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
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

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.

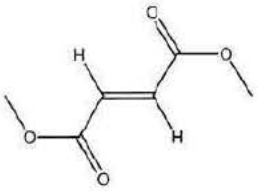
- The applicant proposed that no drug substance or drug product manufacturing process parameters be designated as critical. The firm was advised to submit the development reports that included the rationale why there are no critical process parameters, including parameters that were not studied.

- 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) The applicant indicates that dimethyl fumarate should be classified as BCS Class 1. (b) (4) The drug substance is not hygroscopic; however, it is reported to be (b) (4) The chemical structure of dimethyl fumarate is:



The bulk drug substance is manufactured (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 (b) (4) . [Module 3.2.S.2.2]
- (b) (4)
- Different control strategies will be used during manufacture at the two sites. (b) (4) (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 [1]	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 [1]	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 [1]			
	Talc			
	Colloidal silicon dioxide			
	Subtotal			
	Methacrylic acid copolymer, Type A [2]			
	(b) (4)			
	Methacrylic acid copolymer dispersion (includes Sodium lauryl sulfate, Polysorbate 80) [2]			
	Triethyl citrate			
	(b) (4)			
	Simethicone			
	(b) (4)			
TOTAL				

(b) (4)

(b) (4)

(b) (4)

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