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Paper 23
Entered: September 2, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS V LLC,
Petitioner,

v.

BIOGEN MA INC.,
Patent Owner.

Case IPR2015-01136
Patent 8,399,514 B2

Before FRED E. McKELVEY, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*.

McKELVEY, *Administrative Patent Judge*

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. Introduction

Pending before the Board is Petitioner's First Amended Petition[1] ("Pet.") (Paper 9) seeking entry of an order instituting an *inter partes* review.

Patent Owner timely filed a Preliminary Response. ("Prelim. Resp.") (Paper 21).

II. Background

A. Parties

Petitioner is Coalition for Affordable Drugs V LLC along with ten other entities.[2] Pet. 1–2.

Patent Owner is Biogen MA Inc. Prelim. Resp. 1.

B. Involved Patent

The involved patent is U.S. Patent 8,399,514 B2 ("the '514 Patent") issued 19 March 2013. Ex. 1001A.

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[1] An earlier version of the Petition appears in the record. *See* Paper 2 (1 May 2015). We have considered only the First Amended Petition (Paper 9, filed 27 May 2015) in resolving whether to institute an *inter partes* review trial.

[2] The ten other entities are identified as:

(1) Hayman Credes Master Fund, L.P. ("Credes"),
(2) Hayman Orange Fund SPC ("HOF"),
(3) Hayman Capital Master Fund, L.P. ("HCMF"),
(4) Hayman Capital Management, L.P. ("HCM"),
(5) Hayman Offshore Management, Inc. ("HOM"),
(6) Hayman Investments, L.L.C. ("HI"),
(7) nXn Partners, LLC ("nXnP"),
(8) IP Navigation Group, LLC ("IPNav"),
(9) J. Kyle Bass, and
(10) Erich Spangenberg.

The application which matured into the '514 Patent was filed on 13 February 2012. Ex. 1001A, 1 (22).

The '514 Patent claims priority based on several applications; the earliest of which was filed on 8 February 2007. *Id*. (60).

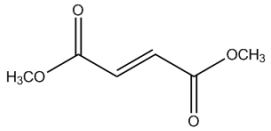
The '514 Patent contains claims 1–20. Ex. 1001A, cols. 27–30.

Petitioner challenges all of the claims, *viz*., claims 1–20. Pet. 1:2–4.

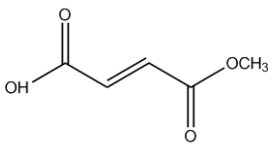
C. Abbreviations

DMF	Dimethyl fumarate[3]
EDSS	Expanded disability status scale—mentioned in Kappos
MMF	Monomethyl fumarate[4]
MRI	Magnetic resonance imaging—mentioned in Kappos
MS	Multiple sclerosis
PO	Per os (by mouth or orally)
RRMS	Relapsing-remitting multiple sclerosis—mentioned in Kappos

[3] The structural formula for DMF is:



[4] The structural formula for MMF is:



D. Prior art

The prior art relied upon is:

Kappos et al. "Kappos"	J. Neurol. (2005) 252 [Suppl. 2]:A *Randomized, placebo-controlled phase II trial of a novel oral single-agent fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis*	2005	Ex. 1003A
ICH Guideline	*Dose-Response Information to Support Drug Registration E4*	10 Mar. 1994	Ex. 1004A
ClinicalTrials NCT00168701 "ClinicalTrials"	*Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Efficacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis*	Dated: 14 Sept. 2005, identified as downloaded from ClinicalTrials.gov archive, U.S. National Institutes of Health	Ex. 1022A

In addition, Petitioner relies on what it characterizes as an "admission of prior art" and specifically a statement in the written descriptive portion of the Specification of the '514 patent. Ex. 1001A, col. 5:6–7: "Fumaric acid

esters, such as DMF [dimethyl fumarate], have been proposed for treatment of MS [multiple sclerosis]" (Pet., page 6:4–5), citing (Ex. 1001A, col. 5:7), *inter alia*, *BG 12*, 6 Drugs R&D 229–30 (2005) (Ex. 1021A).

