CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204063Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	2/11/13
From	Billy Dunn, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	204063
Applicant	Biogen Idec
Date of Submission	2/27/12
PDUFA Goal Date	3/27/13
Proprietary Name / Established (USAN) names	Tecfidera/dimethyl fumarate
Dosage forms / Strength	Oral delayed release capsules/120 mg, 240 mg
Proposed Indication(s)	Treatment of patients with relapsing forms of multiple sclerosis (b) (4)
Recommended:	Approval

1. Introduction

The sponsor (Biogen Idec) has submitted a new drug application (NDA) to support the marketing of dimethyl fumarate (Tecfidera), a new oral drug with a proposed indication for the treatment of patients with relapsing forms of multiple sclerosis (MS) (b) (4) .

Dimethyl fumarate (DMF) has not been previously approved and is categorized as a new molecular entity. A related drug product, a combination of DMF with other fumarate esters including the primary metabolite of DMF, monomethyl fumarate (MMF), was approved in Germany in 1994 for the treatment of psoriasis and is marketed as Fumaderm. The proposed mechanism of action of DMF in MS is activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway that is involved in the cellular response to oxidative stress, ostensibly reducing inflammatory responses in both peripheral and central cells and promoting cytoprotection of central nervous system cells against toxic oxidative insults.

The review team for this NDA included the following primary reviewers:

Chemistry – David Claffey, PhD
Chemistry (Methods Validation Inspection) – Michael Trehy
Chemistry (Biopharmaceutics) – Elsbeth Chikhale, PhD
Office of Manufacturing and Product Quality (Inspections) – Derek Smith, PhD
Nonclinical – Melissa Banks-Muckenfuss, PhD
Nonclinical (Carcinogenicity) – Steven Thomson, PhD
Clinical Pharmacology – Jagan Parepally, PhD

Clinical Pharmacology (IRT-TQT) – Qianyu Dang, PhD
Division of Bioequivalence and GLP Compliance (Inspection) – Michael Skelly, PhD
Statistics – Xiang Ling, PhD
Clinical (Efficacy) – Heather Fitter, MD
Clinical (Safety) – Gerard Boehm, MD
Division of Medication Error Prevention and Analysis – Julie Neshiewat, PharmD
Division of Risk Management – Kendra Worthy, PharmD
Division of Medical Policy Programs – Shawna Hutchins, MPH, RN
Pediatric and Maternal Health Staff (Maternal) – Carrie Ceresa, PharmD
Pediatric and Maternal Health Staff (Pediatric) – Nadia Hejazi, MD
Controlled Substance Staff – Alicja Lerner, MD, PhD
Division of Pharmacovigilance – Andrew Fine, PharmD
Division of Professional Drug Promotion – Quynh-Van Tran, PharmD
Division of Consumer Drug Promotion – Meeta Patel, PharmD
Study Endpoints and Labeling Development – Elizabeth Donohoe, MD
Office of Scientific Investigations – Antoine El-Hage, PhD

I discuss below the key conclusions of each reviewer and provide my recommendations regarding this submission.

2. Background

DMF is not an approved drug product anywhere in the world. It has been under investigational development (IND 73061) in the United States for the treatment of multiple sclerosis since 2006. As noted above, Fumaderm is approved in Germany for the treatment of psoriasis.

As primary support for the proposed indication, the sponsor presents the results from two controlled Phase 3 efficacy study (studies 109MS301 and 109MS302). Both studies were of similar design and evaluated the effect of 240 mg bid and 240 mg tid of DMF in patients with MS on a variety of outcomes. In addition, as further support, the sponsor presents the results of a controlled Phase 2 dose-finding study (study C-1900) and interim results of an ongoing open-label, dose and rater-blinded extension study (109MS303).

One meeting with the sponsor focused on this submission took place, a pre-NDA meeting on 1/25/12. There are no significant outstanding issues from this meeting.

3. CMC/Device

Dr. Claffey reviewed this submission and found it acceptable.

Dr. Chikhale reviewed this submission and found it acceptable.

Mr. Trehy reviewed this submission and found it acceptable.

Dr. Smith completed the manufacturing inspection and found it acceptable.

There are no outstanding CMC issues. There are no CMC post-approval recommendations.

4. Nonclinical Pharmacology/Toxicology

Dr. Thomson reviewed this submission and found the statistical considerations of the carcinogenicity studies acceptable.

Dr. Banks-Muckenfuss reviewed this submission and found it unacceptable. She does not recommend approval. She bases her recommendation on nonclinical findings of renal toxicity, including tumors in rodents, at clinically relevant doses in all species assessed.

As described by Dr. Banks-Muckenfuss, animal data have demonstrated that DMF causes multiple toxicities across organ systems, including "kidney, testes, stomach (nonglandular), pancreas, liver, thymus, lymphatic system, and eye (retina)."

It is the renal toxicity that is most concerning. The renal tubular and interstitial toxicity seen in animals was widespread and somewhat insidious. It appears to occur at lesser doses with increasing duration of exposure, and damage may not clearly be seen in studies of lesser duration. Predictors of toxicity in the animals were not seen consistently in different species (urinary protein only in rats) and the utility of such assessments in humans as predictors of toxicity is uncertain. The renal findings in rodents included renal tumors. These tumors may or may not be species specific. In addition to tumors, the renal findings may be irreversible, as seen in the chronic monkey study.

Dr. Banks-Muckenfuss is concerned that the toxicities, particularly the carcinogenicity, may be compatible with the known actions of DMF. (Dr. Boehm discusses this to some degree, as well). She is perhaps most troubled by the notion that the enhanced clinical monitoring in humans may have been inadequate and that the toxicity may not yet be seen in trials of possibly insufficient duration. Taken together, she is left to conclude that the safety database from the clinical trials was potentially inadequate to detect possible "irreversible tissue damage and loss of function" along with renal tumors associated with human doses of DMF that are linked to relevant toxic doses in animals. She does acknowledge that the relevance of the animal findings to human risk is unclear.

Dr. Banks-Muckenfuss's supervisor, Dr. Lois Freed, performed an independent secondary review with specific attention to renal factors. She, too, observed evidence of widespread multi-organ toxicity across multiple species (rodent, dog, monkey), with clear evidence of renal toxicity.

Upon detailed review of the data, she is somewhat more hopeful, though still cautious, that predictive human monitoring (urinary albumin) may be useful in the avoidance of potential renal toxicity. That said, the chronic toxicity study in monkey and dog resulted in the development of irreversible interstitial fibrosis consistent with low level chronic renal toxicity

and, while BUN and creatinine were decreased (consistent with the findings in rat) there were no urinary findings consistent with renal toxicity.

Given the availability of Fumaderm clinical data, Dr. Freed briefly reviewed its toxicology studies and found a similar, though perhaps somewhat less severe, toxicological profile.

