No.

IN THE

Supreme Court of the United States

ARGENTUM PHARMACEUTICALS LLC,

Petitioner,

v.

NOVARTIS PHARMACEUTICALS CORPORATION,

Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR WRIT OF CERTIORARI

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QUESTIONS PRESENTED

Introducing generic alternatives that compete with previously approved drugs requires market approval through the Food and Drug Administration ("FDA"). To do so, competitors submit an Abbreviated New Drug Application ("ANDA") that relies on the safety and efficacy data of the previously approved brand name drug. When that previously approved drug is covered by a patent, however, the mere act of filing the required ANDA subjects the competitor to an immediate patent infringement suit by the brand name company. Such suits are common. By filing an infringement action, the brand name company obtains an automatic 30-month stay during which the FDA cannot approve the competitor's ANDA.

The real and immediate risk of an infringement suit extends equally to all members of joint ventures that work towards FDA market approval. Petitioners formed a joint venture with a manufacturing partner to develop a generic alternative to Respondent's brand name drug. Fearing an infringement suit, Petitioner challenged the validity of Respondent's patent through an administrative proceeding created by Congress under the Leahy-Smith America Invents Act. Petitioner did not prevail on the challenge and appealed the adverse decision.

The questions presented are:

Did the Federal Circuit categorically and erroneously preclude redress for injured members of joint ventures in the pharmaceutical industry by only recognizing (1) the manufactuing partner in the joint venture, and (2) the partner applying for FDA marketing approval in the joint venture, as having demonstrable injury-in-fact for Article III standing?

Did the Federal Circuit err by rejecting the Leahy-Smith American Invents Act's statutory estoppel provisions as a basis to demonstrate injury-in-fact for Article III standing?

PARTIES TO THE PROCEEDINGS BELOW

Petitioner Argentum Pharmaceuticals LLC ("Argentum") respectfully brings this petition for a writ of certiorari from the United States Court of Appeals for the Federal Circuit's decision in *Argentum Pharmaceuticals LLC v. Novartis Pharmaceuticals Corp.*, 956 F.3d 1374 (Fed. Cir. 2020) (App. 1a-8a).

Argentum was one of eight petitioners in an *inter partes* review ("IPR") proceeding before the United States Patent and Trademark Office's Patent Trial and Appeal Board ("Board"), by which Argentum challenged the validity of United States Patent No. 9,187,405 owned by Respondent Novartis Pharmaceuticals Corporation ("Novartis").

Argentum identified and represented its manufacturing partner KVK-Tech, Inc. ("KVK") as a real party in interest throughout the IPR proceeding and on appeal at the Federal Circuit. The other IPR petitioners were Apotex Inc., Apotex Corp., Actavis Elizabeth LLC, Teva Pharmaceuticals USA, Inc., Sun Pharmaceutical Industries, Ltd., Sun Pharmaceutical Industries, Inc., and Sun Pharma Global FZE.

Argentum and the other petitioners appealed from the Board's adverse decision and briefed all issues together in a consolidated appeal. Teva Pharmaceuticals, Actavis, and Sun Pharmaceutical Industries settled before oral argument. App. 2a n.1. Apotex settled after oral argument. *Id.* Argentum remained the only appellant in the appeal after oral argument, and during the subsequent petition for rehearing *en banc*.

RULE 29.6 STATEMENT

Pursuant to Supreme Court Rule 29.6, Argentum discloses that Intelligent Pharma Research LLC, APS GP LLC, and APS GP Investors LLC are parent corporations or own 10% or more of the Argentum's stock.

LIST OF RELATED PROCEEDINGS

Pursuant to Supreme Court Rule 14.1(b)(iii), Argentum discloses that this petition is directly related to and arises from:

Argentum Pharms. LLC v. Novartis AG, No. IPR2017-01550 (PTAB July 11, 2018);

Apotex Inc. and Apotex Corp., Argentum Pharms. LLC, Actavis Elizabeth LLC, Teva Pharms. USA, Inc., Sun Pharmaceutical Industries, Ltd., Sun Pharmaceutical Industries, Inc., and Sun Pharma Global FZE v. Novartis AG, No. IPR2017-00854 (PTAB July 11, 2018);[1]

Apotex Inc., Apotex Corp., Sun Pharmaceutical Industries, Ltd., Sun Pharmaceutical Industries, Inc., Sun Pharma Global FZE, Actavis Elizabeth LLC, Teva Pharm. USA, Inc., and Argentum Pharm. LLC, v. Novartis Pharms. Corp., Nos. 18-2209, -2230, -2260, -2273 (Fed. Cir.);[2]

Argentum Pharms. LLC v. Novartis Pharms. Corp., 956 F.3d 1374 (Fed. Cir. Apr. 23 2020); and

Argentum Pharms. LLC v. Novartis Pharms. Corp., No. 2018-2273 (Fed. Cir. Jul. 9, 2020).

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[1] This case consolidated the following IPR proceedings: IPR2017-01550, IPR2017-01946, and IPR2017-01929.

[2] These appeals were consolidated. Appellants Apotex Inc., Apotex Corp., Actavis Elizabeth LLC, Teva Pharmaceuticals USA, Inc., Sun Pharmaceutical Industries, Ltd., Sun Pharmaceutical Industries, Inc., and Sun Pharma Global FZE eventually settled with Novartis at different stages of the appeal. Those appeals were voluntarily dismissed pursuant the parties' respective settlements.

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APPENDIX[3]

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[3] In addition to the Appendix, this Petition also cites to submissions in appeals before the Federal Circuit by referring to the corresponding appeal numbers and ECF numbers. Submissions in the lead appeal are cited under "Appeal No. 18-2209," and submissions in Argentum's *en banc* proceeding are cited under "Appeal No. 18-2273." The appendix of record before the Federal Circuit is available in the lead appeal under ECF No. 105. All citations to the Federal Circuit's appendix are in the form "CAFC-Appx."

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PETITION FOR WRIT OF CERTIORARI

Petitioner Argentum prays for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit ("Federal Circuit") dismissing Argentum's appeal from an adverse final decision in an *inter partes* review ("IPR") proceeding before the United States Patent and Trademark Office's Patent Trial and Appeal Board ("Board").

OPINIONS BELOW

Argentum challenged the validity of U.S. Patent No. 9,187,405 ("'405 patent") owned by Respondent Novartis. The Board first instituted trial on all grounds of invalidity in IPR2017-00854 brought by other parties, and subsequently instituted trial on all grounds of invalidity presented by Argentum in IPR2017-01550. The Board consolidated these IPR proceedings. The Board's institution decisions are unreported and are reprinted at 76a-112a.

On July 11, 2018, the Board issued a final written decision finding that the IPR petitioners had not shown that the claims of the '405 patent are invalid in view of the asserted prior art. The Board's final written decision is unreported and is reprinted at 12a-75a.

On April 23, 2020, the Federal Circuit dismissed Argentum's appeal from the Board's final written decision, holding that Argentum lacks Article III standing. The Federal Circuit's opinion is reported at 956 F.3d 1374, and is reprinted here as 1a-8a. On July 9, 2020, the Federal Circuit denied Argentum's petition for rehearing *en banc*. That order is unreported and is reprinted at App. 9a-10a.

JURISDICTION

Pursuant to 28 U.S.C. § 1254(1), this Court has jurisdiction to review the Federal Circuit's judgment by writ of certiorari. The Federal Circuit issued its opinion on April 23, 2020. Argentum timely filed a petition for rehearing *en banc*, which the Federal Circuit denied on July 9, 2020. On March 19, 2020, this Court ordered that the deadline to file any petition for writ of certiorari is extended to 150 days from an order denying petition for rehearing. Argentum's petition has been timely filed.

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

This case involves standing under Article III, § 2 of the United States Constitution. This case further involves statutory provisions regarding patent matters under 35 U.S.C. § 271, the Hatch-Waxman Act under 21 U.S.C. § 355, the Leahy-Smith America Invents Act under 35 U.S.C. §§ 315(e) and 319, and regulatory provisions under 37 C.F.R. § 42.73(d). They are reprinted at App. 113a-163a.

STATEMENT OF THE CASE AND FACTUAL BACKGROUND

For over four years, Argentum and its manufacturing partner KVK have been working together under a formal joint venture to develop and commercialize generic drugs. One such drug is fingolimod for the treatment of relapse-remitting multiple sclerosis—a debilitating disease suffered by millions around the world. Argentum has invested significant resources in the joint venture's efforts. Its tireless work with KVK has culminated in an affordable, market-ready generic drug from which millions of patients will benefit.

Standing between Argentum and market entry of its generic fingolimod is the pharmaceutical giant Novartis. Since 2010, Novartis has maintained a firm monopoly over fingolimod treatment of multiple sclerosis with its blockbuster drug Gilenya. Costing each patient an average of nearly $100,000 annually, Gilenya generates approximately $3 billion in annual revenues for Novartis. To date, Gilenya remains the only 0.5 mg dosage fingolimod drug approved in the United States for treating relapse-remitting multiple sclerosis.

Novartis's longstanding monopoly in this market stems from an interplay of patent rights and the statutory framework for FDA approval. Novartis owns the '405 patent at issue in this case, and has listed it in the FDA's so-called "Orange Book" as covering its Gilenya blockbuster drug. In doing so, Novartis has provided notice that *any competitor* seeking FDA approval for a generic version of Gilenya will be subject to a patent infringement suit. 21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.53(b)(1).

To enter the market with a generic alternative to Gilenya, Argentum is first *required* to seek FDA approval. Under the Hatch-Waxman Act enacted by Congress, this can be done by filing an ANDA. The filing of an ANDA, however, statutorily constitutes an act of patent infringement. 35 U.S.C. 271(e)(2). Argentum will, therefore, be subject to an immediate patent infringement suit by Novartis upon the filing of an ANDA. Specifically, Novartis is statutorily entitled to file a patent infringement suit against Argentum within 45 days of receiving a required notice. And by filing suit, Novartis obtains an automatic stay of 30 months during which the FDA cannot approve the ANDA.

This stay automatically precludes Argentum from obtaining FDA approval during the statutory period. *See* 21 U.S.C. § 355(j)(5)(B)(iii). Novartis can also extend this stay (*id.*), and seek injunctive relief. *See* 35 U.S.C. § 271(e)(4). This combination of an automatic stay and injunctive relief is significant for purposes of market exclusivity.

Novartis has, in fact, *sued each and every competitor* that sought FDA approval for a generic version of Gilenya. Over 20 lawsuits and counting, Novartis has garnered full market exclusivity with injunctions against each potential competitor. Argentum is simply next in line. Tellingly, Novartis has refused to disclaim suing Argentum and its manufacturing partner KVK. CAFC-Appeal 18-2273, ECF 12 at 10.

The real and immediate risk of an infringement suit and the resulting automatic stay block Argentum from market entry. Argentum thus stands to lose significant investment in its joint development of a market-ready generic fingolimod. With projected annual revenues approaching $50 million, Argentum loses expected profits from its joint venture with every day that goes by.

To eliminate that barrier, Argentum directly challenged the '405 patent's validity in an IPR proceeding against Novartis—a proceeding enacted by Congress specifically as a more cost-effective and expedited alternative to district court litigation. The Board's adverse decision regarding the validity of the '405 patent directly affects Argentum. If the decision stands, Novartis will continue to block Argentum's generic fingolimod for another seven years—the remainder of the life of the '405 patent.

The Federal Circuit nonetheless denied Argentum any redress from the Board's decision on a statutory appeal. Under the guise of a constitutional limitation on standing, the Federal Circuit's decision turns upside down the framework Congress established to allow unlawful patents to be challenged and to allow generic drugs to be brought expeditiously to market. Denying the right to appeal to an entity that has pursued an administrative challenge to a patent, precisely because that entity is ready and eager to bring a competitive generic to market, disregards the basic financial motivation and interest that has always been held to properly ground Article III standing.

That the case involves a joint venture partner—a common arrangement in the pharmaceutical industry—cannot change the outcome because it does not diminish Argentum's constitutional rights and interests in the outcome of the case. There is no dispute that the '405 patent is a barrier to Argentum's market entry, nullifying its previous investment and depriving it of the profits that entering the market will bring. Nor is there a dispute that Argentum is subject to suit by Novartis as soon as an ANDA is filed for FDA approval. And, indeed, there is no doubt that the Board's adverse decision statutorily estops Argentum from arguing in any other litigation that the '405 patent is invalid on the same grounds or other grounds that reasonably could have been raised.

The Federal Circuit focused on the fact that KVK will be the manufacturing entity and the entity filing for regulatory approval, which the Federal Circuit deemed to render Argentum's injury not personal. Its holding departs from the constitutional norms for Article III standing and this Court's precedent.

"At bottom, 'the gist of the question of standing' is whether petitioners have '*such a personal stake in the outcome of the controversy as to assure that concrete adverseness* which sharpens the presentation of issues upon which the court so largely depends for illumination.'" *Massachusetts v. E.P.A.*, 549 U.S. 497, 517 (2007) (quoting *Baker v. Carr*, 369 U.S. 186, 204 (1962)) (emphasis added). As this Court explained, "'[i]njury in fact' reflects the statutory requirement that a person be 'adversely affected' or 'aggrieved,' and it serves to distinguish a person with a direct stake in the outcome of a litigation—even though small—from a person with a mere interest in the problem." *United States v. Students Challenging Regulatory Agency Procedures (SCRAP)*, 412 U.S. 669, 689 n.14 (1973).