E. Related Proceeding

The '514 Patent is also involved in *Biogen MA Inc. v. Forward Pharma AS*, Interference 106,023 (PTAB Declared 13 Apr. 2015) (Interference 106,023, Paper 1).

In the interference, Forward Pharma was authorized to file, and has filed, Forward Pharma Motion 7 seeking entry of a judgment against Biogen alleging that the claims of the '514 Patent are unpatentable under 35 U.S.C. § 103(a) over the prior art. Interference 106,023, Paper 167. An Opposition to the Motion has not yet been filed.

In determining whether to institute a trial in this IPR, we have *not* considered any of the evidence offered, or arguments made, by Forward Pharma in support of its Motion 7.

F. Challenges

While Petitioner mentions only a "Ground 1," there are in fact three challenges—which we identify as Challenges 1–3. Pet. 6.

Challenge No.	Claims	35 U.S.C.	Prior art forming basis of challenge
1	1–20	§ 103(a)	Kappos and ICH Guideline
2	1–20	§ 103(a)	ClinicalTrials and ICH Guideline
3	1–20	§ 103(a)	Prior art admissions and ICH Guideline

G. Claims 1, 11, 15, and 20 of the ’514 Patent

The claimed invention is readily understood from the independent claims.

Claim 1

Claim 1 of the ’514 Patent reads [indentation added]:

> A method of treating a subject in need of treatment for multiple sclerosis comprising
>
> orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of
>
> (a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and
>
> (b) one or more pharmaceutically acceptable excipients,
>
> wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

Claim 11

Claim 11 of the ’514 Patent reads [indentation added]:

> A method of treating a subject in need of treatment for multiple sclerosis consisting essentially
>
> of orally administering to the subject about 480 mg per day
>
> of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

Claim 15

Claim 15 of the ’514 Patent reads [indentation added]:

> A method of treating a subject in need of treatment for multiple sclerosis comprising
>
> orally administering to the subject pharmaceutical composition consisting essentially of

(a) a therapeutically effective amount of dimethyl fumarate and

(b) one or more pharmaceutically acceptable excipients,

wherein the therapeutically effective amount of dimethyl fumarate is about 480 mg per day.

Claim 20

Claim 20 of the '514 Patent reads [indentation added]:

A method of treating a subject in need of treatment for multiple sclerosis comprising

treating the subject in need thereof with a therapeutically effective amount of

dimethyl fumarate, monomethyl fumarate, or a combination thereof,

wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

III. Analysis—Challenge 1

Challenge 1 is limited to Kappos and ICH Guideline.

Kappos describes the following (Ex. 1003A, page ll/148, cols. 1–2:P574) (italics added):

Objective: *To determine the efficacy and safety* of a novel single-agent oral fumarate therapy, BG00012,[5] in patients with relapsing-remitting multiple sclerosis (RRMS).

Background: An open-label *pilot study* demonstrated that a product containing a mixture of *fumaric acid esters* significantly reduced the number and

[5] The active ingredient of BG12 or BG00012 is dimethyl fumarate. *See* Exhibit 1 forming part of Ex. 1007A (page 16 of 87; ¶ 5).

volume of gadolinium-enhancing (Gd+) lesions in patients with RRMS. *BG00012 is being investigated* for the treatment of psoriasis and other autoimmune diseases, *including MS* [multiple sclerosis]. This phase II study was designed to evaluate the efficacy of three doses of BG00012 on brain lesion activity as measured by magnetic resonance imaging (MRI) in patients with RRMS.

Design: This is a randomized, double-blind, placebo-controlled, phase II study being conducted at 45 clinical centers in Europe. Patients were included in the study if they were between 18 and 55 years of age, had a definite diagnosis of RRMS, and an Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0. In addition, patients must have either experienced at least 1 relapse within 12 months prior to randomization with lesions on cranial MRI consistent with MS, or had Gd+ lesions on a cranial MRI performed within 6 weeks of randomization. Eligible patients were randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240 mg PO three times daily (720 mg/day), or placebo. The study consists of 2 phases: a 24-week double-blind treatment phase followed by a 24-week, blinded, safety-extension phase in which all patients will receive some level of BG00012. The primary endpoint is the total number of Gd+ lesions over four MRI scans at weeks 12, 16, 20, and 24 (calculated as the sum of these four MRI scans). Secondary MRI endpoints include the cumulative number of new Gd+ lesions and the number of new or newly enlarging T2-hyperintense lesions at week 24 compared with baseline. Additional endpoints include: the number of new T1-hypointense lesions at week 24 compared to baseline, safety and tolerability, disability progression as measured by EDSS, relapse rate, and proportion of relapse-free patients.