A re-evaluation of mouse and rat carcinogenicity data by the sponsor's expert consultant resulted in no substantial change in the findings of the mouse study but, in the rat study, a reconsideration of the renal tumors resulted in a change in renal tumor incidence such that their incidence was only slightly increased, only in females, and was no longer considered drug-related.

Reproductive and developmental toxicity findings remained significant.

Taken together, Dr. Freed feels the sponsor has conducted an adequate battery of nonclinical studies to support marketing of DMF for treatment of patients with relapsing forms of multiple sclerosis.

She finds that rodent forestomach, rodent and dog testes, and pan-species (mouse, rat, dog, monkey) kidney were the primary target organs. She describes that forestomach is of questionable relevance to humans. She feels that testicular findings can and should be described in clinical labeling. Finally, she agrees with Dr. Banks-Muckenfuss that the data demonstrate a potential for human renal toxicity, suggesting the possibility of irreversible injury due to low level chronic injury and repair.

Recognizing that the review team is in agreement that clinical trial monitoring may not have been able to detect renal injury consistent with that seen in animals, Dr. Freed feels that the efficacy findings in clinical trials along with the available safety data from those clinical trials, limited though it may be, combined with the Fumaderm postmarketing experience (namely, no indication of renal toxicity with longer-term exposure) are sufficient to support approval. She agrees with the plans for the large 5 year observational post-approval study discussed below.

Thus, with appropriate labeling, she recommends approval, along with a nonclinical postmarketing requirement to conduct a juvenile animal toxicology study to support pediatric clinical development.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Parepally, Dr. Dang, and Dr. Skelly reviewed this submission and found it acceptable.

Detailed labeling recommendations are found in the clinical pharmacology review.

The clinical pharmacology review notes that MMF is the active metabolite of DMF and that DMF is not detectable in systemic circulation due to rapid and complete hydrolysis. The conclusions below were based on evaluation of plasma concentrations of MMF.

There are no outstanding clinical pharmacology issues. There are no clinical pharmacology post-approval recommendations.

Pharmacokinetics
Although MMF exposure in individuals was highly variable, overall exposure increased approximately proportionally in response to single and multiple doses of 120-360 mg of DMF. Tmax was achieved in 2 to 2.5 hours in the fasted state. Protein binding was 27-45%. MMF has a volume of distribution of 53-73 liters. DMF was extensively and rapidly metabolized to MMF, the only active metabolite, which is further metabolized through the citric acid cycle. The elimination half-life was 0.5 to 1.4 hours, leading to no accumulation with multiple doses. The major elimination route of MMF was exhalation as carbon dioxide, accounting for 60% of the dose. Urinary and fecal elimination were minor routes at 15% and 1%, respectively.

Food effect
Food roughly doubled the Tmax. It also led to a modest reduction in flushing from 94% to 68%.

Pharmacodynamics
The mechanism of action may be activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, reducing inflammation and promoting cytoprotection.

Intrinsic factors
Age and race – no dose adjustments are recommended, although no meaningful conclusions can be drawn regarding race or the elderly due to a lack of patient variability.

Gender – no dose adjustments are recommended.

Renal impairment – not studied as this was a minor route of elimination.

Hepatic impairment – not studied as this was a minor route of elimination.

Drug-drug interactions
No effects were seen. The potential for interactions is low.

Thorough QT study
DMF did not show any potential for prolonging the QTcF interval compared with placebo.

Pharmacometrics
N/A

Pharmacogenomics
N/A

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Dr. Ling and Dr. Fitter reviewed this submission. Both recommend approval.

As discussed by Dr. Ling and Dr. Fitter, as primary support for the application, the sponsor submitted two adequate and well-controlled efficacy studies, 109MS301 and 109MS302 (study 301 and study 302).

Studies 301 and 302 were multi-national, multi-center, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of two doses of DMF (240 mg bid and 240 mg tid) in patients with relapsing-remitting multiple sclerosis (RRMS). Dosing was initiated in each group at half the target dose for one week before escalating to the full dose (120 mg bid and 120 mg tid for 7 days, followed by 240 mg bid and 240 mg tid long-term).

Study 302 also included an additional open-label active comparator arm using glatiramer acetate. As Dr. Fitter discusses on page 85 of her review, although the sponsor argues that DMF was superior to the active comparator, these data are essentially uninterpretable by design and I will not discuss them further.

Enrollment criteria for studies 301 and 302 were typical of MS trials including the following notable key criteria: diagnosis (per 2005 revised McDonald criteria) of RRMS with EDSS of 0 to 5, at least 1 relapse over the preceding year with MRI findings consistent with MS, and no relapses in the 50 days prior to randomization with a stable clinical course at the time of randomization.

The primary efficacy endpoint for study 301 was the proportion of subjects relapsed (PR) at 2 years.

The primary efficacy endpoint for study 302 was the annualized relapse rate (ARR) at 2 years.

The "key" secondary efficacy endpoints for study 301 were, in rank order, number of new or newly enlarging T2 hyperintense lesions, number of Gd-enhancing lesions, ARR, and disability progression.

The "key" secondary efficacy endpoints for study 302 were, in rank order, number of new or newly enlarging T2 hyperintense lesions, number of new T1 hypointense lesions, proportion of subjects relapsed, and disability progression.

Disability progression was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS of 1.0 or greater or a 1.5 point increase on the EDSS from a baseline EDSS of 0 that was sustained for 12 weeks.

The above primary and secondary endpoints were analyzed in a hierarchical fashion.

Dr. Ling and Dr. Fitter have provided a discussion of these various measurements and the statistical approach used in their analyses. Their use in these trials is acceptable.

Study 301

A total of 1237 patients were randomized while 1234 were randomized and treated as follows:

408 subjects to placebo
410 subjects to 240 mg bid
416 subjects to 240 mg tid

Patients were enrolled from 198 centers in 28 countries. Approximately 15% were from the United States. Overall, patients were distributed widely throughout the world.

The MRI cohort comprised 540 treated subjects, well balanced across all three treatment groups.

282 patients, well balanced across all three treatment groups, did not complete the study. The discontinuation rate was considered by both Dr. Ling and Dr. Fitter. Neither concluded that they called the results of the study into question.

Demographic and baseline characteristics of the patients were well-matched. As is typical for MS trials, most patients were relatively young white women.

The results for the primary outcome in the standard ITT population (assigned treatment at randomization with at least 1 day of study medication exposure), presented by the sponsor and confirmed by the review team, are below:

	PR	risk reduction compared to placebo	p-value
240 mg bid	0.27	49%	< 0.0001
240 mg tid	0.26	50%	< 0.0001
Placebo	0.46		

Dr. Ling (pages 17-18 of her review) conducted or confirmed multiple sensitivity analyses, including worst case scenario analyses designed to account for treatment discontinuation and potential biased relapse assessment due to unblinding, and found that all analyses were highly consistent with the primary analysis. She also examined the effect of flushing on treatment effect to account for unblinding and found the treatment effect preserved. Dr. Fitter also presents and discusses these analyses on pages 53-54 of her review. Taken together, these various analyses are strongly supportive of the primary analysis.

