012) has been developed by Biogen-Idec as a novel treatment for relapsing forms of multiple sclerosis (MS). The pharmacological properties of BG00012 appear to be predominately mediated through activation of the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2 or Nrf2) antioxidant response pathway, which is the primary cellular defense system for responding to a variety of potentially toxic stimuli.

The current NDA provides for a delayed release dimethyl fumarate capsule formulation (b) (4). Two strengths are proposed, 120 mg and 240 mg. The product is intended for use in the treatment of patients with relapsing forms of multiple sclerosis (MS) (b) (4).

The recommended starting dose is 120 mg taken twice daily for seven days, followed by increase to the target dose of 240 mg taken twice daily.

Prior to submission of the NDA the applicant sought Agency feedback during a Type C CMC-only meeting held on 21-Jul-2011. Minutes for the meeting can be found in DARRTS. Additionally, the briefing package for the meeting, submitted on 20-Jun-2011 to IND 73,061, is available in the EDR. Key issues addressed during the meeting are summarized below.

- Based on information provided in the briefing package, the Agency agreed to designation of (b) (4) as the regulatory starting material.
- There is a potential for formation of (b) (4) during manufacture of the drug substance. The applicant proposed not including a test for (b) (4) in the drug product specification based on kinetic modeling and spiking experiments. The Agency initially

recommended that the applicant continue testing (b) (4) in at least the first ten commercial batches before requesting deletion of the test from the specification. During the meeting, however, the Agency agreed that the firm could present the rationale for deleting the specification, and additional supporting data not included in the briefing package, in the NDA filing for review.

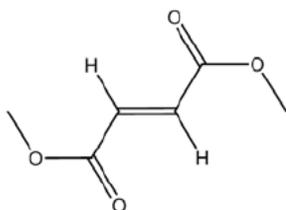
- The applicant proposed that no drug substance or drug product manufacturing process parameters be designated as critical. The firm was advised to submit the development reports that included the rationale why there are no critical process parameters, including parameters that were not studied.
- The applicant requested concurrence with the proposed dissolution method and was advised to submit a full method development report before a decision could be made. It is noted that there were several communications after the meeting but the Agency has not yet concurred with the proposed method.
- The Agency agreed that the proposed characterization testing to qualify the higher strength (240 mg capsule) would be adequate provided the applicant conduct the proposed bioequivalence study. With respect to the proposed stability package for the higher strength, the firm was advised that the expiration dating period assigned would be limited based on the stability data to be provided in the NDA, i.e., 3 months at submission and 6 months update during the review cycle.

### Drug Substance

The active ingredient, dimethyl fumarate [systematic name: (E)-2-butenedioic acid dimethyl ester], is a neutral small molecule with molecular formula  $C_6H_8O_4$  and molecular weight 144.13. The drug substance is slightly soluble in water (2.84 mg/mL) and aqueous buffers. (b) (4)

(b) (4) The applicant indicates that dimethyl fumarate should be classified as BCS Class 1. (b) (4)

(b) (4) The drug substance is not hygroscopic; however, it is reported to be (b) (4)



The bulk drug substance is manufactured (b) (4)

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

(b) (4) All information regarding manufacturing and characterization of the drug substance is provided in the NDA itself; no DMFs are referenced. It is noted that although two separate 3.2.S modules are provided for the two suppliers, the

information provided in both modules is virtually identical. The following differences were noted during the initial assessment.

- Commercial batch scale will [redacted] (b) (4) .  
[Module 3.2.S.2.2]
- [redacted] (b) (4)
- Different control strategies will be used during manufacture at the two sites. [redacted] (b) (4)  
[redacted] (b) (4)
- Although the same analytical procedures are used by both manufacturers; separate methods validation reports for drug substance assay/related substances (HPLC) and residual solvents (GC) are provided. [Modules 3.2.S.4.3 and 3.2.R]
- Batch analysis data provided in Module 3.2.S.4.4 are specific to each manufacturer.

The proposed drug substance specification is given in applicant's **Table 1** [Module 3.2.S.4.1], which is reproduced in the following page.