> Results: This paper *will present* details of the study design, as well as the baseline demographic and clinical characteristics of enrolled patients.
>
> Conclusions: This dose-ranging study *will determine the efficacy of BG00012* on brain lesion activity in patients with RRMS.

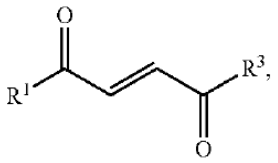
According to Petitioner's witness Dr. Steven E. Linberg, Kappos "discloses a pilot study that orally administered to patients what appears to be a therapeutically effective amount of fumaric acid esters, indicated by a 'significantly reduced the number of gadolinium-enhancing (Gd+) lesions in patients with RRMS.'" Ex. 1005A, 14:1–4.

From this testimony, Petitioner invites us to find that Kappos describes the use of DMF as a compound useful for treating multiple sclerosis. We decline the invitation.

First, a copy of a description of the "pilot study" has not been made of record. Hence, we have not been favored with a description of the details of the pilot study.

Second, at best Dr. Linberg said only that it "appears" that therapeutically an effective amount of fumaric acid esters was tested. What counts is what is described, not what appears to have been tested (a prior use, public or otherwise, is not prior art available in an IPR).

Third, a description of a "fumaric acid ester" may or may not be a description of DMF. There are fumaric acid esters other than DMF which have been described as potentially useful for treating multiple sclerosis. *See*, *e.g.*, Ex. 1001A, col. 11:11–24:

> In some embodiments, the [fumaric acid ester] compound . . . has the structure of Formula IV:
>
> (IV)
>
> 
>
> or a pharmaceutically acceptable salt thereof, wherein:
>
> R^1 and R^3 are independently selected from OH; O^-; (C_{1-24})alkoxy . . . .

Formula (IV) is DMF when R^1 and R^3 are both C_1-alkoxy (–OCH_3).

Formula (IV) is MMF when R^1 is –OH and R^3 is C_1-alkoxy (–OCH_3).

Consistent with *In re Hughes*, 345 F.2d 184 (CCPA 1965) (if a reference is subject to two interpretations, then it will not support an anticipation rejection), we are unable to find that "a fumaric acid ester" as described by Kappos is DMF or MMF.

Fourth, and perhaps most important, is that Kappos tells one skilled in the art that there was a pilot study and that a Phase II study will be undertaken to evaluate efficacy of BG00012 *inter alia* for treatment of MS.

The nature of the pilot study is not apparent. Petitioner has not established the precise nature of the study and whether researchers were determining a therapeutically effective amount. The Pilot Study is not a description that DMF is useful for treating MS; rather, at best it is a "hope" that DMF will turn out to be useful for treating MS. A hope may or may not come true and does not establish that DMF is useful for treating MS.

Assuming Phase I does not reveal unacceptable toxicity, FDA Phase II may determine whether a "drug works in people who have a certain disease or condition." *Id*. Phase II may or may not establish that DMF is

useful for treating MS. However, prior to completion and evaluation of Phase II, one skilled in the art would not necessarily understand from Kappos that DMF is useful for treating MS.

We wish to make clear that we are not engrafting into the § 103(a) obviousness evaluation whether DMF as a drug is effective. *In re Anthony*, 414 F.2d 1383 (CCPA 1969) (FDA, not USPTO, is responsible for safety of drugs which are sought to be patented); *In re Watson*, 517 F.2d 465 (CCPA 1975) (Congress has given responsibility to FDA, not USPTO, to determine in the first instance whether drugs are safe); *Purdue Pharma L.P. v. Endo Pharmaceuticals Inc.*, 438 F.3d 1123, 1134 (Fed. Cir. 2006) (quantum of proof necessary for FDA approval is significantly higher than the proof required in the USPTO). Nevertheless, Petitioner has bottomed its case on a publication describing potential FDA phase I and II testing and we have considered the content of Kappos to determine if it describes DMF as being known to be useful in treating MS. We are unable, consistent with the "description" requirement of § 102(b), to find a reasonable likelihood that Kappos teaches that DMF was known to be useful in treating MS.