At its core, the Federal Circuit's decision departs from this maxim and precludes Argentum from redress on appeal simply because it is in a joint venture. In the process, it slams the door on any pharmaceutical joint venture partner seeking to invalidate a patent that blocks market entry, where that partner is not the entity manufacturing the product or submitting the ANDA for FDA approval. This is particularly problematic in industries where, as here, joint ventures between non-manufacturing and manufacturing partners are very common.

This Court's intervention is, therefore, needed to ensure that Article III is not improperly invoked to eliminate an entire class of appellants with a direct financial interest in the outcome of a case and adversely impacted by the results of an adversarial administrative proceeding in which they participated as a party.

A. Argentum's Generic Version of Gilenya Will Provide Affordable Treatment to Millions Suffering from Relapse-Remitting Multiple Sclerosis

"Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with chronic inflammatory demyelination leading to progressive decline of motor and sensory functions and permanent disability." App. 17a. Features of the disease "include inflammation, demyelination and axonal and oligodendrocyte loss." App. 86a. In other words, the disease eats away at the protective coating of nerve cells leading to progressive decline in motor functionality and even permanent disability. *See* CAFC-Appeal 18-2273, ECF 20 at n.1.

According to the National MS Society, nearly 1 million individuals in the United States and 2.3 million individuals worldwide suffer from multiple sclerosis.[4] Novartis's brand name drug Gilenya is an oral dosage form for the treatment of multiple sclerosis based on a daily dosage of 0.5 mg of fingolimod.

The use of fingolimod in the treatment of multiple sclerosis has been long known. CAFC-Appx1019-20. Publications prior to the '405 patent also expressly disclose the use of a 0.5 mg fingolimod dosage. *See* CAFC-Appeal 18-2209, ECF 69. To date, however, Gilenya remains the exclusive 0.5 mg dosage fingolimod drug that is available in the United States.

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[4] *Multiple Sclerosis: Facts, Statistics, and You*, https://www.healthline.com/health/multiple-sclerosis/facts-statistics-infographic.

According to the Healthcare Bluebook, treating the lifelong condition of multiple sclerosis with Gilenya costs each patient approximately $100,000 a year. *See* CAFC-Appeal 18-2273, ECF 20 at 2. Gilenya's worldwide sales generate approximately $3 billion in annual revenue for Novartis. *Id.*

It is well-known that generic drugs are more affordable than brand name drugs, and that delta increases as more generics are available. Prices are lower by 39% with one generic, by 54% with two generics, and by 79% with four generics.[5] Argentum and its manufacturing partner KVK have been working to commercialize an affordable, generic version of Gilenya. CAFC-Appeal 18-2209, ECF 44-3 ¶¶11, 14. This joint venture is ready to bring a generic version to market. The only hindrance is an imminent patent infringement suit by Novartis—which is a virtual certainty under the Hatch-Waxman framework. *Id.* ¶¶12, 15.

B. The '405 Patent Bars Market Entry Under the Hatch-Waxman Act

Novartis received FDA approval for Gilenya in September 2010. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1320 (Fed. Cir. 2017). With its New Drug Application ("NDA"), Novartis submitted a list of patents that it contends cover Gilenya. Novartis's patents have been listed in the FDA's so-called Orange Book. *See* CAFC-Appx3130-31.

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[5] Conrad, Ryan et al., *Generic Competition and Drug Prices: New Evidence Linking Greater Generic Competition and Lower Generic Drug Prices*, at 2-3, https://www.fda.gov/media/133509/download.

By listing its patents, Novartis effectively provided notice that any competitor seeking FDA approval to make a generic version of Gilenya is subject to a patent infringement suit. *See* 21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.53(b)(1). Two of those patents listed by Novartis recently expired. All claims of the third patent, U.S. Patent No. 8,324,283, have been held invalid. *See Novartis*, 853 F.3d at 1319. The '405 patent was the fourth patent listed by Novartis. CAFC-Appx3131. It is the patent at issue in this case. Absent reversal of the Board's decision, the '405 patent will provide Novartis with exclusivity for the fingolimod treatment of multiple sclerosis until June 25, 2027. *Id.*

In order to seek FDA approval for a generic version of Gilenya, any competitor must file an application known as an ANDA. Such ANDA incorporates the safety and effectiveness data submitted by the original drug manufacturer and requires only bioequivalence studies to demonstrate that the drugs can be substituted for each other. This is intended to streamline the process by which generic companies can seek FDA market approval. 21 U.S.C. § 355(j).

Filing an ANDA, however, also requires certification that the '405 patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). This certification is then followed by service of a required notice on Novartis, providing "[a] detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed." 21 U.S.C. § 355(j)(2)(B)(iv)(II).

This process in turn triggers an opportunity for Novartis to sue for patent infringement within 45 days so as to obtain an automatic stay of 30 months, within which the generic competitor's ANDA cannot be approved by the FDA. *See* 21 U.S.C. § 355(j)(5)(B)(iii). This stay can be further extended. *Id.* And Novartis can, of course, also seek injunctive relief against the generic competitor. *See* 35 U.S.C. § 271(e)(4).

These statutory ANDA requirements, automatic stays, and potential patent infringement liability under 35 U.S.C. § 271(e)(2) in combination present a significant market barrier for generic competition. Importantly, ***patent infringement liability is not limited to ANDA filers***. A non-filer engaged in joint development efforts with an ANDA filer is equally subject to liability for indirect infringement. *See*, *e.g.*, *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1272 (Fed. Cir. 2007).

C. Novartis Has Been Consistently Blocking Generic Competition, Including Argentum

Novartis has maintained a firm monopoly over Gilenya by enforcing its '405 patent. Over the past decade, numerous competitors have sought FDA approval to market a generic version of Gilenya.[6] Novartis has brought suit for patent infringement ***against each and every one*** of those pharmaceutical companies and their subsidiaries or affiliates—totaling over 20 patent infringement suits to date.

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[6] FDA-Approved Drugs, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process, (searching for "fingolimod").

Notably, Novartis has sought and obtained permanent injunctions against each defendant in cases that have terminated. *See*, *e.g.*, Case No. 1:18-cv-01043 (D. Del.) (injunctions against Teva Pharmaceuticals, Mylan, Dr. Reddy's, Sun Pharma, Actavis, Accord Healthcare, Hetero Labs, Torrent Pharma, Glenmark Pharmaceuticals, Alkem, HEC Pharm, Strides Pharma, Emcure Pharmaceuticals, Heritage Pharmaceuticals, Bionpharma, Prinston Pharmaceuticals, Ezra Ventures, Cadila Healthcare, Zydus Pharmaceuticals, Aurobindo Pharma); Case No. 1:19-cv-01118 (D. Del.) (injunction against Mylan); Case No. 1:18-cv-01039 (injunctions against Teva, Actavis). In other words, Novartis has thus far successfully precluded *all* competitors from selling a generic alternative to Gilenya.

Following its proven pattern of enjoining any competition through serial patent litigation, Novartis has also refused to disclaim suing Argentum and its manufacturing partners. *See* CAFC-Appeal 18-2273, ECF 12 at 10. On February 10, 2020, Argentum's counsel sought confirmation from Novartis that it does not intend to enforce the '405 patent against Argentum and its manufacturing partners for infringement "in connection with their manufacturing and commercialization activities." *Id.* Novartis never responded to the letter. It is clear that Novartis intends to enforce the '405 patent against Argentum and its manufacturing partner KVK as soon as an ANDA is filed in accordance with the Hatch-Waxman statutory framework.

D. The Joint Venture Between Argentum and Its Manufacturing Partner KVK to Develop a Generic Version of Gilenya

Argentum is a generic drug company with core competencies in pharmaceutical operations and the development of generic versions of branded drugs. *See*, *e.g.*, CAFC-Appeal 18-2209, ECF 44-3 at 23. Since its inception in May 2015, Argentum has been partnering with branded and generic pharmaceutical companies to develop and bring to market generic products. *Id.* ¶¶3-4. To date, Argentum has successfully pursued generic versions of several brand name drugs. *Id*. Those include, for instance, generic versions of Vimpat®, Zytiga®, Afinitor®, Dymista®, Jublia®, Restasis®, Cialis®, and Pazeo®. *Id.* ¶¶2-14.

To be sure, these types of partnerships with manufacturing companies are very commonplace in the pharmaceutical industry.[7] Some conventions are, in fact, organized for the purpose of bringing these types of partnerships to fruition.[8] These joint ventures allow companies to combine their respective levels of expertise, including product development, regulatory approval, manufacturing, and marketing.

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[7] Research and Markets Report: Global Joint Venture Partnering Terms and Agreements in Pharma, Biotech and Diagnostics 2014-2020 (Oct. 2020), https://www.researchandmarkets.com/reports/2986980/global-joint-venture-partnering-terms-and?utm_source=CI&utm_medium=PressRelease&utm_code=rxr9xh&utm_campaign=1451641+-+Latest+Joint+Venture+Agreements+Announced+in+the+Pharmaceutical%2c+Biotechnology+and+Diagnostic%2c+2020&utm_exec=chdo54prd

[8] Informa Markets, CPhi Worldwide Post Show Report 2019, https://www.cphi.com/content/dam/Informa/cphi/europe/en/2020/pdf-files/HLN19CPW-SP-Post%20Show%20Report.pdf

Novartis itself also routinely engages in joint ventures and collaborations. Gilenya, for instance, was the result of a partnership between Novartis and Mitsubishi Tanabe Pharma Corporation. *See Novartis*, 853 F.3d at 1319-20; *Novartis AG v. Ezra Ventures, LLC*, No. 4:15-cv-00095, 2015 WL 4197692, at *1 (E.D. Ark. July 10, 2015). Notably, Argentum's efforts to develop and bring to market a generic version of Pazeo® are the result of an agreement between *Argentum and Novartis* company Alcon Research. Ltd. in 2016. CAFC-Appeal 18-2209, ECF 44-3 ¶3.[9]

Since January 2016, Argentum has joined forces with its manufacturing partner KVK under a formal agreement to develop and commercialize generic versions of brand name drugs. *Id.* ¶¶4-7. KVK is a manufacturer of pharmaceutical drug products, employs over 50 research scientists, and has well over 30 approved ANDAs. ECF 44-2 ¶¶1-2. Partnering with KVK allows Argentum to produce several billion tablets and capsules annually. *Id.* ¶2.

Under the agreement, Argentum and KVK combined forces as a "Joint Venture" to:

- "collaborate using their internal resources to develop and commercialize pharmaceutical products, including generic drug products";
- "prepare, prosecute, and defend IPRs and litigation under the Hatch-Waxman Act and other patent-related strategies germane to the availability and costs of pharmaceutical products"

[9] Unless indicated otherwise, all ECF citations in this section (D) refer to CAFC-Appeal 18-2209.

- "share in external costs" by either Argentum or KVK for all aspects of performance under the agreement; and
- "share any financial benefits" from projects under the Joint Venture, including equal profit distribution between Argentum and KVK based on revenues resulting from the activities of the Joint Venture.

ECF 44-3 ¶7.

The activities of the Joint Venture are governed by a formal charter and overseen by a "Joint Development Committee" made up of members from Argentum and KVK. *Id.* ¶9. In other words, the Joint Venture's governance, operations, activities, and financial costs as well as benefits are borne by both Argentum and KVK.

As part of this Joint Venture, Argentum is equally responsible for development activities and seeking regulatory approval. *Id.* ¶¶4-9. Argentum is also the sole party responsible for representing the Joint Venture's interests in any patent-related litigation arising from their joint projects. *Id.* ¶7. That includes challenging patents in administrative proceedings and defending both members of the Joint Venture in patent infringement actions.

KVK is in turn responsible for manufacturing the generic drug products. *Id.* ¶6. Since their Joint Venture, KVK has expanded its facilities by over 200,000 square feet and "intends to use these facilities to manufacture drugs developed through its collaboration with Argentum." ECF 44-2 ¶4. Argentum and KVK have already manufactured two generic drug products from the expanded KVK facilities. *Id.*

The generic version of Gilenya will also be produced and commercialized from these facilities. *Id.* ¶¶4-5; *see also* ECF 44-3 ¶¶9-11; ECF 88-2 ¶¶2-3. All necessary work to commercialize the generic version of Gilenya has been completed. *Id.* In other words, Argentum's generic version of Gilenya is market ready subject to FDA approval.

This is the culmination of shared resources and extensive work between Argentum and KVK. ECF 44-3 ¶¶11, 14. Both partners stand to gain and lose equally from the Joint Venture. *Id.* ¶7. With its investments and expected revenues approaching $50 million annually, Argentum has a concrete and personal stake in bringing its fingolimod to market free of any encumbrances by the '405 patent and threats of litigation by Novartis. *Id.* ¶¶12, 15.