**Table 1: Release Specification for Drug Substance**

Attribute	Test	Acceptance Criteria
Description <sup>1</sup>	Visual inspection	(b) (4)
Identification:		
Identification A	HPLC	Retention time of the sample peak corresponds to the retention time of the reference standard
Identification B	IR	IR spectrum of the sample corresponds to the IR spectrum of the reference standard
Assay <sup>1</sup>	HPLC	(b) (4)
(b) (4)		

The specification for dimethyl fumarate includes test parameters that are typical for a small molecule. Assay and Related Substances are determined by a (b) (4) HPLC method using an acetonitrile/0.1% aqueous phosphoric acid mobile phase and UV detection at 210 nm. There are two specified impurities, (b) (4). As noted above, the applicant proposes to exclude (b) (4) from the specification. The justification provided is based on the chemistry of the synthesis, kinetic modeling experiments, spiking studies, and batch analyses.

The drug substance primary stability package includes long-term (25°C/60% R. H.) and intermediate data (30°C/65% R. H.) through 60 months and accelerated data (40°C/75% R. H.) through six months for three commercial scale batches manufactured (b) (4). Six months of data are provided for three commercial scale batches manufactured (b) (4); however, for (b) (4) batches only samples stored the intermediate and accelerated conditions were tested. Additional supportive data are also provided. A (b) (4) retest date is proposed.

Drug Product

The proposed dosage form is a delayed release capsule consisting of size 0 hard gelatin capsules (b) (4). Two capsule strengths are proposed. The 120 mg capsules have a white body with green (b) (4); 240 mg capsules have a green body (b) (4). Both strengths will be printed with a product identifier (not specified in the application). The compositions (b) (4) presented in Module 3.2.P.1 are summarized in Table 2 below.

**Table 2: Theoretical Composition of Dimethyl Fumarate (b) (4)**

Component	Ingredient	Function	Amount per capsule (mg)	
			120 mg	240 mg
(b) (4)	Dimethyl fumarate	Active ingredient	120.0	240.0
	Croscarmellose sodium	(b) (4)		
	Microcrystalline cellulose (b) (4)			
	(b) (4)			
	Silicified microcrystalline cellulose (b) (4)			
	Magnesium stearate <sup>1</sup>			
	Talc			
	Colloidal silicon dioxide			
	Subtotal			
	Methacrylic acid copolymer, Type A <sup>2</sup>			
	(b) (4)			
	Methacrylic acid copolymer dispersion (includes Sodium lauryl sulfate, Polysorbate 80) <sup>2</sup>			
	Triethyl citrate			
	(b) (4)			
	Simethicone			
	(b) (4)			
<b>TOTAL</b>				

(b) (4)

(b) (4)

(b) (4)

(b) (4) are proportional. The finished 120 mg capsules contain (b) (4); 240 mg capsules contain (b) (4).

The formulation and manufacturing process development history for Dimethyl Fumarate Capsules are presented as narratives in the Pharmaceutical Development Section; however, limited data are provided. Note that the manufacturing process (b) (4)

(b) (4). It is recommended that the applicant's explanation for the difference, and supporting data, be evaluated carefully.

The applicant does not include detailed information for investigational formulations; however it is noted that the 120 mg capsules used in clinical trials and primary stability batches were blue-white capsules rather than the proposed green-white. Additional information will be requested.

Dimethyl Fumarate Capsules will be manufactured (b) (4)

(b) (4) The manufacturing process development report presents a traditional approach to process development. Limited data are provided to support the selected process parameters and operating ranges.

The proposed specifications for Dimethyl Fumarate Capsules are summarized in **Table 3**. The drug substance process impurities, (b) (4) are both specified as potential degradation products, with higher limits than for the drug substance.

**Table 3: Specifications for Dimethyl Fumarate Capsules**

Attributes	Test	Acceptance Criteria	
		120 mg	240 mg
Description		(b) (4)	
Capsule (b) (4)	Visual Inspection	(b) (4)	
	Visual Inspection	(b) (4)	
	HPLC	Retention time of the sample peak corresponds to the retention time of the reference standard	
	UV	UV spectrum of the sample peak corresponds to the UV spectrum of the reference standard	
	HPLC	(b) (4)	
	HPLC	(b) (4)	
	GC	(b) (4)	
	USP <905>, Ph. Eur. 2.9.40	(b) (4)	
	USP <711>, Ph. Eur. 2.9.3	(b) (4)	
Karl Fischer	(b) (4)		