Because Petitioner has failed to establish that Kappos teaches that DMF would be useful for treating MS, we need not evaluate whether the claimed dosage would or would not have been obvious based on ICH Guideline.

We decline to institute an *inter partes* review trial on the basis of Challenge 1.

Petitioner has failed to establish that there is a reasonable likelihood that it will prevail as to any claim on the basis of Kappos and ICH Guideline.

IV. Analysis—Challenge 2

Challenge 2 is based on ClinicalTrials and ICH Guideline.

ClinicalTrials is a copy of a U.S. National Institutes of Health document found by Petitioner on the internet.

Patent Owner argues that ClinicalTrials "is [not] a prior art printed publication." Prelim. Resp. 22:10.

Because we decline to institute an *inter partes* review, we will assume, without deciding, that ClinicalTrials is a printed publication.

A relevant portion of ClinicalTrials reveals the following. Ex. 1022A, 1–2 of 6 (italics added; citations omitted):

> *DMF*, the active ingredient in BG00012, is an immunomodulator demonstrating definite therapeutic efficacy in psoriasis . . . and *possible therapeutic efficacy in MS*. . . . *However, the target site of action and the exact mechanism of action of DMF are unknown*.
>
> Like psoriasis, MS has been postulated to be driven by a Th1 cytokine reaction and to therapeutically respond to either immunosuppression or Th2 suppression . . . . Putative effects of BG00012 include suppression of circulating T cell population, down regulation of adhesion molecule expression, modulation of the Th1/Th2 cytokine expression profile, inhibition of neutrophil burst, and TNF-induced CD62E expression through suppression of NF-kB nuclear translocation.
>
> Methyl fumaric acid esters (FUMADERMÒ) have been shown to reduce peripherally in vivo circulating CD4+, CD8+ and CD52+ mononuclear cells . . . . This circulatory reduction has been associated with a decrease in intradermal mononuclear cell infiltration in psoriasis patients (another T cell-mediated disease) . . . . DMF

> was recently shown to induce substantial plasma membrane alterations potentially linked to the deactivation via apoptosis of lymphocytes . . . .
>
> Methylfumarates have been shown to modulate in vitro T cell cytokine profile from Th1 to Th2 . . . . DMF and MMF inhibit the proliferation of keratinocytes, possibly due to a temporary rise in the intracellular calcium concentration . . . . Methylfumarates have been shown to prevent acute and chronic rejection in rat kidney transplantation models . . . .
>
> . . . It is difficult to assess the validity of some in vitro data that have been derived using doses that exceed serum levels found in human trials . . . .
>
> In summary, the putative immunomodulatory effects, the psoriasis efficacy of FUMADERM®, and the efficacy data in *the pilot MS study of BG00012 support a proof of concept study in MS*.

ClinicalTrials is deficient as a prior art teaching of DMF being useful to treat MS for many of the same reasons that Kappos is deficient.

Nowhere does ClinicalTrials state that DMF is useful for treating MS. Rather, what is described is a "pilot MS study of BG00012" (not of record) and based on that study going forward with "a proof of concept study in MS." Ex. 1022A 1–2. ClinicalTrials, at best, describes a "possible therapeutic efficacy in MS," citing a 2001 article by Schimrigk et al. (not of record).

Petitioner makes an attempt to bolster the effectiveness of DMF for treating MS based on Phase II tests described as showing DMF effectiveness on psoriasis. However, on the record before us, we find the connection between psoriasis and MS too speculative to support a finding that because

DMF is effective for treating psoriasis that it also would be effective for treating MS. There is insufficient evidence to find that one skilled in the art would find that there is a reasonable likelihood of success at the end of DMF testing for MS.