The results for the secondary outcomes described above, assessed in hierarchical fashion, presented by the sponsor and confirmed by the review team, are below:

	T2 lesions	risk reduction compared to placebo	p-value
240 mg bid	2.6	85%	<0.0001
240 mg tid	4.4	74%	<0.0001
Placebo	17.0		

	Gd T1 lesions	risk reduction compared to placebo	p-value
240 mg bid	0.1	90%	<0.0001
240 mg tid	0.5	73%	<0.0001
Placebo	1.8		

	ARR	risk reduction compared to placebo	p-value
240 mg bid	0.172	53%	<0.0001
240 mg tid	0.189	48%	<0.0001
Placebo	0.364		

	disability progression	risk reduction compared to placebo	p-value
240 mg bid	0.164	38%	0.0050
240 mg tid	0.177	34%	0.0128
Placebo	0.271		

Dr. Ling describes various sensitivity analyses of these secondary outcomes on pages 18-21 of her review, and all are consistent with the findings described above except for an analysis of disability progression sustained for 24 weeks (rather than 12 weeks as was pre-specified). Although it numerically favored DMF, it did not reach significance for either group, as can be seen below:

	disability progression	risk reduction compared to placebo	p-value
240 mg bid	0.128	23%	0.1893
240 mg tid	0.119	31%	0.0760
Placebo	0.169		

Dr. Fitter examined this issue (page 58 of her review) and postulates that the larger number of placebo patients who began alternative MS medications after progression (there were no such patients in the DMF groups) could have disproportionately reduced the number of patients with 24 week sustained progression in the placebo group.

Overall, Dr. Ling and Dr. Fitter agree that study 301 provides convincing evidence of effectiveness on the primary and all secondary endpoints.

Dr. Fitter also provides an exploration of various exploratory endpoints on pages 58-64 and 102-106. None of her findings argue against the findings described above.

Study 302

A total of 1430 patients were randomized while 1417 were randomized and treated as follows:

363 subjects to placebo
359 subjects to 240 mg bid
345 subjects to 240 mg tid
350 subjects to glatiramer acetate (again, these subjects will not be discussed below; they are included for the sake of completeness with regard to the total number of patients in the trial; it is also worth noting that patients randomized to this group constitute 10 of the 13 patients who were randomized but not dosed, and 8 of those 10 withdrew consent upon learning of their open-label treatment assignment)

Patients were enrolled from 200 centers in 28 countries. Approximately 20% were from the United States. Overall, patients were distributed widely throughout the world.

The MRI cohort comprised 681 treated subjects, well balanced across all four treatment groups.

290 patients, well balanced across all four treatment groups, did not complete the study. The discontinuation rate was considered by both Dr. Ling and Dr. Fitter. Neither concluded that they called the results of the study into question.

Similar to study 301, demographic and baseline characteristics of the patients were well-matched, and most patients were relatively young white women.

Analyses and analytic strategy for study 302 are similar to those for study 301 and will be presented below in a similar fashion.

The results for the primary outcome in the standard ITT population (assigned treatment at randomization with at least 1 day of study medication exposure), presented by the sponsor and confirmed by the review team, are below:

	ARR	risk reduction compared to placebo	p-value
240 mg bid	0.224	44%	<0.0001
240 mg tid	0.198	51%	<0.0001
Placebo	0.401		

Dr. Ling (pages 21-22 of her review) conducted or confirmed multiple sensitivity analyses, including worst case scenario analyses designed to account for treatment discontinuation and potential biased relapse assessment due to unblinding, and found that all analyses were highly consistent with the primary analysis. She also examined the effect of flushing on treatment effect to account for unblinding and found the treatment effect preserved. Dr. Fitter also presents and discusses these analyses on page 76 of her review. Taken together, these various analyses are strongly supportive of the primary analysis.

The results for the secondary outcomes described above, assessed in hierarchical fashion, presented by the sponsor and confirmed by the review team, are below:

	T2 lesions	risk reduction compared to placebo	p-value
240 mg bid	5.1	71%	<0.0001
240 mg tid	4.7	73%	<0.0001
Placebo	17.4		

	T1 lesions	risk reduction compared to placebo	p-value
240 mg bid	3.0	57%	<0.0001
240 mg tid	2.4	65%	<0.0001
Placebo	7.0		

	PR	risk reduction compared to placebo	p-value
240 mg bid	0.29	34%	0.0020
240 mg tid	0.24	45%	< 0.0001
Placebo	0.41		

	disability progression	risk reduction compared to placebo	p-value
240 mg bid	0.128	21%	0.25
240 mg tid	0.130	24%	0.20
Placebo	0.169		

Dr. Ling describes various sensitivity analyses of these secondary outcomes on pages 22-24 of her review, and all are consistent with the findings described above except for analyses of disability progression. In this case, as the disability findings were not statistically significant, the sensitivity analyses could not confirm the finding regardless of the outcome. That said, the pre-specified sensitivity analysis of disability progression sustained for 24 weeks (rather than 12 weeks as was primarily pre-specified) neared statistical significance in the bid dose group, as seen below:

	disability progression	risk reduction compared to placebo	p-value
240 mg bid	0.078	38%	0.0630
240 mg tid	0.086	33%	0.1172
Placebo	0.125		

Dr. Ling again conducted a sensitivity analysis of disability sustained through the end of the study, with a significant result in the bid dose group, as seen below:

	disability progression	risk reduction compared to placebo	p-value
240 mg bid	0.064	48%	0.0200
240 mg tid	0.091	27%	0.2123
Placebo	0.125		

Dr. Fitter points out the sponsor's comment that the placebo disability progression rate was low in study 302, approximating the treated progression rate in the study 301. She argues that the primary findings of the trial trump this post-hoc cross-study comparison, a reasonable and valid position. She also notes that a baseline imbalance in the placebo group in study 302 might support the notion of an unusually low disability progression rate, but she points out that such an imbalance did not exist. Given the similarity in the trials, Dr. Fitter performed a pooled analysis for the 12 week disability secondary outcome assessed in both trials:

	disability progression	risk reduction compared to placebo	p-value
240 mg bid	0.146	32%	0.0034
240 mg tid	0.155	30%	0.0059
Placebo	0.222		

Dr. Ling and Dr. Fitter agree that study 302 provides convincing evidence of effectiveness on the primary and all secondary endpoints, except for disability progression.

Dr. Fitter again provides a similar exploration of various exploratory endpoints on pages 82-87 and 102-106.