E. The IPR Litigation Between Argentum and Novartis

To remove the '405 patent as a market barrier, Argentum filed an IPR petition challenging its validity. Representing both members of the Joint Venture, Argentum identified KVK as a real party in interest. *See* IPR2017-01550, Paper No. 1 at 21.

1. IPR Proceedings Under the AIA

The Leahy-Smith America Invents Act ("AIA") provides adversarial proceedings for challenging the validity of a patent before the Board. Congress created these proceedings for the purpose of "providing quick and cost-effective alternatives to litigation." H.R. Rep. No. 112-98, pt. 1, at 48 (2011); *see also* S. Rep. No. 110-259 at 20 (2008) (they are "quick, inexpensive, and reliable alternative[s] to district court litigation"). One such proceeding is known as an IPR. *See* 35 U.S.C. §§ 311 *et seq*.

As an alternative to district court litigation, an IPR proceeding is statutorily estopped "if, before the date on which the petition for such a review is filed, *the petitioner or real party in interest* filed a civil action challenging the validity of a claim of the patent." 35 U.S.C. § 315(a)(1) (emphasis added). Similarly, statutory estoppel applies to challenging the same patent in any other litigation once a final decision has been issued in an IPR proceeding. The petitioner and "*the real party in interest or privy of the petitioner*" are both statutorily estopped from challenging the same patent on "any ground that the petitioner raised or reasonably could have raised during that inter partes review." 35 U.S.C. § 315(e)(1)-(2) (emphasis added).

A non-party is a "real party in interest" if it "is a clear beneficiary that has a preexisting, established relationship with the petitioner." *Applications in Internet Time, LLC v. RPX Corp.*, 897 F.3d 1336, 1351 (Fed. Cir. 2018), *cert. denied*, 139 S. Ct. 1366 (2019). Here, KVK is a real party in interest and was identified as such in Argentum's IPR petition and on appeal before the Federal Circuit.

2. The IPR Proceeding

The Board consolidated Argentum's petition with three other petitions against the '405 patent. App. 76a-82a. Novartis opposed the petitions and filed a preliminary response. App. 85a. After considering the respective arguments, the Board instituted trial on all challenged grounds. App. 76a-112a. The Board found that petitioners have shown a reasonable *likelihood that all claims of the '405 patent are unpatentable*. App. 111a.

Novartis submitted further briefing and sought to amend several claims of the '405 patent in an effort to escape an invalidity finding. App. 2a. After a year of litigation, the Board issued a final written decision finding that petitioners have not shown the claims of the '405 patent are unpatentable. App. 12a-75a.

3. The Appeal

On August 16, 2018, Argentum filed a notice of appeal from the Board's final written decision to the Federal Circuit—which had jurisdiction pursuant to 35 U.S.C. §§ 141(c), 319. As with the IPR proceedings, Argentum's appeal was consolidated with several other appeals.

Novartis filed a motion to dismiss Argentum's appeal for purported lack of Article III standing. Novartis's argument was initially predicated on the incorrect notion that Argentum is not at risk of an infringement suit because it is purportedly "a non-practicing entity." CAFC-Appeal 18-2209, ECF 33 at 2.[10] Argentum's opposition established that it is not a non-practicing entity. ECF 44-1.

Novartis then shifted its theory to argue that Argentum could not have standing because its manufacturing partner KVK will be making the purportedly infringing generic product and filing the corresponding ANDA for regulatory approval. ECF 45-1. Novartis never disputed that KVK itself would have Article III standing, but instead sought to differentiate KVK's standing from its equal Joint Venture partner Argentum.

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[10] Unless indicated otherwise, all ECF citations in this section (E) refer to CAFC-Appeal 18-2209.

The Federal Circuit denied Novartis's motion. ECF 47. In its merits briefing, Novartis raised a new argument that Argentum purportedly cannot show standing based on infringing activities without showing "evidence that any scientific work has been done on the ANDA to date." ECF 69 at 39. Argentum proffered additional declarations showing that all scientific work has been done and that its generic version of Gilenya is market ready. ECF 88-2, 88-3.

The appeal proceeded through all stages. At oral argument, the Federal Circuit's panel asked no questions regarding Article III standing. Argentum's counsel presented oral argument on behalf of Argentum and one other remaining appellant.

4. The Federal Circuit's Opinions

After all other appellants settled with Novartis, the Federal Circuit dismissed Argentum's appeal for lack of Article III standing. App. 1a-8a. The court provided three purported bases for its decision.

First, the court held that Argentum does not "bear the risk of any infringement suit" because "any ANDA to be filed 'will be filed by KVK, Argentum's manufacturing and marketing partner.'" App. 4a-6a (citations omitted).

Second, the court disagreed that Argentum "will incur significant economic injury as its investments in developing a generic version of Gilenya and preparing an ANDA would be at risk with a 'looming infringement action by Novartis.'" App. 6a. Differentiating once again between the interests of Argentum and KVK, the court held that Argentum's injury is "entirely speculative and *not personal to Argentum*." *Id.* (emphasis added).

Third, the court "rejected invocation of the [AIA's statutory] estoppel provision as a sufficient basis for standing." App. 8a. Argentum filed a petition for *en banc* rehearing, which was denied. App. 9a-10a.

REASONS FOR GRANTING THE WRIT

The Federal Circuit's decision erected a barrier to appeal that demands far more than the constitutional requirements under Article III. At its core, the Federal Circuit's decision constructs a heightened standard for standing in patent cases that involve pharmaceutical products developed by joint ventures. The only injuries recognized by the Federal Circuit's decision as sufficient to ground Article III standing are those borne by either (1) the manufactuing partner in the joint venture, or (2) the partner submitting an application for FDA approval. App. 1a-8a. In other words, members of the joint venture with material and equal financial interests are precluded from redress simply because they occupy a non-manufacturing role in the partnership.

This new standing construct, purportedly grounded on the Constitution, is not only erroneous under prevailing law, it also has enormous ramifications for joint ventures in the pharmaceutical industry. Stating that joint ventures are common in the pharmaceutical industry is an understament. *Supra* n.7. In recent years, joint ventures have become the norm—and for good reason. They allow companies to combine their respective resources and expertise in research and development, clinical trials, regulatory approval, manufacturing, marketing, and defending joint interests through legal proceedings. Each element is an important contribution that comes with significant investment.

That is the case here. Argentum has been in a joint venture with its manufacturing partner KVK for several years. As part of this Joint Venture, Argentum is equally responsible for development activities and seeking regulatory approval. CAFC-Appeal 18-2209, ECF 44-3 ¶¶4-9. Argentum is also the sole party responsible for representing the Joint Venture's interests in any patent-related litigation. *Id.* ¶7.

Even though the joint venture is a fairly young one, their efforts have already resulted in several successful product launches. *Supra* §D. To launch a generic alternative to Gilenya, however, Argentum and KVK will have to seek FDA approval first. Under the framework of the Hatch-Waxman Act, Argentum and KVK will then be subject to a patent infringement suit by Novartis as soon as an ANDA is filed. *Supra* §B.

Novartis can and will file suit against Argentum. Novartis has, in fact, done so against all competitors that have filed an ANDA with the FDA for a generic version of Gilenya. *Id*. To be sure, Novartis can file suit both against the actual ANDA applicant for direct infringement *and* against any non-filer engaged in joint development efforts for indirect infringement. *See*, *e.g.*, *Forest Labs.*, 501 F.3d at 1272 (enjoining non-manufacturing business partner because "the plan to manufacture, import, market, and sell the [] products described in the ANDA was undoubtedly a cooperative venture" such that the non-manufacturing partner "Cipla has therefore actively induced the acts of Ivax that will constitute direct infringement upon approval of the ANDA"). Argentum is, therefore, subject to suit for either direct or indirect infringement.

In other words, it is a virtual certainty that Novartis will sue Argentum as soon as an ANDA is filed with the FDA regardless of whether it is filed by KVK or Argentum. By not suing Argentum, Novartis would not only diverge from a long-standing track record of blocking competition in this field, but would also forego an automatic market exclusivity. *See* 21 U.S.C. § 355(j)(5)(B)(iii). Simply put, Novartis has every incentive to bring suit.

Moreover, the ostensible constitutional bar to appeal erected by the Federal Circuit fundamentally undermines the careful structure established by Congress to facilitate the introduction of generic drugs, and allow for challenges to the validity of patents that may be unlawfully obstructing lawful competition. The ANDA process works hand in hand with the IPR process, which offers the potential manufacturer of a generic drug the opportunity to challenge the validity of a patent that may be standing in its way. To deprive the potential generic manufacturer—ready, willing and able to introduce the competitive product if the existing patent is found invalid—of the right to appeal an adverse Board decision fundamentally undermines the utility of this mechanism as a means of gaining market entry.

Yet, the Federal Circuit has denied standing to Argentum simply because it is not the manufacturing partner in its joint venture with KVK. This categorical denial of standing is inconsistent with the Constitution and this Court's precedent. The same is true for the Federal Circuit's categorical denial of standing based on statutory estoppel that arises from an IPR proceeding. This Court should reverse the Federal Circuit's decision and grant Argentum the redress to which it is entitled.

I. The Federal Circuit Erroneously Held That Argentum Lacks Article III Standing Simply Because Its Joint Venture Partner Manufactures the Generic Drug and Will Apply for FDA Approval

Standing under Article III requires an appellant to have "(1) suffered an injury in fact, (2) that is fairly traceable to the challenged [action], and (3) that is likely to be redressed by a favorable judicial decision." *Spokeo, Inc. v. Robins*, 136 S. Ct. 1540, 1547 (2016). The only element at issue here is the requirement of an injury in fact (App. 1a-8a)—the "[f]irst and foremost" of the three constitutional requirements for standing. *Steel Co. v. Citizens for a Better Env't*, 523 U.S. 83, 103 (1998).

This Court has also consistently explained that, "'the gist of the question of standing' is whether petitioners have '*such a personal stake in the outcome of the controversy as to assure that concrete adverseness* which sharpens the presentation of issues upon which the court so largely depends for illumination.'" *Massachusetts*, 549 U.S. at 517 (citations omitted) (emphasis added). In other words, the injury-in-fact requirement is intended to "distinguish a person with a direct stake in the outcome of a litigation—*even though small*—from a person with a mere interest in the problem." *SCRAP*, 412 U.S. at 689 n.14 (emphasis added); *see also Lujan v. Defs. of Wildlife*, 504 U.S. 555, 582 (1992) (Stevens, J., concurring) ("Indeed, this Court has often held that [small] injuries to such interests are sufficient to confer standing, and the Court reiterates that holding today.") (citing *SCRAP*, 412 U.S. at 686-87).

To be sure, the injury must be "a concrete and particularized, actual or imminent invasion of a legally protected interest." *Lujan*, 504 U.S. at 112. "For an injury to be 'particularized,' it 'must affect the plaintiff in a personal and individual way.'" *Spokeo*, 136 S. Ct. at 1548. An injury is concrete when it is "real and not abstract." *Id.* (citations omitted). "Concrete is not, however, necessarily synonymous with 'tangible.'" *Id.* at 1549.

Here, Argentum has met all elements of an injury in fact. After years of investment into the Joint Venture with KVK, Argentum has a personal and concrete stake in obtaining a judgment of invalidity against Novartis's '405 patent. Absent redress on appeal, Argentum will be blocked from introducing a generic fingolimod alternative to Novartis's Gilenya. As a result, Argentum will continue to lose both the benefit of its investment as well as projected revenues.

This is precisely the type of particularized and concrete injury that confers Article III standing under this Court's precedent. *See*, *e.g.*, *Monsanto Co. v. Geertson Seed Farms*, 561 U.S. 139, 149-50 (2010) (holding petitioners had standing because they were unable to sell or license their products until receiving agency approval); *see also Asarco Inc. v. Kadish*, 490 U.S. 605, 617-18 (1989) (holding petitioners had standing because they could not exploit mineral leases absent redress on appeal). If Argentum prevails on appeal, the '405 patent will no longer constitute a barrier to Argentum's market-ready generic version of Gilenya. Without available redress on appeal, however, Argentum will continue to be harmed by being deprived from realizing the benefits of its four-year long investment.

Notwithstanding Argentum's financial and practical stake in the outcome of the dispute over the '405 patent, the Federal Circuit drew a sharp line between the standing of Argentum and its manufacturing partner KVK. There is no dispute that KVK would have standing. Nor is there any dispute that Argentum represents the legal interests of the Joint Venture. Yet, the Federal Circuit held that the Constitution itself bars Argentum's appeal.

First, the Federal Circuit failed to recognize that multiple parties can have an economic interest in the success of a generic drug, crediting only the entity actually producing the generic drug product as having an economic injury as a result of Novartis's monopoly. This Court has, however, repeatedly held that financial or economic interests are "legally protected right[s]" for standing purposes. *See*, *e.g.*, *Vermont Agency of Nat. Res. v. U.S. ex rel. Stevens,* 529 U.S. 765, 772-77 (2000); *Clinton v. City of New York*, 524 U.S. 417, 432 (1998); *Sierra Club v. Morton*, 405 U.S. 727, 733-34 (1972). There can be no reasonable dispute that Argentum has economic interests that turn on the outcome of this case.