Analytical procedures are straightforward. Assay, and Content Uniformity are determined using the reverse phase HPLC [C18 column, pH 3.15 phosphate buffer—methanol 50:50 mobile phase and UV-PDA detection at 223 nm]. A related HPLC method using a 60:40 buffer—methanol mobile phase is used for determination of impurities. Dissolution is determined using USP Apparatus 2 at 100 rpm with 0.1 N HCl as the acid stage and pH 6.8 phosphate buffer as the buffer stage. Dissolution is quantitated by HPLC; the conditions are stated to be similar to the Assay conditions. With respect to methods validation, only summary data is provided in Module 3.2.P.5.5; the methods validation reports are provided in Module 3.2.R.

Dimethyl Fumarate Capsules will be packaged in HDPE bottles with aluminum foil induction seal, white polypropylene (b) (4) closure and cotton filler, (b) (4) Module 3.2.P.7 contains information regarding four sizes of HDPE bottles (u) (4) however the details of the proposed commercial presentations (capsule strength, bottle count and bottle size) are not provided.

The NDA stability package is summarized in Tables 4 and 5. The applicant proposes a (b) (4) expiry for both strengths in (b) (4) HDPE bottles.

(b) (4)



**Table 4: Summary of Dimethyl Fumarate Capsule Batches Packaged in HDPE Bottles**

Batch Type	Capsule Strength	Capsule Color	Batch Numbers	Capsule Count/ Bottle Size	Storage Condition	Data Available (Months)
Primary Validation	120 mg	Blue-white	27664 27666	Not described in NDA	25°C/60% R. H. 30°C/65% R. H. 40°C/75% R. H.	48 48 6
	240 mg	(b) (4)	56060 56061 56062	Not described in NDA	30°C/65% R. H. 40°C/75% R. H.	0 0
Registration	120 mg	Green-white	47823	14/60 cc 42/120 cc 180/325 cc	30°C/65% R. H. 40°C/75% R. H.	18 6
			47824	14/60 cc 120/215 cc 180/325 cc		
	47825		42/120 cc 120/215 cc			
	240 mg		54164 54165 54166	14/60 cc 60/120 cc 90/215 cc	30°C/65% R. H. 40°C/75% R. H.	3 3

(b) (4)

With respect to the stability data and proposed expiry the following key points are noted.

- The principal degradation pathway for dimethyl fumarate is (b) (4) in (b) (4) HDPE bottles and is likely to be the stability limiting factor. The applicant has provided the results of

regression analyses for (b) (4) 120 mg capsules as graphical presentations; it is recommended that detailed information be requested.

(b) (4)

- With respect to 120 mg capsules packaged in HDPE bottles, additional information is needed to determine whether the data provided would support the proposed expiry. For the registration batches, the applicant used a bracketing approach based on bottle fill and container size; however no information (e.g., headspace, surface to volume) to demonstrate that the chosen configurations studied are relevant to the commercial package configurations was provided. The Agency was not consulted prior to initiation of the bracketing stability protocol. It is also not clear whether the data from the primary validation batches would support assignment of a shelf life; only two batches were placed on stability and details of the package configurations were not provided.
- Stability data for 240 mg capsules in (b) (4) HDPE bottles are limited to 3 months for all storage conditions. The applicant proposes the same expiry (b) (4) for 240 mg capsules based on comparability of the 240 mg formulation to the 120 mg formulation. As summarized in **Table 2** above, however, the formulations are qualitatively and quantitatively different. The firm was advised during the pre-NDA meeting that the assigned expiry would be limited based on the stability data provided.

### *Critical issues for review*

#### Drug Substance

The equivalence of drug substance sourced (b) (4) and the corresponding manufacturing processes, should be evaluated carefully. The process descriptions given in Module 3.2.S.2.2 for the two sites are similar; but sketchy. It is recommended that the reviewer refer to the master batch record from each site (provided in Module 3.2.R) to evaluate the similarity of the processes.

The applicant's justification for not testing for (b) (4) in the final drug substance specification should be evaluated carefully based on the data provided for full scale production batches. The applicant will be asked to provide the method for determination (b) (4), plus supporting validation data for review.