Dr. Ling (pages 25-28 of her review) conducted subgroup analyses by demographic and baseline characteristics of study 301 and 302 and found that the results were generally consistent across all subgroups, with no findings suggesting a particularly different pattern of effect than that seen in the main group analyses.

Overall, based upon both study 301 and 302, both Dr. Ling and Dr. Fitter feel that DMF had a convincing and significant effect on all primary and secondary endpoints except for disability progression in study 302. Despite this, both are supportive of DMF's nominal effect on disability, variously citing the strong results in study 301, the possibility of a somewhat underpowered sample size in study 302 relative to study 301, and the suggestion of benefit in various additional analyses of study 302 as well as the pooled data from both studies.

Dr. Ling feels that both doses of DMF used in studies 301 and 302 are efficacious.

Dr. Fitter agrees that both doses of DMF are efficacious and supports the approval of the 240 mg bid regimen. She argues that as the 240 mg tid regimen confers no apparent benefit over the 240 mg bid regimen, the latter is the correct choice for approval. I note that while the 240 mg bid regimen was numerically superior on nearly all endpoints in study 301, the 240 mg tid regimen was numerically superior on all endpoints in study 302. Further, the differences favoring each regimen were not particularly dramatic in either study, and they did not appear on face to represent clinically meaningful effects.

Dr. Fitter also discusses study C-1900 on pages 28-30 of her review. This was a dose-finding study that assessed imaging outcomes of 256 MS patients in four dose groups: placebo, 120 mg daily, 120 mg tid, and 240 mg tid. According to the sponsor's pre-specified analysis strategy, only the 240 mg tid dose group demonstrated a significant effect on imaging

outcomes (Gd T1 lesions on MRI). Additional analyses supported the superiority of the 240 mg tid dose, leading to its use in the study 301 and 302.

Finally, Dr. Fitter discusses study 109MS303 (study 303) on pages 88-90 of her review. This is an ongoing long-term extension of studies 301 and 302 primarily intended to assess safety, although efficacy measures are being assessed. Subjects who completed study 301 or 302 either continued on their current dose of DMF or, if originally randomized to placebo or glatiramer acetate, were re-randomized to one of the two dose groups of DMF used in the original study. In this manner, all patients in study 303 receive DMF in a blinded fashion. Interim efficacy data as of August 3, 2011, were submitted by the sponsor and are descriptive in nature. They are unable to contribute to a determination of effectiveness.

8. Safety

Dr. Boehm reviewed this submission and found no obstacles to approval related to safety.

As noted above, though DMF has not been previously approved, Fumaderm, a combination of DMF with other fumarate esters including the primary metabolite of DMF, monomethyl fumarate (MMF), was approved in Germany in 1994 for the treatment of psoriasis.

EXPOSURE

As Dr. Boehm discusses, the safety database for DMF exceeds standard ICH guidelines for the characterization of common adverse events at the intended recommended dose. Safety data on 3424 subjects in clinical trials of healthy volunteers, MS, psoriasis, and rheumatoid arthritis were submitted by the sponsor.

A total of 2665 MS subjects have received at least one dose of DMF. Of these 2665 MS patients, 1787 were exposed for at least 1 year, 1198 were exposed for at least 2 years and 712 were exposed for at least 3 years.

The intended recommended dose is 240 mg bid and 2537 MS patients have received this dose or greater. Of those 2537, 1136 received the intended recommended dose.

The bulk of the safety analysis stems from two pools of MS subjects:

Pool A – data from placebo-controlled trials in MS (C-1900 part 1, 109MS301, and 109MS302) representing 1720 subjects (2323.5 patient years of exposure).

Pool B – data from placebo-controlled and uncontrolled trials in MS (C-1900 parts 1 and 2, 109MS301, 109MS302, and 109MS303) representing 2513 subjects (4306.7 patient years of exposure).

A similar arrangement exists for two pools of psoriasis subjects:

Pool C – data from placebo-controlled trials in psoriasis representing 213 subjects (52.5 patient years of exposure).

Pool D – data from placebo-controlled and uncontrolled trials in psoriasis representing 296 subjects (317.7 patient years of exposure).

Additional clinical development safety data comes from assorted small early phase trials.

Finally, the sponsor submitted post-marketing safety data for Fumaderm.

Overall, little difference was seen between the MS data and the psoriasis data, and the MS data will be emphasized.

DEATHS

There were 11 deaths in the DMF clinical development program (9 on drug, 1 on glatiramer acetate, and 1 on placebo). Of the 9 on drug, 7 occurred in MS trials, and 2 in psoriasis trials. These are briefly described below:

1. A 54 year old woman with MS treated with 120 mg bid for 5 days died from a traumatic brain injury resulting from a bicycle accident.
2. A 38 year old woman with MS treated with 240 mg tid for 61 days died from a motor vehicle accident.
3. A 55 year old woman with MS treated with either 240 mg bid or tid for 196 days died from an acute malignant tumefactive MS relapse with eventual intraventricular hemorrhage.
4. A 31 year old woman with severe MS treated with 240 mg bid for 848 days died from an MS relapse accompanied by infection leading to cardiopulmonary arrest.
5. A 40 year old woman with MS treated with 240 mg tid for 760 days died from suicide.
6. A 32 year old woman with MS treated with 240 mg bid for 346 days (interrupted) died from sepsis from decubitus ulcers.
7. A 49 year old woman with MS treated with 240 mg bid for 406 days died from mesothelioma.
8. A 44 year old man with psoriasis and multiple cardiovascular risk factors treated with 240 mg tid for 75 days died from likely sudden cardiac arrest.
9. A 48 year old man with psoriasis and multiple cardiovascular risk factors treated with 240 mg tid for at least 249 days died from likely sudden cardiac arrest.

As Dr. Boehm discussed in his review on page 21, the Pool A deaths do not seem to differ in frequency among treatment groups.

SERIOUS ADVERSE EVENTS (SAEs)

In Pool A, there was no individual SAE reported by at least 1% of DMF patients and more commonly compared to placebo (Dr. Boehm's review, page 24). In fact, the overall frequency of SAEs was slightly greater in the placebo group.

In Pool B, Dr. Boehm notes that the only SAE that occurred in ≥1% of DMF exposed patients was MS relapse (9%, 227/2513). In Pool A, MS relapse was more common in placebo subjects.

The psoriasis pools (C and D) were equally unconcerning.

On pages 26-29 of his review, Dr. Boehm explores several sporadic SAEs of potential concern (including skin reactions and allergic reactions) and finds nothing to clearly implicate DMF and plausible alternative explanations. I will not repeat those here.

ADVERSE EVENTS (AEs) LEADING TO STUDY DISCONTINUATION

Below is the incidence of discontinuations due to adverse reactions in Pools A and B:

Pool A	Placebo n=1720 11%	Low dose n=128 9%	240 bid n=769 14%	240 tid n=823 14%

Pool B	All DMF n=2513 16%

Pool C and D are not interpretable for AEs leading to discontinuation for reasons detailed by Dr. Boehm.