The Federal Circuit also mistakenly held that Argentum does not have standing because its manufacturing partner KVK will likely be named as the ANDA filer for the generic drug. In other words, despite Argentum having a clear stake of its own in the dispute over the validity of Novartis's patent, the Federal Circuit arbitrarily held that only the entity named as the ANDA filer will have a cognizable injury in fact under Article III. This ignores the elementary fact that Argentum is also subject to suit for indirect infringement by inducing KVK to file an ANDA.

Second, the Federal Circuit incorrectly rejects statutory estoppel as a basis for standing. Litigation estoppel is often recognized as an injury in fact for Article III standing. Here, the injury is particularly extensive because Argentum, its real parties in interest, and privies are statutorily estopped from challenging the '405 patent in any other litigation on the same grounds or any grounds that reasonably could have been raised.

A. Argentum Has Suffered an Economic Injury from Novartis's Market Barrier

The Federal Circuit's decision ignores that Argentum is suffering a legal injury arising under the statutory framework of the Hatch-Waxman Act. "Ordinarily, a potential competitor in other fields is legally free to market its product in the face of an adversely-held patent. In contrast, under the Hatch–Waxman Act an ANDA filer … is not legally free to enter the market because federal statutes prohibit it." *Teva Pharm. USA, Inc. v. Novartis Pharm. Corp.*, 482 F.3d 1330, 1345 (Fed. Cir. 2007).

Just as in *Teva*, Argentum "suffers a direct legal injury from … Novartis' listing of [its] patents in the Orange Book …." *Id.* Novartis's Orange Book listing "represents that 'a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale' of generic [drugs] covered by the claims of its listed . . . patents." *Id.* at 1341 (citing 21 U.S.C. § 355(b)(1)). This is "a circumstance to be considered in determining whether a justiciable controversy exists under the totality of the circumstances." *Id.* at 1341-42.

Thus, when properly considered, Argentum is directly injured by the continued enforceability of the '405 patent listed in the Orange Book as covering Gilenya. That Novartis will sue Argentum and KVK for infringement upon filing of an ANDA is a virtual certainty. To date, Novartis has refused to confirm that it will not sue Argentum. And Novartis has sued *every single competitor* that filed an ANDA for a generic version of Gilenya. There is no dispute as to these facts.

Here, Argentum opted to file an IPR petition to preemptively challenge the '405 patent before filing an ANDA and being exposed to an infringement suit. But that process, and appeal from that process, cannot be treated differently than bringing a declaratory judgment action seeking to invalidate the '405 patent. The Hatch-Waxman Act, in fact, provides authority for generic competitors to "obtain patent certainty" by bringing an action for declaratory judgment of invalidity. 21 U.S.C. § 355(j)(5)(C). Congress created IPR proceedings specifically to provide an alternative to such expensive district court litigation. *See* H.R. Rep. No. 112-98(I), at 48 (IPRs are a "quick and cost effective alternative to litigation"); *id.*, at 46-47 ("The Act converts inter partes reexamination from an examinational to an adjudicative proceeding"); *see also* S. Rep. No. 110-259, at 20 (2008). Setting a higher standard for Article III standing in appeals from IPR proceedings would effectively undermine Congress's intent to create an alternative venue to litigate patent validity.

Just as in the ordinary Hatch-Waxman framework, Argentum's success on appeal and a finding of invalidity will lift the market barrier imposed by Novartis's listing of the '405 patent in the

Orange Book. In contrast, the Board's decision maintains the status quo, under which Argentum is legally barred from entering the market. Absent recourse on appeal, Argentum will be required to wait another seven years before it can legally enter the market, incurring significant losses for a generic product that is ready to launch. This Court has recognized standing under analogous circumstances. *See*, *e.g.*, *Monsanto*, 561 U.S. at 149-50.

B. The Federal Circuit's Preclusion of Standing for a Non-Manufacturing Partner of a Joint Venture Is Improper

Focusing on the fact that KVK would be the manufacturing arm in this joint venture, the Federal Circuit incorrectly held that Argentum's economic injury is "entirely speculative and *not personal to Argentum*." App. 6a (emphasis added). The Federal Circuit's decision is inconsistent with constitutional standards and the realities of the pharmaceutical industry.

First, the Federal Circuit's decision is contrary to well-established principles of relationship standing. Courts have long held that standing is appropriate where "the interests of parties and nonparties are so intermingled that all rights and interests should be considered together." Wright & Miller, 13A Fed. Prac. & Proc. Juris. § 3531.9.3 (3d ed.); *see also Tyndale House Publishers, Inc. v. Sebelius*, 904 F. Supp. 2d 106, 118 (D.D.C. 2012) (finding standing and holding "[r]egarding the 'close relationship' requirement, the plaintiff and third party have a 'congruence of interests' such that the plaintiff will be a 'motivated, effective advocate for the [third party's] rights.'").

This Court has similarly held that such circumstances are present when "the party asserting the right has a 'close' relationship with the person who possesses the right," and "there is a 'hindrance' to the possessor's ability to protect his own interests." *Kowalski v. Tesmer*, 543 U.S. 125, 130 (2004); *see also Sessions v. Morales-Santana*, 137 S. Ct. 1678, 1683 (2017) (same). These elements of relationship or third-party standing are readily met in this case. Argentum and KVK are equal partners in a Joint Venture directed to the development and commercialization of generic drug products, including a generic version of Novartis's Gilenya drug. The Joint Venture's governance, operations, activities, and financial costs as well as benefits are borne equally by Argentum and KVK. That is, the economic interests of Argentum and KVK are directly linked and intertwined under the Joint Venture. *Supra* §D.

Indeed, under the terms of the agreement, Argentum is also the sole party responsible for representing the Joint Venture's interests in patent-related litigation. *Id*. Argentum has, therefore, the right to bring the claims of KVK and defend the interests of KVK with respect to any projects under the Joint Venture. And because their agreement only provides Argentum the rights to litigate IPR proceedings, KVK has a significant contractual obstacle to assert its equal share of rights in such litigation. In other words, Argentum properly represents the rights and injuries of both entities such that it has relationship or third-party standing. *See Sessions*, 137 S. Ct. at 1683 (finding third-party standing); *see also Liberty Mut. Ins. Co. v. Travelers Indem. Co.*, 78 F.3d 639, 642 (D.C. Cir. 1996) (finding relationship standing).

By distinguishing two intricately intertwined business partners in a Joint Venture, the Federal Circuit's decision is directly at odds with principles of relationship and third-party standing. The Federal Circuit's artificial distinction for Article III standing between Argentum as a non-manufacturing partner and KVK as a manufacturing partner should be rejected accordingly.[11]

C. The Federal Circuit Improperly Rejected Argentum's Economic Injury for a Lack of Accounting

The Federal Circuit's decision improperly creates a requirement to account for investments and losses with specific evidence to show an economic injury. In particular, the Federal Circuit found that "Argentum has not provided sufficient evidence to establish an injury in fact through economic harm" in large part because "its assertion that it will suffer at least $10–50 million per year in lost profits once the FDA grants provisional approval to the ANDA is both conclusory and speculative." App. 6a-7a. The court also found that Argentum "failed to provide sufficient evidence that it invested in KVK's generic Gilenya product or ANDA" because "it stated only in generalities that … '[e]xternal costs are shared by Argentum and KVK on an opportunity-by-opportunity basis.'" App. 7a. The court reached this conclusion despite sworn declarations from Argentum and KVK.

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[11] This Court has also found Article III standing for subsidiaries that represent the legal rights and injuries of a parent company and vice versa. *See*, *e.g.*, *Franchise Tax Bd. of Cal. v. Alcan Aluminium Ltd.*, 493 U.S. 331, 336 (1990) (holding that two foreign parent companies of U.S. subsidiaries had Article III standing to challenge U.S. tax laws affecting the subsidiaries).

In other words, the Federal Circuit requires a more specific accounting, but this requirement of specificity has no place in the Article III inquiry. This Court has repeatedly held that financial or economic interests are "legally protected interests" for standing purposes. *See Vermont,* 529 U.S. at 772-77; *Clinton*, 524 U.S. at 432; *Sierra Club*, 405 U.S. at 733-34. A financial loss, or likely financial loss, is sufficient, and no specific accounting is required. The amount is, in fact, immaterial. *See SCRAP*, 412 U.S. at 689 n.14 ("We have allowed important interests to be vindicated by plaintiffs with no more at stake in the outcome of an action than a fraction of a vote …").

Indeed, applying this Court's precedent, other circuits "have explained that where a plaintiff alleges financial harm, standing 'is often assumed without discussion.'" *Cottrell v. Alcon Labs.*, 874 F.3d 154, 163 (3d Cir. 2017) (quoting *Danvers Motor Co. v. Ford Motor Co.*, 432 F.3d 286, 293 (3d Cir. 2005)); *see also Carter v. HealthPort Techs., LLC*, 822 F.3d 47, 55 (2d Cir. 2016) ("Any monetary loss suffered by the plaintiff satisfies [the injury-in-fact] element; '[e]ven a small financial loss' suffices.") (citations omitted).

There is no dispute that Argentum has challenged the validity of Novartis's '405 patent precisely because it has a financial interest in invalidating the patent in order to introduce a generic alternative to Novartis's blockbuster drug Gilenya. Argentum's financial interest in invalidating that patent is thus reflected in the capital it has already invested to develop the generic drug, and in the expectation that if it can introduce that generic, it will receive substantial revenue. *Cottrell*, 874 F.3d at 168 ("Plaintiffs' claimed financial harm has already occurred, it is not merely possible, or even probable.");

see also Lewert v. P.F. Chang's China Bistro, Inc., 819 F.3d 963, 966-67 (7th Cir. 2016); *Maya v. Centex Corp.*, 658 F.3d 1060, 1069 (9th Cir. 2011) ("Allegedly, plaintiffs spent money that, absent defendants' actions, they would not have spent. … This is a quintessential injury-in-fact.").

The sworn declarations provided to the Federal Circuit are more than sufficient to show that injury. Based on the evidence submitted, Argentum's Joint Venture with its manufacturing partner KVK have expressly agreed to: (1) "collaborate using their internal resources *to develop and commercialize pharmaceutical products*, including generic drug products"; (2) "prepare, prosecute and defend IPRs and litigation under the Hatch-Waxman Act …"; (3) "*share in external costs*"; and (4) "*share in any financial benefits*." CAFC-Appeal 18-2209, ECF 44-3 ¶7. As a result of the continued enforceability of the '405 patent, Argentum is and continues to be deprived of expected revenues from its Joint Venture with KVK. That must be enough for Article III standing.[12]

D. The Federal Circuit Erred by Creating A Rule That Distinguishes Standing on Appeal Between ANDA and Non-ANDA Filers

The Federal Circuit erroneously held that Argentum lacks Article III standing because "[n]o ANDA has been filed here, and Argentum has not

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[12] The Federal Circuit's decision also effectively creates a split in the exclusive appellate court for patent cases. In the context of patent pools and expected revenues from licensing arrangements, the Federal Circuit has found Article III standing. *See*, *e.g.*, *Samsung Elecs. Co. v. Infobridge Pte. Ltd.*, 929 F.3d 1363, 1368 (Fed. Cir. 2019).

provided evidence showing that it would bear the risk of any infringement suit." App. 6a. In particular, the Federal Circuit held that Argentum cannot have standing here because "any ANDA to be filed 'will be filed by KVK, Argentum's manufacturing partner.'" App. 4a-5a. By distinguishing between an ANDA filer and its joint venture partner, the Federal Circuit ignores the threat of indirect infringement allegations.

It is certainly true that filing an ANDA exposes KVK to *direct* infringement charges under 35 U.S.C. § 271(e)(2)(A). The planned ANDA submission, however, has been a culmination of a Joint Venture between Argentum and KVK. Argentum has been working directly *with* KVK to develop the fingolimod generic, and the two entities have been working together to file the ANDA. *Supra* §D. The Joint Venture efforts, therefore, also give rise to an imminent suit by Novartis against Argentum for *indirect* infringement under 35 U.S.C. § 271(b) predicated on KVK's ANDA filing. *See Forest Labs.*, 501 F.3d at 1272 (regarding a joint venture between Cipla and Ivax, where only one party was the ANDA filer, finding the inducing partner also liable for infringement and subject to the injunction, stating "They are partners. Cipla would be contributing to the infringement by Ivax, so the injunction should cover both partners."). Given Novartis's pattern of enforcing the '405 patent and seeking injunctions against *all competitors and related entities*, a suit against Argentum and KVK is inevitable. *Supra* §C. Argentum's immediate risk of suit for indirect infringement by Novartis constitutes an injury-in-fact sufficient for Article III standing.