ClinicalTrials might support a finding that one skilled in the art "hopes" DMF will be useful in treating MS. However, as noted in our discussion of Kappos, a "hope" may or may not come to pass.

We decline to institute an *inter partes* review trial on the basis of ClinicalTrials and ICH Guideline.

Petitioner has not established that a reasonable likelihood that it will prevail as to any claim attached on the basis of Challenge 2.

V. Analysis—Challenge 3

Challenge 3 is based on admissions said to have been in the '514 Patent and ICH Guideline.

The admission is believed to be the following:

> Fumaric acid esters, such as DMF, have been proposed for treatment of MS (see, e.g., [1] Schimrigk et al., Eur. J. Neurol., 2006, 13(6):604-10; [2] Drugs R&D, 2005, 6(4):229-30).

Ex. 1001A, col 5:6–8.

Patent Owner attacks use of the admission on the ground that "an alleged admission is not a patent or printed publication and therefore cannot be a basis to institute *an inter partes* review. 35 U.S.C. § 311(b)." Prelim. Resp. 25.

The "admission" (or statement in the '514 Patent) is supported by a citation to Drugs R&D, a document in the record of this IPR (Ex. 1021A). Petitioner did not place Schimrigk (2006) in the record.

We do not reach, leaving for another day, any issue of whether an "admission" per se can be relevant prior art in an IPR. Given the citation to Drugs R&D (of the record), we will consider the "admission" in context with Drugs R&D.

When the "admission" in the context of Drugs R&D is considered on the merits, it fares no better than Kappos and ClinicalTrials.

Drugs R&D says that Fumapharm AG developed a second-generation fumarate ("fumaric acid"—which is not DMF) for oral treatment of psoriasis. It goes on to state that Biogen is currently evaluating "the product" in trials as an oral treatment for MS and suggests that the trials are FDA Phase II trials. *See* the discussion in the first paragraph of the Abstract, Ex. 1021A.

The remaining portions of Drugs R&D for the most part describe treatment of psoriasis, not MS. In Table II there is mention of drug development history referring specifically to a Nov 2004 "Phase–II in Multiple sclerosis in Europe (PO)." The result of the Phase II European trials is not in the record. Nevertheless, nothing in the admission or Drugs R&D supports a finding that DMF is useful for treating MS. In other words, as of the date of the admission or Drugs R&D, we are back to a "hope" that DMF will be useful in treating MS.

We decline to institute an *inter partes* review trial on the basis of any admission or Drugs R&D and ICH Guideline.

Petitioner has not established that a reasonable likelihood that it will prevail as to any claim attached on the basis of Challenge 3.

VI. Motion for Additional Discovery

Patent Owner has requested additional discovery. *See* Paper 15, filed 29 June 2015. The additional discovery is said to be necessary to investigate possible sanctions. *Id*. at 3.

Granting of additional discovery is discretionary with the Board. *See* 35 U.S.C. § 316(a)(5)(B) ("discovery shall be limited to — what is otherwise necessary in the interest of justice"); *see also Cochran v. Kresock*, 530 F.2d 385, 396 (CCPA 1976) (whether a party is entitled to additional discovery is discretionary with the board); *Keebler Co. v. Murray Bakery Products*, 866 F.2d 1386, 1388 n.1 (Fed. Cir. 1989) (standard of review of discovery order on appeal is abuse of discretion).

Because we decline to institute an *inter partes* review based on Petitioner's failure to establish a likelihood of success as to any challenged claim, we see no need for prolonging this case. This case has ended. Authorizing additional discovery in this case at this time would be inconsistent with a speedy and inexpensive resolution of the case. 37 C.F.R § 42.1(b).

VII. Order

We have considered all arguments presented by Petitioner, but find that none justify instituting an *inter partes* review.

Upon consideration of the Petition (Paper 9) and the Preliminary Response (Paper 21), and for the reasons given, it is

ORDERED that the Petition is *denied* as to all challenged claims, and

a trial will not be instituted.

Upon consideration of Patent Owner's motion for additional discovery, and for the reasons given, the motion is *dismissed*.

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