Below is the incidence of AEs greater than placebo leading to discontinuation in Pool A:

Term	Placebo	Low dose	240 bid	240 tid
Vascular	<1%	<1%	3%	2%
GI	<1%	3%	4%	6%
Skin	<1%	<1%	2%	2%
Investigations	2%	3%	1%	<1%

The vascular term is due to flushing. It will be discussed below.

The GI term is driven by a constellation of nausea, vomiting, diarrhea, and abdominal pain.

The investigations term is due to 2 excess cases of ALT increase (7 total DMF/5 placebo).

These terms also occasionally led to dose interruptions or reductions.

Discontinuations in Pool B were for similar reasons, and 16% of DMF subjects discontinued due to AEs.

COMMON AEs

Page 75-76 of Dr. Boehm's review describes the common AEs (≥ 2%) from Pool A for which the incidence on any dose of drug is at least 1.5 times greater than that on placebo and is reproduced below:

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Any AEs	89% (114)	95% (733)	93% (767)	94% (1614)	92% (769)	87% (304)
Flushing	51% (65)	34% (265)	29% (240)	33% (570)	5% (39)	2% (6)
Diarrhea	9% (11)	14% (107)	17% (136)	15% (254)	10% (86)	4% (14)
Nausea	8% (10)	12% (93)	14% (115)	13% (218)	9% (72)	5% (16)
Abdominal pain upper	7% (9)	10% (76)	11% (94)	10% (179)	6% (47)	1% (4)
Abdominal pain	3% (4)	9% (73)	8% (69)	8% (146)	4% (37)	1% (5)
Pruritis	9% (11)	8% (62)	8% (64)	8% (137)	4% (35)	2% (7)
Vomiting	2% (3)	8% (65)	7% (58)	7% (126)	5% (38)	3% (9)
Rash	6% (8)	8% (58)	7% (58)	7% (124)	3% (29)	3% (9)
Hot flush	5% (6)	7% (52)	7% (55)	7% (113)	2% (16)	1% (5)
Erythema	2% (2)	5% (36)	7% (54)	5% (92)	1% (10)	2% (6)
Sinusitis	2% (2)	5% (35)	6% (52)	5% (89)	4% (31)	3% (11)
Bronchitis	2% (3)	5% (35)	6% (49)	5% (87)	4% (32)	5% (16)
Albumin urine	0	6% (46)	4% (36)	5% (82)	3% (27)	5% (18)
Dyspepsia	2% (3)	5% (35)	5% (42)	5% (80)	3% (23)	2% (6)
Muscle spasms	<1% (1)	4% (27)	6% (50)	5% (78)	4% (35)	2% (8)
Microalbuminuria	0	5% (35)	4% (36)	4% (71)	3% (24)	4% (15)
AST increased	2% (2)	4% (33)	4% (32)	4% (67)	2% (18)	4% (14)
Gastrointestinal disorder	2% (3)	2% (18)	4% (34)	3% (55)	<1% (8)	<1% (2)
Hyperhidrosis	2% (2)	2% (17)	3% (27)	3% (46)	1% (11)	1% (5)
Abdominal discomfort	5% (6)	2% (19)	2% (15)	2% (40)	2% (13)	<1% (1)
Influenza like illness	4% (5)	1% (10)	2% (17)	2% (32)	2% (14)	<1% (3)
Viral URI	3% (4)	2% (13)	1% (10)	2% (27)	1% (12)	2% (7)

These findings are largely consistent with the analyses of AEs leading to discontinuation and the findings in other Pools and do not raise particular additional concern.

LABORATORY DATA

As reviewed in detail by Dr. Boehm (pages 78-98) and summarized by Dr. Sally Yasuda, Safety Team Leader, in her supervisory memo, laboratory findings of potential importance

(excluding those discussed in association with other safety issues of concern, below) include lymphopenia, eosinophilia, and parathyroid hormone changes. I refer to Dr. Yasuda's summary on pages 10-13 of her memo and Dr. Boehm's summary of these issues on pages 7-8 of his review, and will briefly address these three concerns.

DMF administration is associated with lymphopenia. Lymphocyte counts begin a prompt decline within 4 weeks of first administration, reaching a rough nadir at 48 weeks of a 30% reduction from baseline (mean 1.34 $x10^9$/L at week 48) with only slight further decrease in general to 34% at 96 weeks. A concomitant effect on WBC count was seen. Further analysis, however, revealed that 6% of bid patients (the intended recommended dose) in Pool A had a lymphocyte count <0.5 $x10^9$/L compared to <1% of placebo patients. Upon cessation of DMF, counts begin to recover but remain reduced at about 20% below baseline 4 weeks after the final dose. Modest reductions in neutrophils, hemoglobin, hematocrit, and platelets accompany the effect on lymphocytes, though not as severe, with no significant differences on outlier analyses.

Dr. Boehm's review notes that the approved MS drugs fingolimod and teriflunomide have similar degrees of associated lymphopenia.

There is an increase in eosinophils that occurs during the first 4 weeks of treatment and then rapidly resolves over the subsequent 4 weeks.

Despite these hematologic findings, there were no associated significant clinical events, either SAEs or clinical AEs. Four patients discontinued due to low counts without associated overt clinical findings.

DMF administration is also associated with an increase in parathyroid hormone and a reduction in vitamin D. Dr. Boehm conducted a thorough review of this finding (pages 90-98) and found that not only was its clinical importance unclear, its relationship to MS itself was unclear. I refer to his analysis for further detailed discussion, but the finding does not appear to be of any significant concern based on the data at hand.

Liver and kidney laboratory parameters are discussed below.

Other laboratory data were unremarkable.

VITAL SIGNS

There were no significant findings of concern.

OTHER SAFETY ISSUES OF CONCERN

Flushing

Flushing is a prominent finding. Characterized as a constellation of redness, warmth, tingling, or itching, usually on the face and neck but also in the arms and chest or of a generalized

nature (referred to as "flushing-related symptoms", a broader category than the AE term "flushing" in the table above, as described on page 35 of Dr. Boehm's review), it occurs in nearly half of treated patients (45% in the bid group and 9% in placebo). It appears unrelated to the eosinophilia described above. Most flushing episodes are mild (67%); very few are severe (4%). It occurs rapidly after dosing, early in the course of treatment, and usually resolves over the course of the first month of treatment, but can persist in about 25% of patients.

Given the frequency and prominence of flushing, the sponsor undertook a descriptive study (109HV106) to assess the impact of various maneuvers to ameliorate flushing.

Dose was a questionable contributor, as the highest dose (above the clinically proposed dose) had the lowest flushing score.