II. The Federal Circuit Improperly Rejects Injury in Fact Based on Statutory IPR Estoppel

The Federal Circuit's rejection of statutory estoppel as a basis for the injury-in-fact requirement is contrary to the AIA, real-world consequences of a final written decision in an IPR proceeding, and precedent on other forms of estoppel forming the basis for standing. The Federal Circuit's rejection is predicated on the notion that a party must show first that it will be subject to an infringement suit such that statutory estoppel applies. While statutory estoppel may apply in the context of an infringement suit, the Federal Circuit's rationale ignores that it also automatically applies to *any further proceedings before the Board*. 35 U.S.C. § 315(e)(1). The statutory estoppel has, therefore, already attached regardless of whether Argentum is sued for infringement in district court. It has, in fact, even attached to KVK and other real parties in interest as well as privies. *Id.*

Under similar circumstances, circuits have held that litigation estoppel can indeed form the basis for Article III standing on appeal. In *AT&T*, for instance, the District of Columbia held that standing was warranted in view of already operative collateral estoppel effects. *AT&T Corp. v. F.C.C.*, 317 F.3d 227, 238 (D.C. Cir. 2003). Similarly, Argentum is already statutorily estopped from raising challenges to the '405 patent in any future proceedings on the same grounds or grounds that reasonably could have been raised. Based on Novartis's litigation, it is all but a certainty that the parties will have future litigation on the '405 patent—unless, of course, the Board's decision is reversed and the patent is found invalid.

CONCLUSION

For at least the foregoing reasons, the petition should be granted.

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APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-2273

ARGENTUM PHARMACEUTICALS LLC,

Appellant

v.

NOVARTIS PHARMACEUTICALS CORPORATION,

Appellee

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-00854, IPR2017-01550, IPR2017-01929, IPR2017-01946.

Decided: April 23, 2020

TERESA STANEK REA, Crowell & Moring, LLP, Washington, DC, argued for appellant. Also represented by DEBORAH YELLIN.

JANE M. LOVE, Gibson, Dunn & Crutcher LLP, New York, NY, argued for appellee. Also represented by ROBERT TRENCHARD.

Before LOURIE, MOORE, and REYNA, *Circuit Judges.*

MOORE, *Circuit Judge*.

On February 3, 2017, Apotex Inc. and Apotex Corp. (collectively, Apotex) filed a petition for *inter partes* review of Novartis Pharmaceuticals Corporation's U.S. Patent No. 9,187,405. The Board instituted proceedings on July 18, 2017, and granted Sun Pharmaceutical Industries, Ltd., Sun Pharmaceutical Industries, Inc., and Sun Pharma Global FZE's (collectively, Sun); Teva Pharmaceuticals USA, Inc. and Actavis Elizabeth LLC's; and Argentum Pharmaceuticals LLC's requests for joinder under 35 U.S.C. § 315(c). After institution, Patent Owner, Novartis, filed a contingent motion to amend. On July 11, 2018, the Board concluded that Apotex, Sun, Teva, Actavis, and Argentum (collectively, Petitioners) had not demonstrated unpatentability of the claims and denied the motion to amend as moot. Petitioners appealed the Board's findings. During the appeal process, all Petitioners other than Argentum settled their respective appeal with Novartis.[1]

On August 29, 2018, before opening briefs had been filed, Novartis filed a motion to dismiss Argentum's appeal for lack of standing. Argentum opposed the motion on September 10, 2018, and included declarations of Jeffrey Gardner, Argentum's CEO, and Anthony Tabasso, President and CEO of KVK-Tech, Inc., Argentum's manufacturing and marketing partner. We directed Argentum and Novartis to address Argentum's standing in their briefs, which they did. Initially, Argentum argued that we need not reach the

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[1] Teva, Actavis, and Sun settled before argument and Appeal Nos. 18-2260 (Teva and Actavis) and 18-2230 (Sun) were dismissed, respectively. Apotex settled after argument and Appeal No. 18-2209 was dismissed.

issue of its standing because only one party must have standing for an action to proceed in an Article III Court, and "the other seven appellants undisputedly have standing." Appellant's Br. viii. Following the settlement of all parties other than Argentum, Novartis submitted a notice of supplemental authority under Federal Rule of Appellate Procedure 28(j) stating that "now that Argentum is the only appellant, Article III standing has become a threshold issue" and that we must assess our "jurisdiction under Article III of the Constitution before addressing the merits of the case." D.I. 131 at 2 (citing *Phigenix, Inc. v. Immunogen, Inc.*, 845 F.3d 1168, 1171 (Fed. Cir. 2017)).[2]

Because we hold that Argentum lacks Article III standing, we dismiss the appeal and do not reach the merits of the Board's ruling on the claims of the '405 patent.

DISCUSSION

"Although we have jurisdiction to review final decisions of the Board under 28 U.S.C. § 1295(a)(4)(A), an appellant must meet 'the irreducible constitutional minimum of standing.'" *Amerigen Pharm. Ltd. v. UCB Pharma GmBH*, 913 F.3d 1076, 1082 (Fed. Cir. 2019) (quoting *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560 (1992)). This holds true "even if there is no such requirement in order to appear before the administrative agency being reviewed." *Id.* (citing *Consumer Watchdog v. Wis. Alumni Research Found.*, 753 F.3d 1258, 1261 (Fed. Cir. 2014)). To prove standing, Argentum bears the burden of showing that it has "(1) suffered an injury in fact, (2) that is fairly traceable to

[2] All citations to the court's docket are to *Apotex Inc. v. Novartis Pharmaceuticals Corp.*, Appeal No. 2018-2209.

the challenged conduct of the defendant, and (3) that is likely to be redressed by a favorable judicial decision." *Spokeo, Inc. v. Robins*, 136 S. Ct. 1540, 1547 (2016). Argentum must "'supply the requisite proof of an injury in fact when it seeks review of an agency's final action in a federal court,' by creating a necessary record in this court, if the record before the Board does not establish standing." *JTEKT Corp. v. GKN Automotive LTD.*, 898 F.3d 1217, 1220 (Fed Cir. 2018) (quoting *Phigenix, Inc.*, 845 F.3d at 1171–72). "To establish injury in fact, a[n appellant] must show that he or she suffered 'an invasion of a legally protected interest' that is 'concrete and particularized' and 'actual or imminent, not conjectural or hypothetical.'" *Spokeo*, 136 S. Ct. at 1548 (quoting *Lujan*, 504 U.S. at 560). An injury is particularized if it "affect[s] the [appellant] in a personal and individual way." *Lujan*, 504 U.S. at 560 n.1.

Argentum argues that it demonstrated at least three concrete injuries in fact. First, Argentum argues that without an opportunity to seek this Court's redress, it faces a real and imminent threat of litigation as it jointly pursues, along with its partner KVK-Tech, Inc., a generic version of Novartis' Gilenya® product for which they are in the process of filing an ANDA. It argues that given that Novartis already sued multiple generic companies to protect Gilenya®, "it is virtually certain that Novartis will sue Argentum and KVK," which is "far from conjectural" and "constitutes an imminent injury for purposes of standing." Appellant's Reply Br. 28.

Novartis argues that any ANDA to be filed for a generic version of Gilenya® "will be filed by KVK, Argentum's manufacturing and marketing partner" (*see* D.I. 44-3 (Gardner Dec.) ¶ 11), and thus KVK, not

Argentum is at risk of being sued. And even if the litigation were personal to Argentum, it would not confer standing because it is merely conjectural. Appellee's Br. 39 (citing *AVX Corp. v. Presidio Components, Inc.*, 923 F.3d 1357, 1367 (Fed. Cir. 2019) (concluding that appellant did not "sufficiently allege[] current or nonspeculative activities of its own that arguably fall within the scope of the upheld claims" to amount to harm to it)). It argues that there is no evidence of "concrete plans for future activity that creates a substantial risk of future infringement or [will] likely cause the patentee to assert a claim of infringement." Appellee's Br. 39 (quoting *JTEKT Corp.*, 898 F.3d at 1221).

Citing our decision in *Altaire Pharmaceuticals, Inc. v. Paragon Bioteck, Inc.*, Argentum responds that "showing a concrete injury-in-fact does not necessitate an already-filed ANDA." Appellant's Reply Br. 27 (citing 889 F.3d 1274, 1282–83 (Fed. Cir. 2018), *remand order modified by stipulation*, 738 F. App'x 1017 (Fed. Cir. 2018)). Argentum's contentions are unavailing. In *Altaire*, Altaire was the company which intended to file an ANDA and would be at imminent risk of being sued. We held that Altaire had standing because the threat of litigation was "real" and "imminent" and Altaire was affected "in a personal and individual way." *See Altaire*, 889 F.3d at 1282–83; *see also General Electric Co. v. United Techs. Corp.*, 928 F.3d 1349, 1353–54 (Fed. Cir. 2019) (determining there was no "concrete and imminent injury to GE," and that GE asserted "only speculative harm"). Unlike in *Altaire*, according to Mr. Gardner, any ANDA to be filed "will be filed by KVK, Argentum's manufacturing and marketing partner." D.I. 44-3 (Gardner Dec.) ¶ 11. And Mr. Gardner stated that "Novartis will inevitably sue Argentum's manufacturing and marketing

partner KVK for patent infringement upon KVK's filing an ANDA for a generic version of GILENYA® . . . ." *Id.* ¶ 14; *see also id.* ¶ 15. No ANDA has been filed here, and Argentum has not provided evidence showing that it would bear the risk of any infringement suit or anything related to its involvement in the ANDA process beyond generic statements. *See, e.g.*, *id.* ¶ 11.

Second, Argentum argues that it will incur significant economic injury as its investments in developing a generic version of Gilenya® and preparing an ANDA would be at risk with a "looming infringement action by Novartis." Appellant's Br. 49. Specifically, it asserts that it will suffer at least $10–50 million per year in lost profits once the FDA grants provisional approval to the ANDA. Appellant's Reply Br. 28–29 (citing D.I. 44–3 (Gardner Dec.) ¶ 12). Novartis argues that Argentum's alleged "economic injury," which is entirely speculative and not personal to Argentum, does not suffice to establish injury in fact because it is not concrete or particularized.

Argentum has not provided sufficient evidence to establish an injury in fact through economic harm. *General Electric*, 928 F.3d at 1354–55 (rejecting GE's economic loss allegation of increased research and development costs where GE failed to provide details such as "an accounting for the additional research and development costs expended" or "evidence that GE actually designed a [product covered by the upheld claims]"). Argentum's or KVK's purported investments include KVK's renovation of manufacturing facilities that "KVK intends to use . . . to manufacture drugs developed through its joint collaboration with Argentum." D.I. 44–2 (Tabasso Dec) ¶ 4. However, Mr. Tabasso specifically states that "[t]he generic version of PAZEO®," a drug unrelated to the patent at issue,

"will be produced in KVK's new manufacturing space which will come online in the next year." *Id.* And Mr. Gardner declared that "Argentum has partnered with KVK . . . to develop generic versions of multiple generic drug products" without providing evidence specific to a generic Gilenya® product. *See* D.I. 44-3 (Gardner Dec.) ¶ 4; *see also id.* ¶ 6.

Argentum likewise has failed to provide sufficient evidence that it invested in KVK's generic Gilenya® product or ANDA. It stated only in generalities that both "KVK and Argentum have been diligent in working toward FDA submission of the ANDA" and that "Argentum has invested significant man-power and resources to the endeavor." D.I. 44-3 (Gardner Dec.) ¶ 11; *see also id.* ¶ 8 (stating that "[e]xternal costs are shared by Argentum and KVK on an opportunity-by-opportunity basis"); *id.* ¶ 9 (generally stating that "[a] number of products are currently being jointly developed by Argentum and KVK" but listing an unrelated generic product). And its assertion that it will suffer at least $10–50 million per year in lost profits once the FDA grants provisional approval to the ANDA is both conclusory and speculative. *See* Appellant's Reply Br. 28 (citing D.I. 44-3 (Gardner Dec.) ¶ 12). This cannot suffice to establish an injury in fact that is "'concrete and particularized' and 'actual or imminent, not conjectural or hypothetical.'" *Spokeo*, 136 S. Ct. at 1548 (quoting *Lujan*, 504 U.S. at 560).

Third, Argentum argues that absent relief from this court, Argentum would be estopped under 35 U.S.C. § 315(e) from raising the patentability and validity issues in a future infringement action. Novartis argues that Argentum has not shown that it will be harmed by estoppel where it has not established there is risk of an infringement suit. Appellee's Br. 42–43

(citing *JTEKT Corp.*, 898 F.3d at 1221). As the court stated in *AVX*, "we have already rejected invocation of the estoppel provision as a sufficient basis for standing." 923 F.3d at 1362–63 (citing *Phigenix*, 845 F.3d at 1175–76 ("§ 315(e) do[es] not constitute an injury in fact when, as here, the appellant is not engaged in any activity that would give rise to a possible infringement suit.") (alteration in original) (internal quotations omitted)); *see also JTEKT*, 898 F.3d at 1221; *General Electric*, 928 F.3d at 1355. Accordingly, we hold that Argentum has failed to prove that it has suffered an injury in fact necessary to establish standing.

CONCLUSION

We have considered the parties' remaining arguments and do not find them persuasive. Because Argentum failed to establish an injury sufficient to confer Article III standing, we dismiss the appeal.

DISMISSED

COSTS

Costs to Novartis.

APPENDIX B

NOTE: This order is nonprecedential

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-2273

ARGENTUM PHARMACEUTICALS LLC,

Appellant

v.