#### Drug Product

Critical issues are discussed in the summary above. A number of deficiencies are identified and should be communicated to the applicant.

### ***Additional issues***

*Environmental Assessment:* The firm has submitted a claim for categorical exclusion under 21 CFR 25.31(b) which states that the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below one part per billion (1 ppb).

*Establishment Evaluation:* A full list of facilities involved in the manufacture, packaging and testing of dimethyl fumarate and Dimethyl Fumarate Delayed Release Capsules is provided in the submission. Facilities requiring compliance evaluation were submitted in EES on 08-Mar-2012.

*Labeling/Established Name:* The active ingredient, dimethyl fumarate, is a neutral molecule. Therefore there are no issues of consistency between the established name “dimethyl fumarate delayed release capsules” and the labeled potency.

*Methods Validation--*The drug substance is a new molecular entity; therefore, methods validation studies by the DPA St. Louis laboratory should be requested if the application is filed. It is recommended that the drug product assay and related substances methods be validated.

### ***Comments for 74-Day Letter***

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

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

Revise the composition (b) (4) [Table 2, Module 3.2.P.1] to include the actual amounts of polysorbate 80 and sodium lauryl sulfate present (b) (4).

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

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

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

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

With regard to drug product stability:

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

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

You have provided graphical presentations of regression analyses [REDACTED] (b) (4) [REDACTED] in 120 mg capsules in Module 3.2.P.8.1. Provide details of the of the statistical analyses performed, including batches analyzed, whether data from batches were pooled, and statistical output.

### **Review, Comments and Recommendation:**

The NDA is fileable from a CMC perspective; however additional information should be requested in the 74-Day letter.

The drug substance is a well-characterized small molecule and the drug product is a simple immediate release tablet. There are no QbD aspects to the NDA submission. It is recommended that the review team include a single CMC reviewer and a Biopharmaceutics reviewer. The drug substance is a new molecular entity; therefore, a Division-level regulatory briefing would be appropriate. Methods Validation studies should be requested if the application is filed.

*{See appended electronic signature page}*

Martha R. Heimann, Ph.D.  
CMC Lead, DNDQA-1, ONDQA

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief, DNDQA-1, ONDQA

**ATTACHMENT 1**

**Manufacturing Establishments for Dimethyl Fumarate Capsules**

Manufacturing information is reproduced from the attachment to Form 356h.

**DRUG SUBSTANCE**



(b) (4)

**DRUG PRODUCT**



(b) (4)

All facilities have been submitted in EES.

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR A NEW NDA/BLA**

**NDA Number:**  
204-063

**Supplement Number and Type:**  
N/A

**Established/Proper Name:**  
Dimethyl Fumarate Delayed Release  
Capsules

**Applicant:**  
Biogen Idec

**Letter Date:**  
24-Feb-2012

**Stamp Date:**  
27-Feb-2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	N/A		
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>		X	

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESSMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion claimed.

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	A detailed listing of clinical batches and clinical studies will be requested however, the proposed commercial products are linked to Phase 3 formulation as follows: 120 mg difference is capsule (b) (4) color – dissolution data 240 mg by bioequivalence comparison to 2 x 120 mg
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		(b) (4) HDPE bottles proposed and described; however, details about commercial HDPE presentations (capsule count and bottle size) need to be clarified.
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?		X	Not critical for review of electronic submission.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	N/A		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
				(b) (4) 04-May-2011	
				04-May-2011	
				03-May-2011	
				10-Jan-2011	
				04-May-2011	
				04-May-2011	
				03-May-2011	
				27-Jun-2011	
				17-Jan-2012	
				17-Jan-2012	
				05-May-2011	
				27-Jun-2011	
				04-May-2011	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	Is the product quality section of the application fileable?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	N/A		Describe filing issues here or on additional sheets
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			Describe potential review issues here or on additional sheets

*{See appended electronic signature page}*

Martha R. Heimann, Ph.D.  
CMC Lead, DNDQA-1, ONDQA

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief, DNDQA-1, ONDQA

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARTHA R HEIMANN  
03/14/2012