Pre-treatment with aspirin (perhaps due to theorized mechanistic similarity to niacin-associated flushing) was evaluated, and though the sponsor concluded that it reduced flushing, Dr. Boehm argues otherwise. He cites the small size of the study with only 6 to 8 patients per group, and a minimal effect at the intended dose, with 3/6 pre-treated experiencing flushing compared with 5/6 experiencing flushing without such treatment. Differences in flushing severity scores are difficult to interpret, though they were somewhat lower with aspirin.

The effect of food on flushing was assessed in a randomized food-effect trial (C-1903), demonstrating that 34/36 patients experienced flushing when fasted compared with 23/34 when fed.

Finally, in Pool A MS trials, the dose of DMF could be held or reduced (for up to one month) if patients experienced flushing, but an assessment of the impact of these maneuvers was unclear, as it applied to all patients.

Dr. Boehm argues for inclusion of a statement in labeling regarding the effect of food on flushing.

Hepatotoxicity

Prompted by cases of serious hepatic injury (3 hepatic SAEs) and hepatic enzyme findings in the safety database, a causal relationship of DMF with hepatotoxicity was explored. As noted above, there was a slight increase in aminotransferase elevations compared to placebo using a cutoff of the upper limit of normal. There were no differences seen with a cutoff of three times the upper limit of normal. There was no difference compared to placebo in the risk of elevated bilirubin, nor did any isolated cases of hepatic enzyme elevation above three times the upper limit of normal occur in conjunction with a bilirubin twice the upper limit of normal.

Although there were three hepatic SAEs, they appeared unlikely to be related to DMF. One was suicide by a hepatotoxic agent, and the other two were chronic hepatitis with persistent elevation in the absence of drug, and cholestatic hepatitis with onset after a long period (over one year) on drug in the setting of a history of hyperbilirubinemia.

While there appears to be a small excess of a mild degree of transaminitis occurring in the drug group, it does not appear to be clinically significant.

Renal toxicity (excluding neoplasia)

Given the nonclinical renal findings referenced above, increased vigilance for renal events was part of the safety monitoring in the MS trials. Dr. Boehm details the nature of the monitoring. Careful review of the renal data in the safety database did not indicate that DMF was associated with increased overt renal toxicity. There were slight imbalances (2% vs. placebo) in proteinuria, albuminuria, and microalbuminuria in the treated groups but no evidence of renal SAEs in these patients. There were single cases in the treated group of chronic renal failure and renal tubular acidosis, again not as SAEs. There were three renal SAEs in the MS trials. There were 16 discontinuations (11 separate AEs, n=1 to 3 per AE) for renal events. Dr. Boehm has thoroughly discussed these cases and Dr. Yasuda has summarized them. In short, both have concluded that a causal relationship has not been established, as many of the AEs were present at baseline, recurred off DMF, or occurred while taking placebo.

Renal laboratory monitoring did not reveal substantial differences between DMF exposed patients and placebo. Minor differences were seen, as documented by Dr. Boehm (including a finding of quite small mean reductions in creatinine in DMF patients while placebo patients experienced an even smaller increase), but, overall, these differences were negligible. An exception to this is the unexpected and inexplicable finding of ketonuria in Pool A DMF exposed patients (21% bid, 30% tid, 5% placebo). This finding apparently occurred in isolation and without any concomitant adverse clinical findings. Neither associated laboratory data nor a differential occurrence of renal AEs in those with ketonuria were seen. It does not appear to be related to the presence of diabetes when examined in analyses requested of the sponsor and confirmed by Dr. Boehm. Diabetics were neither more likely to develop ketonuria nor to experience renal AEs in its presence. An argument has been advanced by the sponsor that the finding is an artifact of DMF metabolism.

Nephrology consultation in patients with renal laboratory abnormalities was unremarkable, and the nephrology evaluations were secondarily evaluated in a blinded fashion by an independent nephrologist. No evidence of drug-induced nephrotoxicity was seen as result of this evaluation.

With regard to the nonclinical renal toxicity seen in multiple species, both Dr. Boehm and Dr. Yasuda note that the reassurance provided by the lack of evidence from clinical trials that humans are at increased risk of renal toxicity must be tempered by an uncertainty about the length of time that humans may require to develop toxicity in response to DMF exposure. While it is possible that humans may not be similarly affected by the toxicities seen in animals, both Dr. Banks-Muckenfuss and Dr. Freed raise concerns that the duration of human exposure seen in clinical trials thus far may not be adequate to detect renal toxicity that results from a low level of chronic injury and repair with prolonged exposure. Although there are over 700 patients with over 3 years of exposure, conversations with Dr. Banks-Muckenfuss and Dr. Freed suggest that human equivalent exposures to reflect the animal data may require even

longer durations. In addition, it is uncertain whether the enhanced monitoring for renal toxicity implemented in response to the animal data was capable of detecting these toxicities.

Accordingly, Dr. Yasuda notes the sponsor's stated intent to conduct a large observational study, following 5000 patients for up to 5 years, in order to determine the nature of various adverse events, including serious renal events. She is supportive of such a study, and I concur. It should provide a reasonable opportunity to capture toxicities not predicted by the human data obtained thus far.

GI

As noted above, a panoply of uncomfortable and fairly common GI AEs led to occasional discontinuation. These symptoms occur fairly frequently (40% DMF exposed/30% placebo) and typically include diarrhea, vomiting, and abdominal pain. GI SAEs and severe AEs are also slightly more common in DMF patients. They, like flushing, are most common early in treatment. Temporary dose reductions in response to these AEs were allowed in the study, but the efficacy of this approach is unclear. Similarly, the sponsor argues that food may minimize these issues, but the data is limited (nausea is 8%/6% fasted/fed and vomiting is 6%/0% fasted/fed). None of the patients in the food effect study had diarrhea or abdominal pain. While an obstacle to tolerability, GI AEs do not appear to be an obstacle to approval.

Infections

Given the lymphocyte effects described above, and past experience with MS therapies, the risk of infection is crucial to assess. Consistent with our observations throughout clinical development, upon review, DMF displays no significant risk of infection. Most importantly, serious infections and opportunistic infections are not apparent. Dr. Boehm looked at this from a variety of viewpoints, and other than the mild respiratory infections seen in his table on page 67 of his review, other analyses he performed by severity, type, discontinuation, and amount were reassuring. That said, he astutely notes that a diligent approach to the clinical use of DMF will be required, as the selection and monitoring employed in the conduct of the trials will not be available in practice.

Carcinogenicity

In light of the nonclinical findings of renal tumors noted above, the review process carefully considered the issue of DMF-associated carcinogenicity.

Overall, there is no apparent excess in the rate of malignancy between DMF, placebo, or SEER data.

Pool A was well balanced overall, with 2 malignancies in each DMF group and 3 in placebo (the open-label active comparator had 4). The four DMF malignancies were transitional cell carcinoma of the renal pelvis, basal cell cancer of the skin, breast cancer, and cervical cancer.