NOVARTIS PHARMACEUTICALS CORPORATION,

Appellee

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-00854, IPR2017-01550, IPR2017-01929, IPR2017-01946.

ON PETITION FOR REHEARING EN BANC

Before PROST, *Chief Judge*,

NEWMAN, LOURIE, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, HUGHES, and STOLL, *Circuit Judges*

PER CURIAM.

ORDER

Appellant Argentum Pharmaceuticals LLC filed a petition for rehearing en banc. The petition was first referred as a petition for rehearing to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on July 16, 2020.

FOR THE COURT

July 9, 2020
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-2273

ARGENTUM PHARMACEUTICALS LLC,

Appellant

v.

NOVARTIS PHARMACEUTICALS CORPORATION,

Appellee

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-00854, IPR2017-01550, IPR2017-01946, IPR2017-01929.

JUDGMENT

THIS CAUSE having been considered, it is

ORDERED AND ADJUDGED:

DISMISSED

ENTERED BY ORDER OF THE COURT

April 23, 2020

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX D

Trials@uspto.gov Paper: 109
Tel: 571-272-7822 Entered: July 11, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case IPR2017-00854[1]
Patent US 9,187,405 B2

APOTEX INC. and APOTEX CORP., ARGENTUM PHARMACEUTICALS LLC, ACTAVIS ELIZABETH LLC, TEVA PHARMACEUTICALS USA, INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., SUN PHARMACEUTICAL INDUSTRIES, INC., and SUN PHARMA GLOBAL FZE,

Petitioners,

v.

NOVARTIS AG,

Patent Owner.

Before CHRISTOPHER M. KAISER, ROBERT A. POLLOCK, and KRISTI L. R. SAWERT,[2]
Administrative Patent Judges.

POLLOCK, *Administrative Patent Judge*.

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[1] Cases IPR2017-01550, IPR2017-01946, and IPR2017-01929 have been joined with this proceeding.

[2] Replacing Judge Lora M. Green, who has left the Board.

FINAL WRITTEN DECISION

Claims 1–6 Not Shown to Be Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–6 of U.S. Patent No. US 9,187,405 B2 (Ex. 1001, "the '405 patent"). We have jurisdiction under 35 U.S.C. § 6.

For the reasons that follow, we determine that Petitioners have failed to show, by a preponderance of the evidence, that claims 1–6 of the '405 patent are unpatentable.

A. Procedural History

Apotex Inc. and Apotex Corp. ("Apotex") filed a Petition requesting an *inter partes* review of claims 1–6 the '405 patent. Paper 2 ("Pet."). Novartis AG[3] ("Novartis"), filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). We instituted *inter partes* review of each of the challenged claims. Paper 11, 27 ("Dec.").

Three parties filed Petitions substantially the same as Apotex's Petition along with requests for joinder: 1) Argentum Pharmaceuticals LLC ("Argentum") (IPR 2017-01550, Papers 1 and 3); 2) Actavis Elizabeth LLC and Teva Pharmaceuticals USA, Inc. (collectively, "Teva") (IPR2017-01946, Papers 2 and 3); and 3) Sun

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[3] According to Patent Owner, "Novartis AG has assigned its rights in U.S. Patent 9,187,405 to Novartis Pharmaceuticals Corporation (*see* Assignment at Reel 043314/Frame 0800). The real party in interest is Novartis Pharmaceuticals Corporation. Novartis AG and other Novartis subsidiaries may also have an interest." Paper 22.

Pharmaceutical Industries, Ltd., Sun Pharmaceutical Industries, Inc., and Sun Pharma Global FZE (collectively, "Sun") (IPR2017-01929, Papers 2 and 3). We granted each Petition and associated requests for joinder to IPR2017-00854. *See* IPR2017-01550, Paper 10; IPR2017-01946, Paper 9; IPR2017-01929, Paper 7, respectively. Because our grants of joinder were conditioned on Apotex taking the lead role in the joined proceeding, we refer to Apotex, Argentum, Teva, and Sun, collectively, as "Petitioners."

After institution of trial and our grants of joinder, Patent Owner filed a Patent Owner Response (Paper 26, "PO Resp."); Petitioners filed a responsive Reply (Paper 49, "Pet. Reply"); and Patent Owner filed an authorized Sur-Reply (Paper 63, "PO Sur-Reply").

Patent Owner also filed a Corrected Contingent Motion to Amend. Paper 61. Petitioners opposed (Paper 51), and Patent Owner responded with a Reply in support of its motion (Paper 64).

Petitioners rely on the declaration of Dr. Barbara S. Giesser (Ex. 1002), first submitted with Apotex's Petition, and on the later-submitted Reply Declaration of Leslie Z. Benet, Ph.D. (Ex. 1047).

Patent Owner relies on the declarations of Fred D. Lublin, M.D. (Exs. 2003, 2025, 2107, 2097), William J. Jusko, Ph.D. (Exs. 2005, 2024, 2095), Lawrence Steinman, M.D. (Exs. 2022, 2096), and Jerold Chun, M.D., Ph.D, (Ex. 2098). Patent Owner further relies on the declaration of named inventor Christian Schnell. Ex. 2026.

Petitioners filed motions for observations on depositions of Drs. Lublin, Jusko, Steinman, and Chun (Papers 77, 79, 76, and 78, respectively); Patent Owner

filed responses to each of those motions (Papers 90, 93, 91, 92, respectively).

We heard oral argument on May 11, 2018. A transcript of that proceeding is entered as Paper 108 ("Tr.").

The parties filed the following motions. Petitioners filed a motion to exclude evidence (Paper 82); Patent Owner opposed (Paper 89); and Petitioners submitted a reply in support of its first motion to exclude (Paper 98). Patent Owner filed a first motion to exclude evidence (Paper 80); Petitioners opposed (Paper 94); and Patent Owner submitted a reply in support of its first motion to exclude (Paper 97). Patent Owner filed a supplemental motion to exclude evidence (Paper 102); Petitioners opposed (Paper 101); and Patent Owner submitted a reply in support of its supplemental motion to exclude (Paper 103). The parties have also filed six motions to seal. (Papers 36, 50, 83, 99 (by Petitioners); Papers 29, 37 (by Patent Owner)).

B. Related Proceedings

According to Patent Owner, there are no other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding. Paper 4, 2. Petitioners note that in IPR2014-00784, the Board issued a Final Written Decision relating to U.S. Patent No. 8,324,283 B2, and that "[a]lthough not from the same patent family as the '405 patent, the '283 patent included claims to pharmaceutical compositions of fingolimod, or a pharmaceutically acceptable salt thereof, that is suitable for oral administration, as well as claims directed to the treatment of multiple sclerosis using S1P receptor agonists." Pet. 20; *see id.* at 13–14; Paper 49, 7. We are not persuaded, however,

that the Board's prior decision with respect to the '283 patent is probative of the instant proceeding.

C. The '405 Patent and Relevant Background

The '405 patent, titled "S1P Receptor Modulators for Treating Relapsing-Remitting Multiple Sclerosis," issued to Peter C. Hiestand and Christian Schnell from U.S. Application No. 14/257,342 ("the '342 application"), filed April 21, 2014. Ex. 1001, at [21], [60], [71], [72]. The '342 application is a divisional of Application No. 13/149,468 ("the '468 application") (now U.S. Pat. No. 8,741,963). *Id.* at [60]. The '468 application, in turn, is a continuation of Application No. 12/303,765 ("the '765 application."), which is the U.S. entry of PCT/EP2007/005597, filed June 25, 2007. *Id.*; Ex. 1009, 21, 40. PCT/EP2007/005597 claims priority to foreign application GB0612721.1 (Ex. 1012), filed on June 27, 2006. Ex. 1001, at [30]; *see* Ex. 1009, 57–58.

The instant "invention relates to the use of an S1P[4] receptor modulator in the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis." Ex. 1001, 1:5-8. "Characteristic pathological features of demyelinating diseases include inflammation, demyelination and axonal and oligodendrocyte loss. In addition[,] lesions can also have a significant vascular component. A firm link has recently been established between chronic inflammation and angiogenesis and neovascularization seems to have a significant role in the progression of disease." *Id.* at 9:6–12. According to the inventors, "[i]t has now been found that S1P receptor modulators have an inhibitory effect on neo-angiogenesis associ-

[4] S1P refers to sphingosine-1 phosphate, a natural serum lipid. Ex. 1001, 1:13–14.

ated with demyelinating diseases, e.g. MS." *Id.* at 9:13–15.

"Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with chronic inflammatory demyelination leading to progressive decline of motor and sensory functions and permanent disability." Ex. 1001, 8:61–64. The inventors state that S1P receptor agonists or modulators may be useful in the treatment of MS, including the Relapsing-Remitting form (RR-MS), which accounts for 85% of patients' initial experience with the disease and is the precursor to the more debilitating Secondary-Progressive form (SPMS). *Id.* at 9:64–10:21; *see also id*. at 10:3–5 (noting that within 10 years of onset about half of RR-MS patients will develop SPMS); Ex. 1005,[5] 159–60, Fig. 1 (discussing the pathophysiology, classification, and clinical course of MS).

"S1P receptor agonists or modulators are known as having immunosuppressive properties or anti-angiogenic properties in the treatment of tumors . . . ." Ex. 1001, 8:56–60. Preferred compounds stimulate lymphocyte homing, thereby "elicit[ing] a lymphopenia resulting from a redistribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression." *Id.* at 2:17–23. "A particularly preferred S1P receptor agonist . . . is FTY720, i.e., 2-amino-2-[2-(4-octyphenyl)ethyl] propane-1, 3-diol . . . ." *Id.* at 8:17–30. This compound, also known as fingolimod, is the active ingredient in Novartis's Gilenya

[5] Thomson, "FTY720 in Multiple Sclerosis: The Emerging Evidence of its Therapeutic Value," 1(3) CORE EVIDENCE 157-167 (2006). Ex. 1005.

product (fingolimod hydrochloride) approved for the treatment of RR-MS. *See* Ex. 2040, 11; Ex. 2024 ¶ 38.

D. The Challenged Claims

Illustrative claim 3 recites (paragraphing added):

> 3. A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising
>
> orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1, 3-diol, in free form or in a pharmaceutically acceptable salt form,
>
> at a daily dosage of 0.5 mg,
>
> absent an immediately preceding loading dose regimen.

The remaining independent claims differ only in the language of the preamble, such that the "treating" language of claim 3 is replaced with "reducing or preventing or alleviating relapses" (claim 1) or "slowing progression" of RR-MS (claim 5).

Depending from claims 1, 3, and 5, respectively, claims 2, 4, and 6 specify that the 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1, 3-diol is the hydrochloride salt form—i.e., fingolimod hydrochloride.

E. Grounds of Unpatentability

We instituted trial to review the patentability of the challenged claims on each of the three grounds asserted in the Petition:

Ground	Claims	References	Basis
1	1–6	Kovarik[6] and Thomson[7]	§ 103
2	1–6	Chiba,[8] Kappos 2005,[9] and Budde[10]	§ 103
3	1–6	Kappos 2010[11]	§ 102

Paper 11, 27.

II. ANALYSIS

A. Legal Principles

To anticipate a claim under 35 U.S.C. § 102,[12] "a single prior art reference must expressly or inherently

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[6] Kovarik and Appel-Dingemanse, WO 2006/058316, published June 1, 2006. Ex. 1004. ("Kovarik").

[7] Thomson, "FTY720 in Multiple Sclerosis: The Emerging Evidence of its Therapeutic Value," 1(3) Core Evidence 157-167 (2006). Ex. 1005. ("Thomson").

[8] Chiba et al., US 6,004,565, issued Dec. 21, 1999. Ex. 1006. ("Chiba").

[9] Kappos et al., "FTY720 in Relapsing MS: Results of a Double-Blind Placebo-Controlled Trial with a Novel Oral Immunomodulator," 252 (Suppl 2) J. Neurology Abstract O141 (2005). Ex. 1007. ("Kappos 2005").

[10] Budde, et al., "First Human Trial of FTY720, a Novel Immunomodulator, in Stable Renal Transplant Patients," 13 J. Am. Soc. Nephrology 1073-1083 (2002). Ex. 1008. ("Budde").

[11] Kappos et al., "*A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis*," 362(5) N. Engl. J. Med. 387–401 (2010). Ex. 1038. ("Kappos 2010").

[12] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '405 patent have an effective filing date before the effective date of the applicable AIA

disclose each claim limitation." *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *KSR*, 550 U.S. at 418. Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the

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amendments, throughout this Final Written Decision we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted); *see also Belden Inc. v. Berk–Tek LLC,* 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.").

B. Person of Ordinary Skill in the Art

Petitioners propose that a person of ordinary skill in the art as of the date of the invention

> would typically include a person with a medical degree (M.D.) and several years of experience treating multiple sclerosis patients. . . . would be familiar with administering therapeutic agents for the treatment of multiple sclerosis, including RR-MS, and dosing regimens of the various therapeutic agents available for treating RR-MS. . . . [and] would be knowledgeable about the multiple sclerosis medical literature available at the relevant time.