RAMESH K SOOD  
03/14/2012

**NDA 204-063**

**TRADENAME**  
**dimethyl fumarate delayed release capsules**

**Biogen Idec Inc**

**Review #1**

**David J Claffey, PhD**  
**ONDQA**

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# Chemistry Review Data Sheet

1. NDA: 204-063
2. REVIEW #: 1
3. REVIEW DATE: 19 NOV 2012
4. REVIEWER: David J Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

N-000

27 FEB 2012

N-0015

8 JUN 2012

N-0028

10 AUG 2012

N-0035

1 OCT 2012

N-038

10 OCT 2012

N-045

14 NOV 2012

N-046

15 NOV 2012

7. NAME & ADDRESS OF APPLICANT:

Name:

Biogen Idec Inc

## Chemistry Review Data Sheet

Address: 14 Cambridge Center, Cambridge, MA  
Representative: Nadine Cohen, Sr. Vice President Regulatory Affairs  
Telephone:

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)  
b) Non-Proprietary Name (USAN): dimethyl fumarate  
c) Code Name/# (ONDC only): BG00012  
d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

## 10. PHARMACOL. CATEGORY: Treatment of Multiple Sclerosis

## 11. DOSAGE FORM: Capsules

## 12. STRENGTH/POTENCY: 120, 240 mg

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

dimethyl (E)-butenedioate (IUPAC name)

dimethyl fumarate

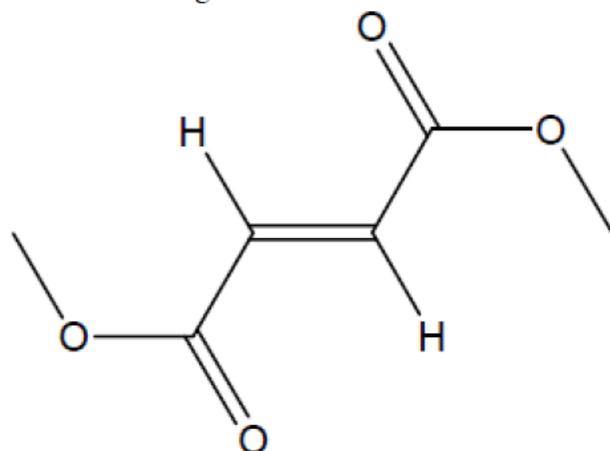
*trans*-1,2-Ethylenedicarboxylic acid dimethyl ester

(E)-2-Butenedioic acid dimethyl ester

fumaric acid, dimethyl ester

2-butenedioic acid, (2*E*)-, dimethyl esterdimethyl (2*E*)-but-2-enedioateC<sub>6</sub>H<sub>8</sub>O<sub>4</sub>

Mol mass: 144.13 g/mol



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4			
	III						
	III			4			
	III			4			
	III			4			
	III			4			
				4			

Chemistry Review Data Sheet

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

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not complete.		
EES	Not complete.		
Pharm/Tox	Not complete.		
Biopharm	Approval		Elsbeth Chikhale
LNC	N/A		
Methods Validation	Acceptable	1 OCT 2012	Michael Trehy, MVP Coordinator
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

## Chemistry Review Data Sheet

## 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

# The Chemistry Review for NDA 204-063

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Recommend that this application be approved from a CMC perspective on receipt of an “acceptable” recommendation from CDER Office of Compliance.

If an approval letter is issued we recommend that it includes a statement that the expiry period be set at 18 months for the 120 mg strength product and nine months for the 240 mg strength product.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

**Drug Substance:** Dimethyl fumarate, is an achiral trans-butene diester. It is a six carbon compound with limited aqueous solubility (3-4 mg/ml) but higher solubility in methanol (ca. 30 mg/ml). (b) (4)

(b) (4) It is non-hygroscopic (b) (4).

It is manufactured by (b) (4)

(b) (4)

(b) (4) The Applicant demonstrated via kinetic studies that (b) (4) a known genotoxic reaction by-product, are unlikely to approach the (b) (4) and that data have shown that it remained below the LOD in all batches tested.