Pool B contributes 15 additional malignancies for a total of 19 cases in 18 DMF patients. No single type accounts for more than 3 cases (breast cancer), and the additional cases include a renal cell cancer and a papillary renal cell carcinoma.

Although the sponsor argues based on growth rates and risk factors that the renal cancers were pre-existing and likely not related to DMF, it is impossible to be certain of this contention.

The renal tumors were subject to particular scrutiny as a result of the nonclinical data. Dr. Boehm identified literature suggesting that fumarate is an oncometabolite contributing to the formation of renal cell cancer (amongst other tumors). His review details the scientific thought underpinning this suggestion. Fumarate is a known metabolite of DMF. A genetic mutation in fumarate hydratase (FH) is known to cause a condition called hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome, characterized by benign cutaneous and uterine leiomyomata, renal cysts, and aggressive collecting duct and Type 2 papillary renal tumors (Dr. Boehm's review, page 110). This is apparently the result, at least in part, of intracellular accumulation of fumarate.

Whether orally administered DMF can result in elevated intracellular fumarate levels is uncertain, and Dr. Boehm has provided a detailed discussion about this issue. The patients who had the renal tumors while taking DMF are unavailable for genetic testing. The risk of DMF contributing to tumor formation through intracellular accumulation of fumarate is only theoretical. It does, however, reinforce the need for surveillance, particularly if there is an excess of renal tumors (or other malignancies) in the clinical database. Overall, this does not seem to be the case. The sponsor argues that this is not the case for renal cell cancers, either. I reproduce the table from page 115 of Dr. Boehm's review below:

Incidence Rate/100,000PY (95% CI) for Malignancies of the Kidney (Excluding Pelvis), Renal Pelvis (Only), and Kidney and Renal Pelvis Combined

Site	BG00012 (Pool B)	US SEER 2008	(b) (4) Claims data
Kidney (excluding pelvis)	44.10 (5.34, 159.31)	14.5 (14.3, 14.8)	(b) (4)
Renal Pelvis (only)	26.29 (0.67, 146.50)	1.0 (0.9, 1.03)	

From ISS table p.98 and SU table p.59

While the rate of kidney tumors is numerically higher than SEER data and insurance estimates, Dr. Boehm points out that this point estimate for renal cell cancer is based on two cases and the confidence intervals for the risk estimates overlap significantly. He also notes that the renal cell cancer incidence is consistent with the incidence observed in the teriflunomide NDA database (recently approved for MS). Finally, he notes that the postmarketing data for Fumaderm, a closely related product that should be subject to similar theoretical issues, includes reports of four renal cell cancers for a rate of 2.4/100,000 person years, a rate below Globocan reference data of 8.6/100,000 person years.

Overall, Dr. Boehm argues that there is little current evidence that DMF is associated with an excess risk of renal cancer (or leiomyomata, for which there is also concern of an excess of risk) but that the underlying issues suggest attention to these entities in the postmarketing setting.

Reproduction and Pregnancy

Pregnant women were excluded from the MS trials. The sponsor has reported 35 pregnancies in patients taking DMF, all but one with MS. Of these, there were 15 live births, 3 spontaneous abortions, 7 elective terminations, and outcomes are not known for 10. No fetal anomalies have been reported.

As noted above, Dr. Boehm finds no obstacles to approval. He recommends postmarketing exploration of potential renal toxicity, renal cell cancer, leiomyomata, infections/opportunistic infections, and ketonuria, as described in his review.

9. Advisory Committee Meeting

N/A

10. Pediatrics

DMF was discussed at a PeRC/PREA Subcommittee meeting on November 28, 2012. The Division presented a request for partial waiver for patients 0-9 years and deferral for patients 10 to 17 years of age. PeRC agreed with the Division.

The following language is being considered:

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

We are waiving the pediatric study requirement from birth to nine years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

Additionally, we are deferring submission of your pediatric study for ages 10 through 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must

be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

Deferred pediatric trial under PREA: A randomized, placebo-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.

11. Other Relevant Regulatory Issues

This application was submitted on 2/27/12. During the course of the review process, a major amendment was submitted by the sponsor in October 2012 and the review clock was extended to its current action date of 3/27/13.

The Division requested an inspection of investigators from study 301 and 302, as data from this study are essential to the approval process. As noted by Dr. El-Hage in his review, four foreign clinical investigators and one domestic site were chosen for inspection of the protocol due to their enrollment of a relatively large number of subjects and significant effect on the primary efficacy results of the study. Although violations were noted for two of the investigators (see Dr. El-Hage's review for details), the inspections revealed no significant problems that would adversely impact data acceptability.

The sponsor did not propose a Risk Evaluation and Mitigation Strategy (REMS) or a risk management plan. Dr. Worthy has reviewed the proposal and does not feel that a REMS is necessary at this time.

Dr. Ceresa reviewed this application and has several recommendations regarding maternal health issues. She recommends that the Division accept the sponsor's proposal to establish a pregnancy registry. She recommends the sponsor submit the registry protocol for review prior to initiation of the registry. She recommends that the Division ask the applicant to include a plan for regular submission of the data collected by the pregnancy registry for Agency review. Finally, she has multiple labeling recommendations.

Dr. Hejazi reviewed this application and has several recommendations regarding the postmarketing pediatric study and the pediatric sections of labeling.

Dr. Fine reviewed this application and found that dimethyl fumarate does not appear to have abuse or misuse potential.

Dr. Lerner reviewed this application and did not find that DMF has had its abuse potential fully characterized. She recommends three abuse characterization studies as postmarketing requirements (see below). She recommends that the sponsor analyze adverse events and report any postmarketing data on abuse, misuse, overdose, and diversion of DMF that becomes available. She recommends that the sponsor evaluate any adverse events potentially related to abuse including suicidality and report this information to FDA as serious adverse events. She

recommends that the sponsor submit an analysis of the abuse potential related adverse events reports of DMF including misuse, overdose, diversion, and suicidality for all studies that have not been submitted. This should include Phase 1 studies, MS studies, and the psoriasis study which were not integrated into the safety data analysis.

12. Labeling

The sponsor submitted proposed labeling. See the separate labeling document for the labeling negotiated with the sponsor.

Dr. Neshiewat reviewed the final proposed trade name, Tecfidera, and found it acceptable. She reviewed the proposed container labels, carton labeling, and insert labeling, and, after negotiation, found the final proposed versions acceptable.

Ms. Hutchins reviewed the proposed Medication Guide and, after negotiation, found it acceptable.

Dr. Tran reviewed the proposed prescribing information and made labeling recommendations.

Dr. Patel reviewed the proposed Medication Guide, as well as Ms. Hutchins's recommendations, and made labeling recommendations.