Pet. 18–19 (citing Ex. 1002 ¶¶ 39–40). Petitioners' proposal is consistent with the definition offered during prosecution that, "[t]he relative skill of those in the art is high, generally that of an M.D. or Ph.D. with expertise in the area of neurology." Ex. 1009, 13. We further note, in focusing on the MS disease state and the conduct of a prophetic clinical trial of fingolimod ("Compound A") in treating RR-MS, the Specification suggests that one of ordinary skill in the art would possess a medical or related doctoral degree and have

experience in the field of MS treatment and clinical research. *See, e.g.*, Ex. 1001, 8:61–9:12, 9:64–10:16, 11:4–12:13.

In the Preliminary Response, Patent Owner argues that Apotex's proposed definition "is plainly incorrect" because "a person of skill in other dosing patent cases almost always includes a pharmacologist," the '405 Patent and relevant references include pharmacologists as "essential contributing authors," and "[p]harmacologists would have to interpret that data before reaching any conclusions about the obviousness of a 0.5 mg daily dose." Prelim. Resp. 39–43.

In our Decision instituting trial, we agreed with Patent Owner that in the context of this proceeding, expertise in pharmacology would be useful in determining obviousness. Dec. 8. We further noted that it was not necessary to decide between the hypothetical medical doctor proposed by Petitioners and the pharmacologist proposed by Patent Owner, as courts and tribunals have frequently identified the hypothetical person of ordinary skill as a composite or team of individuals with complementary backgrounds and skills. Dec. 8–9 (citing *AstraZeneca Pharm. LP v. Anchen Pharm., Inc.,* No. 10-CV-1835 JAP TJB, 2012 WL 1065458, at *19, *22 (D.N.J. Mar. 29, 2012), *aff'd*, 498 F. App'x 999 (Fed. Cir. 2013) (collecting cases); *Helsinn Healthcare S.A. v. Dr. Reddy's Labs. Ltd.*, No. CV 11-3962 (MLC), 2016 WL 832089, at *72 (D.N.J. Mar. 3, 2016) (reversed on other grounds by *Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc.*, 855 F.3d 1356 (Fed. Cir. 2017), *cert. granted*, — S. Ct. —, 2018 WL 1142984 (June 25, 2018)); *Merial, Inc. v. Fidopharm Inc.*, IPR2016-01182, Paper 11 at 9 (PTAB Nov. 7, 2016)).

Accordingly, we determined that one of ordinary skill in the art could be part of a multi-disciplinary research team including 1) a Ph.D. with expertise in the area of neurology and/or an M.D. having several years of clinical experience treating multiple sclerosis patients, and who would be knowledgeable about the multiple sclerosis medical literature, and 2) a pharmacologist with experience in drug development. *Id.* at 9.

Neither party argues that this determination is incorrect. Nor, upon consideration of the complete record, do we find reason to modify our prior determination.

C. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

i. Whether the Preambles are Limiting

The preambles of the independent claims recite methods for "reducing or preventing or alleviating relapses in" (claim 1), "treating" (claim 3), and

"slowing progression of" (claim 5) RR-MS "in a subject in need thereof." This "subject in need thereof" is then reflected in the body of each claim as it recites the step of orally administering fingolimod "to said subject."

Petitioners argue that the preambles of the independent claims should be accorded no patentable weight as they "at most merely describe[] the intended purpose of the method and that the subject receiving fingolimod is a subject with RR-MS." Pet. 24–25; Ex. 1002 ¶¶ 43–45. As we understand the argument, Petitioners propose that "said subject" is any subject with RR-MS, as such persons inherently are, or will be, "in need of a treatment that reduces, prevents or alleviates relapses and slows the progression of RR-MS." *Id.* at 22–23; Ex. 1002 ¶¶ 43–45. Thus, Petitioners argue, the preambles "are not required to breathe life into the claim[s]." *Id.* at 24.

Petitioners' argument, however, conflates the etiology and progression of multiple sclerosis with the plain language of the claims. Thus, for example, Petitioners may be correct that because patients accrue neurologic disability with each relapse episode, "an RR-MS patient is in need of a treatment that reduces, prevents or alleviates relapses and slows the progression of RR-MS," depending on that patient's disease state. *See* Pet. 23. But "[i]n the absence of any evidence to the contrary, we must presume that the use of these different terms in the claims connotes different meanings." *CAE Screen Plates, Inc. v. Heinrich Fiedler GMBH & Co. KG*, 224 F.3d 1308, 1317 (Fed. Cir. 2000). In the present case, Petitioners do not direct us to sufficient evidence that "reduc[ing], prevent[ing] or alleviat[ing] relapses," as set forth in claim 1, is necessarily the same as the arguably broader language, "treating," recited in claim 3.

In contrast to Petitioners' position, Patent Owner contends that the preambles of independent claims 1, 3, and 5, limit the scope of the challenged claims, and are necessary to provide understanding to what the inventors actually invented. Prelim Resp. 29–35. Relying on the testimony of its expert, Dr. Lublin, Patent Owner presents evidence that "a person of skill would not understand reducing relapses, treating the disease, and slowing its progression to mean the same thing." *Id*. at. 32–33 (citing Ex. 2003 ¶¶ 5–7, 43–55). As noted above, we do not ascertain where, on this record, Petitioners or Petitioners' experts argue or present evidence that these three terms are synonymous.

Patent Owner also points out that failing to accord meaning to the differences in the preambles "would eliminate any differences among claims 1–2, 3–4, and 5–6." *Id.* at 30–31. On balance, we agree with Patent Owner that the presumption against claim redundancy weighs against Petitioners' proposed construction.

We also find persuasive Patent Owner's argument that the words in the preambles inform the scope of "said subject" in the body of each claim. Prelim. Resp. 29–35. In particular, the preambles of claims 1, 3 and 5:

> provide[] an antecedent basis for terms used in the body of each claim, specifying the needs of the "subject" alluded to later. This is a classic example of the preamble defining a term—the "subject in need" of certain effects—which then is subsequently used in the body of the claim—"to said subject."

Id. at 34.

Because the three preamble terms, "reducing or preventing or alleviating relapses in" (claim 1), "treating" (claim 3), and "slowing progression of" (claim 5) RR-MS have different meanings, and each informs the scope of the "subject" in the body of the claims, we concluded that the preambles give life and meaning to the balance of the claim. *See Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). Accordingly, we construed the preambles of claims 1, 3, and 5 as limiting, and accord the ordinary and customary meaning to the claim language "reducing or preventing or alleviating relapses in," "treating," and "slowing progression of" RR-MS "in a subject in need thereof." Dec. 12. We further construed the terms "reducing or preventing or alleviating relapses" and "slowing progression" as subsumed within the genus of "treating" RR-MS.[13] *Id.* Upon consideration of the complete record, we find no reason to modify our construction.

ii. Whether the Preambles Invoke an Efficacy Element

The parties do not appear to argue that our construction of the preambles is incorrect, but disagree as to whether they invoke an efficacy element. According to Patent Owner, we should construe the claims to require that administering 0.5 mg fingolimod daily provides the effects recited in the preambles or, in the alternative, require that the drug "be given for the 'intentional purpose for which the method must be performed.'" PO Reply 9; Sur-Reply 3–4 (quoting *Janssen v. Rexall Sundown, Inc.*, 342 F. 3d 1329, 1333 (Fed. Cir. 2003)); Ex. 2095 ¶¶ 9–17. Petitioners, by

[13] Unless specifically indicated otherwise, we refer herein to the more generic "treating" as a matter of convenience.

contrast, contend that the preambles do not create an efficacy requirement but merely inform the scope of "said subject" in the body of the claims, or "describe the intended purpose of the method." Pet. 24–25; Pet. Reply 7–8 (citing *In re Montgomery*, 677 F.3d, 1375, 1380 (Fed. Cir. 2012)); Opp. 5–6.

Consistent with our determination in section II(C)(i), above, administration of fingolimod to "said subject" in the claim body clearly refers to "a subject in need" of treatment of RR-MS in the preambles. Accordingly, at a minimum, we agree with Patent Owner that the claims require that the 0.5 mg daily dosage of fingolimod is given for the purpose of treating RR-MS. Although an understanding that the claims refer to the administration of fingolimod for the purpose of treating RR-MS provides context for understanding Grounds 1–3, counsel for Patent Owner points out that whether the preambles further demand that the orally administered dosage is efficacious is "more important for the motion to amend." Tr. 45:5–10. We agree with Patent Owner. And, as we do not reach the substance of Patent Owner's motion to amend (*see* section II(A), below), we need not further construe the preambles. *See Wellman, Inc. v. Eastman Chem. Co*., 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

iii. Daily Dosage

Illustrative claim 3 recites a method for treating RR-MS in a subject comprising "orally administering to said subject [fingolimod] . . . at a daily dosage of 0.5 mg." The parties disagree as to whether "daily dosage"

requires administration over a course of treatment for more than one day.

Relying on the testimony of Dr. Benet, Petitioners argue that "the broadest reasonable construction of a 'daily dosage of 0.5 mg' includes a total dose of 0.5 mg in 24 hours regardless of what unit doses are used or whether the same dose is repeated on consecutive days." Pet. Reply 8–9 (citing Ex. 1047 ¶¶ 107–116).

According to Patent Owner, considered in context, "'daily' does not mean 'once.' It means 0.5 mg per day for more than one day . . . . [because] therapies like fingolimod require continuous administration to be effective. Giving the drug only once would be meaningless." PO Sur-Reply 3–4. As Dr. Steinman explains, "[a] person of skill with any familiarity with RRMS or disease-modifying therapies like fingolimod would understand that these [disease modifying therapies] are never proposed as a single-dose cure, but are always envisioned to be taken on a regular basis over an extended period." Ex. 2089 ¶ 22; *see* Ex. 2024 ¶ 114. Thus, "[a] skilled person would understand 'daily dosage' to refer to once a day for a number of days." Ex. 2096 ¶ 21; *see also id.* (further noting that "[a] single, one-time dose can be referred to by the phrase 'a dosage' and the word 'daily' is not needed.").

Consistent with Dr. Steinman's testimony, the Specification states that "[d]aily dosages required in practicing the method of the present invention . . . will vary depending upon, for example, the compound used, the host, the mode of administration and the severity of the condition treated . . . . [and] may alternatively be administered intermittently, e.g., at a dose of 0.5 to 30 mg every other day or once a week." Ex. 1001, 11:20–38; *see* Ex. 2089 ¶ 23. Accordingly, the Specification presents intermittent dosing (i.e., not

every day) as an alternative to daily dosing and, in so doing, indicates that either regimen entails administration for more than one day.

As an initial matter, we credit Dr. Benet's testimony that a daily dosage need not be administered as a single unit dose and, thus, refers to the total dose administered in 24 hours. *See* Ex. 1047 ¶¶ 110–111; Ex. 1001, 11:24–25 ("daily dosage" includes "as a single dose or in divided doses"). On balance, however, we find that Patent Owner has the better position with respect to the length of treatment implicit in the claim term. The '405 Patent is directed to the treatment of a chronic and progressively debilitating disease. *See* Ex. 1001, 8:61–9:5, 9:64-10:5; Ex. 1005, 159; *see generally* Ex. 1023, 193–202.[14] As Dr. Steinman indicates, such patients are in need of treatment "on a regular basis over an extended period of time." Ex. 2089 ¶ 22. This is consistent with our reading of the Specification as disclosing daily or intermittent treatment for more than one day. *See* Ex. 1001, 11:20– 38; *see* Ex. 2089 ¶ 23.

Moreover, with respect to Petitioners' argument in their Reply brief that the claim language is broad enough to encompass both single administration and administration on consecutive days (*see* Pet. Reply 8–9), we conclude that, in the context of the '405 patent, Petitioners' proposed definition renders the word "daily" superfluous. Accordingly, we construe "daily dosage of 0.5 mg" as referring to the amount of

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[14] MCALPINE'S MULTIPLE SCLEROSIS, 4th Ed., Compston, ed. (Elsevier, Inc., December 2005).

fingolimod administered per day over the course of a multi-day treatment.[15]

D. Ground I: Obviousness in view of Kovarik and Thomson

Petitioners challenge claims 1–6 under 35 U.S.C. § 103 as obvious in view of Kovarik and Thomson. Pet. 21, 32–48. Patent Owner opposes. We begin with an overview of the asserted references.

i. Overview of Kovarik

Kovarik relates to an improved loading dosage regimen of S1P receptor modulators or agonists for the treatment of transplant patients suffering from autoimmune diseases or disorders, including multiple sclerosis. Ex. 1004, 1, 14. Preferred S1P receptor modulators or agonists "elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression." *Id.* at 2. In a particularly preferred embodiment, the S1P receptor agonist is FTY720 (i.e., fingolimod). *Id.* at 13.