The drug substance specification includes typical tests including that for the specified impurities /degradants. (b) (4) which are controlled (b) (4) levels, respectively. (b) (4) known process impurities, are also controlled at release. Batch analysis data from both sites were comparable and met the

## Executive Summary Section

specification. Stability data through 60 months from three drug substance lots manufactured (b) (4) were provided in addition to six months data at the (b) (4). All lots met the specification through long-term, intermediate and accelerated (six months) storage conditions. The most significant change was the (b) (4) at the 60-month time point. These data demonstrate the robust nature of the drug substance and support the proposed retest period (b) (4) at 25°C/60%RH.

**Drug Product:**

The drug product is supplied in two strengths, 120 mg and 240 mg, in size-0 hard-gelatin capsules (b) (4). The 120 mg strength has a white body with green (b) (4) printed with "BG-12 120 mg". The 240 mg strength has a green body (b) (4) with "BG-12 240 mg". The capsules will be packaged in HDPE bottles. (b) (4)

The drug product formulation was designed to prevent release of the drug substance in the stomach while allowing a rapid release in the intestine. The formulation consists of (b) (4) a size-0 hard gelatin capsule. Although both strengths share the same capsule size, they differ quantitatively and in some more minor respects, qualitatively. (b) (4)

The drug product formulation remained unchanged throughout development with the exception of the capsule color. The drug product is manufactured (b) (4)

(b) (4) In-process tests include the critical friability and disintegration tests (b) (4)

The drug product specification includes tests typical for an (b) (4) capsule. Levels of specified degradants (b) (4) are controlled - (b) (4) is controlled to ensure that (b) (4) (b) (4) The drug product assay and impurities method was found to be acceptable by the Division of Pharmaceutical Analysis.

Thirty commercial-scale (b) (4) drug product lots of the 120 mg strength capsules were manufactured during development. As Phase III studies required daily doses of up to 720 mg (six capsules), a 240 mg strength dosage form was developed to aid in patient compliance and convenience. It was decided to use the same capsule size for both strengths therefore changes were made to (b) (4) accommodate the

## Executive Summary Section

required higher drug load. This also required minor changes in excipients for manufacturability reasons. (b) (4)

The changes in drug product excipient levels were shown to have no significant impact on drug release.

The effect of pH on drug release was as designed – no significant release at pH 5.0 and rapid release at  $\geq$  pH 5.5.

Batch analysis data for 10 lots of the 120 mg strength capsules and six lots of the 240 mg strength were provided. All were commercial-scale batches and all met specifications.

Stability data were provided on three registration batches of each strength in both bottles (b) (4) – six months for the 120 mg strength in bottles (b) (4) and nine months for the 240 mg strength (in bottles (b) (4)). Additional data were provided for the 120 mg strength - (b) (4) (48 months in bottles) (b) (4)

In-use and photostability studies were also carried out. The Applicant proposed a (b) (4) expiry period with storage at  $\leq 30^{\circ}\text{C}$  for the 120 mg strength, however the data more reasonably support a 18 month expiry period. The proposed nine-month expiry period for the 240 mg strength was found acceptable.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is indicated for the treatment of patients with relapsing multiple sclerosis (b) (4)

A starting dose of 120 mg twice daily is recommended for the first seven days and 240 mg twice daily, thereafter. It can be taken with or without food. The 120 mg strength drug product is supplied in 14-count 60 cc bottles. The 240 mg strength product is supplied in 14-count 60 cc bottles, 46 & 60 count 120 cc bottles. The 46-count bottles are part of a 30-day starter pack (along with the initial seven-day supply of 120 mg strength product). The product should be stored at  $15^{\circ}\text{C} - 30^{\circ}\text{C}$  ( $59-86^{\circ}\text{F}$ ). The capsules should be protected from light (by storing in the original container) and once opened the product should be discarded after 90 days. The expiry periods for the 120 mg and 240 mg strength capsules are 18 and 9 months, respectively.

**C. Basis for Approvability or Not-Approval Recommendation**

Sufficient drug substance and drug product data were provided to assure product quality through the expiry period. An approval recommendation was made by

**Executive Summary Section**

biopharm reviewer Elsbeth Chikhale (19 NOV 2012). A final recommendation from a CMC perspective will be made on receipt of CDER Office of Compliance's recommendation. This will be subject of a separate memo.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

**C. CC Block**

115 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DAVID J CLAFFEY  
11/19/2012

RAMESH K SOOD  
11/19/2012