Dr. Donohoe reviewed the proposed prescribing information and made labeling recommendations.

13. Recommendations/Risk Benefit Assessment

I recommend approval of this application.

The effectiveness of DMF for the treatment of the relapsing forms of MS, based upon the results of the 109MS301 and 109MS302 trials, appears compelling.

The sponsor has submitted the results of two large adequate and well-controlled clinical trials that ostensibly demonstrate the effectiveness of DMF. The sponsor has also submitted data from these trials as well as various other supporting data that are sufficient to assess the safety of DMF for its intended use.

The 109MS301 trial is an adequate and well-controlled trial that demonstrates DMF is effective in reducing clinical exacerbations (assessed primarily as a decrease in the proportion of patients relapsing and secondarily as a decrease in the annualized relapse rate) and delaying the accumulation of physical disability. Findings for both the 240 mg bid and 240 mg tid dose groups were highly significant. There was little difference between them.

The 109MS302 trial is an adequate and well-controlled trial that demonstrates DMF is effective in reducing clinical exacerbations (assessed primarily as a decrease in the annualized relapse rate and secondarily as a decrease in the proportion of patients relapsing). Again, findings for both the 240 mg bid and 240 mg tid dose groups were highly significant and there was little difference between them. The trial did not demonstrate a statistically significant effect on delaying the accumulation of physical disability, though there was a numerical reduction that was somewhat less than that seen in the 109MS301 trial. Though not significant, there was little numerical difference between dose groups.

Various imaging findings in both trials are robust and supportive. All findings are highly significant, as has been fairly typical for MS drugs with clear clinical effectiveness. Numerically, the imaging findings favored the 240 mg bid dose group in the first study, and the 240 mg tid dose group in the second study, but overall, the findings are consistent both between studies and between dose groups.

The two trials are similar with obvious capacity for mutual support, and taken together, the data from these trials indicate that both doses (or regimens) have a beneficial effect on clinical exacerbations (relapses). An effect on accumulation of disability clearly has been demonstrated in the first trial, with multiple non-significant trends in the second. Significance was achieved in the second study on an internal analysis of disability sustained through the end of the study. Of uncertain contribution to the second study's disability findings are a lower placebo disability progression rate than the first study and the possibility of inadequate power in the second study to achieve significance. A pooled analysis of the shared accumulation of disability secondary endpoint resulted in a statistically significant effect with both doses. As a result of these findings, I have concluded that substantial evidence of effectiveness has been documented for both doses.

The risks associated with the use of DMF for MS appear relatively benign based on the safety profile seen in its clinical development, notwithstanding the nonclinical findings of concern.

Analyses of deaths and serious adverse events were not concerning.

Adverse events of interest include lymphopenia, flushing, a constellation of gastrointestinal findings, hepatic enzyme elevation, renal toxicity, and malignancy.

Administration of DMF results in prompt lymphopenia that increases over the first year and remains stable thereafter. It is not, however, associated with an increase in overall or serious infections. It did not appear to be dose related. Nevertheless, given the possible clinical significance of lymphopenia in an individual patient, it should be prominently described in labeling along with appropriate recommendations for pre-treatment and periodic monitoring.

Flushing occurs in nearly half of treated patients. Though it most often promptly resolves, it may remain persistent. It led to a slight excess of discontinuations, but for the most part was tolerated. It did not appear to be dose related. Given its frequency and potentially disturbing nature, it warrants prominent description in labeling. The impact on flushing of either aspirin pre-treatment or dose adjustment is uncertain (b) (4). Food

intake, a benign intervention, may mildly reduce flushing and is appropriate for inclusion in labeling.

Gastrointestinal events also occur in just under half of treated patients. Their overall profile is similar to flushing and should be described in labeling.

Increases in hepatic enzymes did not appear to be clinically important but should be described in labeling given its slight prominence in the treated group.

No significant evidence of renal toxicity or malignancy was seen in the clinical development program, despite enhanced monitoring given the prominent nonclinical findings. I agree with Dr. Freed that the totality of the data along with plans for a long-term post-approval observational study provide sufficient reassurance with regard to the nonclinical findings to support approval.

Overall, the benefits of DMF, in my opinion, outweigh its risks. There are no safety findings that argue against approval. There are no convincing data to suggest a separation in effectiveness of the two doses studied. I recommend that the 240 mg bid dose be approved, as the review team has recommended. It appears to be the minimum maximally effective dose. Clinical findings suggest that explorations of lower doses have been adequate. I also recommend approval of a 120 mg dose, as a 120 mg introductory dose was used for the first 7 days in the clinical trials and there are issues of initial tolerability with DMF that make it reasonable to initiate treatment at this lower dose, despite the lack of clear evidence that this is necessary. Accordingly, the labeling should reflect an initial dose of 120 mg bid for 7 days, followed by the maintenance dose of 240 mg bid.

Based on the results of the trials described above in patients with RRMS, I believe DMF should be indicated for the treatment of relapsing forms of MS, consistent with our current understanding of the similar pathophysiological underpinnings of the various relapsing forms of MS (to include the initial presentation of RRMS popularly called clinically isolated syndrome). Such an indication is also consistent with current Divisional thinking regarding the inclusion of outcome data in the clinical studies section of labeling for MS drugs with these types of effects.

I recommend inclusion in labeling of the relapse data and imaging data from studies 109MS301 and 109MS302, and the disability data from study 109MS301. I have discussed above the reasons for inclusion of the disability data. Presentation of these data in labeling is consistent with past approvals, and there is nothing in the current application to alter this approach. The disability data from study 109MS302, while not statistically significant, may be seen as somewhat supportive of the findings from study 109MS301. It may lend further context to the disability effect and is reasonable to consider for description in labeling.

Brief mention is warranted regarding the need for an advisory committee meeting in regard to this application. This was carefully considered, particularly in light of the nonclinical findings. In addition, an independently submitted (from another sponsor) Citizen's Petition cited the published nonclinical findings associated with DMF, and called for advisory

committee review of the current application (and, indeed, of all applications for MS drugs). I refer to the official response to this Citizen's Petition for a detailed discussion of its issues, but the Division took great care to consider the arguments it advanced and, in view of the totality of the data including the clinical safety database included in the NDA that did not identify any significant renal toxicity in humans, concluded that an advisory committee meeting was not warranted as the safety profile of DMF is acceptable for the treatment of patients with relapsing forms of MS. This decision was discussed with and supported by senior management.

A pediatric development program in pediatric patients 10-17 years of age will be required.

I agree with Dr. Worthy that a REMS is not necessary to ensure that the benefits of the drug outweigh the risks.

I agree with the review team that the following studies should be requested as required pediatric assessments and PMRs:

1. Deferred pediatric trial under PREA: A randomized, placebo-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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

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

/s/

WILLIAM H Dunn
03/25/2013