Kovarik teaches that S1P receptor modulators or agonists are used in combination with cyclosporine A and everolimus in transplantation experiments and "[d]ue to their immune-modulating potency . . . are also useful for the treatment of inflammatory and autoimmune diseases." *Id.* at 1. According to Kovarik, "[i]t has now surprisingly been found that a specific dosage regimen, e.g. a loading dose, will provide

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[15] Although our construction of "daily dosage" is helpful to understanding the claims as a whole, our determination with respect to Petitioners' obviousness grounds would be the same under either construction.

further unexpected benefits." *Id.* In particular, an "S1P receptor modulator or agonist . . . is administered in such a way that during the initial 3 to 6 days . . . of treatment the dosage of said S1P receptor modulator or agonist is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage of said S1P receptor modulator or agonist is administered and thereafter the treatment is continued with the standard or a lower daily dosage . . . ." *Id.* at 13–14. "[T]he standard daily dosage (also called maintenance dose) refers to the dosage of an S1P receptor modulator or agonist necessary for a steady-state trough blood level of the medication or its active metabolite(s) providing effective treatment." *Id.* at 14.

According to Kovarik:

> A particularly preferred dosage of . . . the preferred S1P receptor modulator FTY720, is e.g. 2-5, 5-10, 10-15 and 15-20 mg, e.g. a regimen of 2.5mg/5mg/7.5mg/10mg or 5mg/10mg/15mg/20mg, respectively, during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 2.5 mg or 5 mg, or at a lower daily dosage, e.g. 0.1 to 0, 5 [sic] mg.
>
> In a further embodiment of the invention, a preferred loading regimen of . . . the preferred S1P receptor modulator FTY720, may also be e.g. 0.5mg/1 mg/1.5mg/2mg during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 0,5 [sic] mg.

Id. at 15.[16] Kovarik further discloses: "A method for treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5mg." *Id.* at 17.

ii. Overview of Thomson

Thomson teaches that "[fingolimod] elicits lymphocyte sequestration by facilitating a reversible redistribution of lymphocytes from the circulation to secondary lymphoid tissues. This is a unique immunomodulation mechanism whereby T lymphocytes are effectively directed away from inflammatory sites toward the lymphatic system." Ex. 1005, 162; *see also id*. at Abstract ("There is good evidence that FTY720 achieves immunomodulation as shown by a reversible redistribution of peripheral blood lymphocytes after oral administration."). According to Thomson:

> FTY720 has shown promising results in preclinical models of EAE, which in part has led to its clinical evaluation in multiple sclerosis. There is moderate evidence from two meeting abstracts of a phase II study that FTY720 (administered orally once daily for up to 12 months) improved the patient-oriented outcomes of relapse rate and the likelihood of

[16] In our Decision instituting *inter partes* review, we interpreted these passages in Kovarik as teaching the administration of a nominal loading dose of 0.5 mg of fingolimod followed by "maintenance therapy" at the same daily dose. Dec. 18 (citing Ex. 1004, 15). For the reasons set forth on pages 50–51 of the Patent Owner Response, we are persuaded that Patent Owner sufficiently establishes that Kovarik does not teach the administration of a nominal loading dose of 0.5 mg of fingolimod followed by "maintenance therapy" at the same daily dose.

> remaining relapse-free. In addition, there is moderate evidence that disease-oriented outcomes were also improved by FTY720 in that inflammatory disease activity (both new and existing) was reduced as determined by MRI.

Id. at 166–167.

In reviewing the emerging clinical evidence for fingolimod as a treatment for multiple sclerosis, Thomson reports that "[t]wo meeting abstracts have been published showing results obtained with FTY720 in a 12-month phase II clinical trial in patients with active relapsing multiple sclerosis." Ex. 1005, Abstract. These publications disclosed the benefits of fingolimod as compared to placebo at doses of 1.25 and 5 mg per day.[17] *See id*. at 164–65, Table 4.

Thomson also reviews a number of shorter-term clinical trials relating to pharmacodynamic and pharmacokinetic outcomes of fingolimod administration. *Id.* at 162–164, Table 3. With respect to one multi-dose study, Thomson notes that "[p]eripheral blood lymphocyte counts decreased from baseline to nadir (range 3–7 d after first dose) by 80 and 88% in subjects receiving FTY720 1.25 and 5 mg, respectively." *Id.* at Table 3.

With respect to another study involving single doses of 0.25, 0.5, 0.75, 1, 2, or 3.5 milligrams of FTY720, Thomson states: "All FTY720 groups showed a temporal pattern of relative lymphocyte sequestration, seen at the latest 6 h postdose. No clear dose response, but the highest doses showed a more pronounced reduction in lymphocyte numbers." *Id.* (referencing, in part, Budde 2002 (Ex. 1008)); *see also id.* at 163

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[17] We note that one of the referenced studies is Kappos 2005 (Ex. 1007).

("Although the higher doses of FTY720 produced a more rapid and sustained lymphocyte sequestration, the actual degree of this property was similar across the range of doses used in the study and no clear dose–response relationship was detected.").

With respect to yet another study involving renal transplant patients co-administered cyclosporine and 0.25, 0.5, 1, or 2.5 mg doses of fingolimod for twelve weeks, Thomson reports that "lymphocyte sequestration was seen as early as w 1, nadir was reached at w 4 and was fully reversed 4-8 w after cessation of treatment. The pharmacodynamics were not dose-linear over the 10-fold dose range." *Id.* at Table 3; *see id*. at 164.

iii. Analysis of Ground 1

In short, Petitioners argue that the challenged claims would have been obvious over Kovarik and Thomson, because Kovarik teaches a 0.5 mg daily dose of fingolimod for the treatment of multiple sclerosis, whereas Thomson

teaches a range of doses, including 0.5 mg, which result in the lymphocyte homing effect then thought to underlie fingolimod's efficacy in treating RR-MS. In particular, Petitioners contend that "Kovarik discloses that the oral administration of a 0.5 mg daily dose of FTY720 provides effective treatment of multiple sclerosis . . . ." Pet. 36; *see* Ex. 1002 ¶¶ 119, 126; 1047 ¶¶ 25–30. According to Petitioners:

> A person of skill in that art would have read Kovarik's teachings as readily applicable to a patient with the RR-MS form of the disease because RR-MS is by far the most common form of the disease at onset and accounts for approximately 85% of cases. Also, a skilled

> artisan would have known that inflammation is the driver of relapses in RR-MS and that fingolimod hydrochloride was taught to treat MS by reducing inflammation through the accelerated lymphocyte homing mechanism taught by Kovarik.

Pet. 41–42 (internal citations omitted).

Petitioners argue that, "Thomson provides additional motivation to administer 0.5 mg FTY720 to a patient with RR-MS . . . [by] present[ing] an array of evidence supporting the efficacy of FTY720 in treating RR-MS by reducing relapse rates and slowing progression of RR-MS associated with inflammation." Pet. 42 (citing Ex. 1002, ¶ 109). According to Petitioners,

> [t]he skilled artisan would have had a reasonable expectation that the daily oral dose of 0.5 mg FTY720 taught by Kovarik would be therapeutically effective for patients suffering from RR-MS because Thomson describes clinical trials of FTY720 that tested doses in the range of 0.25 mg to 3.5 mg, in which it was found that "the actual degree of this property [lymphopenia] was similar across the range of doses used."

Pet. 43 (citing Ex. 1005, 162–63; Ex. 1002 ¶¶ 112–13).

In response, Patent Owner argues that Kovarik does not sufficiently link the treatment of RR-MS to the administration 0.5 mg daily dosages of fingolimod, but instead is directed to loading dose rates and ratios—elements expressly excluded by the challenged claims. PO Resp. 4, 36–37; Sur-Reply 13–14. We find that Patent Owner has the better position.

Kovarik generally discloses the use of S1P receptor modulators or agonists, such as fingolimod, at daily dosages ranging from 5 mg to 0.1 mg after a loading dose regimen, for a host of conditions, including prolonging allograft survival rates in transplant patients and treating patients suffering from autoimmune diseases, exemplified by "multiple sclerosis, lupus nephritis, rheumatoid arthritis, inflammatory bowel diseases or psoriasis." Ex. 1004, 14. On page 15 of the reference, Kovarik discloses administration of a loading dose regimen followed by maintenance therapy at a daily dosage of, e.g., 0.5 mg of fingolimod per day, without specifying the disease or condition treated. At best, we find that Kovarik teaches that, after a loading dose regimen, an unspecified autoimmune disease may be treated with a daily dosage of "about 0.1 to 0.5mg" of fingolimod." *See id*. at 17 ("A method for treating *an autoimmune disease* in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5mg." (emphasis added)).

Kovarik is directed to the use of loading doses, which, as Dr. Giesser testified and supports with evidence, "are not today, and were not in June 2006, part of the accepted MS or RR-MS treatment protocols. Ex. 1002 ¶ 67; PO Resp. 4, 36–37, 63–64. Ex. 2022 ¶ 8; *see also* Ex. 1047 ¶ 36 ("loading doses are merely to increase the rate at which steady state is achieved"); Ex. 1002 ¶¶ 67, 72, 119, 121–22; Ex. 2024 ¶ 130–133. Considering the testimony of the parties' experts, we credit Patent Owner's argument that Kovarik merely illustrates how a loading dose might be used for an unspecified autoimmune disease, but would have had little relevance to the treatment of RR-MS, and provides no guidance as to dosing for RR-MS with, or without, a loading dose. *See* PO Resp. 36 ("The

example did not cover 'any' or 'all' autoimmune disease(s), only one unspecified condition. RRMS is just one of dozens if not over 100 autoimmune diseases.") (citing Ex. 2022 ¶¶ 145–146); PO Reply 13–14 (citing Ex. 2096 ¶¶ 56–69); Ex. 2024 ¶¶ 141–151. Petitioners have not shown sufficiently how Kovarik links the treatment of RR-MS to the administration of 0.5 mg daily dosages of fingolimod with, or without, a loading dose. Accordingly, Petitioners have not demonstrated that one of ordinary skill in the art would have been motivated to administer 0.5 mg daily dosages of fingolimod to persons in need of treatment for RR-MS.

Petitioners further rely on Thomson as evidence that one of ordinary skill in the art would have recognized that a 0.5 mg daily oral dose of fingolimod would be effective in the treatment of RR-MS. *See* Pet. 42–46. We do not find Petitioners' arguments persuasive. Thomson discloses that fingolimod was effective for the treatment of RR-MS at 1.25 and 5 mg per day—substantially higher than the 0.5 mg daily dosage set forth in the challenged claims. *See* Ex. 1005, 164–165. Although Thomson also references a 0.5 mg dose, this is only in connection with single-dose safety data in renal transplant patients. *Id.* at 163 (discussing Budde, Ex. 1008 (*see* section II(E)(iii), below)). On this record, we agree with Drs. Steinman and Jusko that Thomson, like Kovarik, fails to teach or suggest the administration of 0.5 mg daily dosages of fingolimod to persons in need of treatment for RR-MS. *See* Ex. 2022 ¶¶ 161–162; Ex. 2024 ¶¶ 152–156.

For at least these reasons, we conclude that Petitioners have not demonstrated by a preponderance of evidence claims 1–6 would have been obvious under 35 U.S.C. § 103(a) in view of Kovarik and Thomson.

In section II(E), below, we discuss Patent Owner's arguments and evidence with respect to teaching away. Although not necessary to our determination with respect to Ground 1, our determination that the prior art teaches away from the claimed invention supports our conclusion that Petitioners have not demonstrated by a preponderance of evidence claims 1– 6 would have been obvious under 35 U.S.C. § 103(a) in view of Kovarik and Thomson.

E. Ground 2: Obviousness in view of Chiba, Kappos 2005, and Budde

Petitioners assert that claims 1 and 5 would have been obvious under 35 U.S.C. § 103(a) over the combination of Chiba, Kappos 2005, and Budde. Pet. 48–57. Patent Owner opposes. We begin with an overview of the asserted references.

i. Overview of Chiba

Chiba discloses that fingolimod hydrochloride and related compounds are capable of suppressing the immune response of mammals through accelerated lymphocyte homing ("ALH-immunosuppression"). Ex. 1006, Abstract, 2:35–44, 4:63–5:7. "For example, the compound FTY720 specifically directs lymphocytes to the peripheral lymph nodes, mesenteric lymph nodes, and Peyer's patches. By reversibly sequestering lymphocytes in these tissues, the compounds can inhibit an immune response in a mammal." *Id.* at Abstract; *see id.* at 2:38–40, 17:38–40. Such ALH-immunosuppressive compounds "are useful in for the prevention or treatment of resistance to transplantation or transplantation rejection . . . [and] autoimmune diseases such as . . . multiple sclerosis" (*id.* at 6:26–49) and may be administered "to an adult daily by 0.01-10

mg (potency) in a single dose or in several divided doses." (*id*. at 8:28–34).

ii. Overview of Kappos 2005

According to Kappos 2005, "FTY720 is an oral immunomodulator (sphingosine-1 phosphate receptor (S1P) modulator) that reversibly sequesters tissue damaging T and B cells away from blood and the central nervous system to peripheral lymph nodes. FTY720 has demonstrated both preventive and therapeutic efficacy in several animal models of MS." Ex. 1007, O141. Kappos discloses the clinical and MRI results of a double-blind, placebo-controlled study to evaluate efficacy, safety and tolerability of 1.25 mg and 5.0 mg daily doses of FTY720 in the treatment of RR-MS. *Id.* According to Kappos 2005, the study "demonstrated efficacy of FTY720 on MRI and relapse-related endpoints" and "strongly suggest[s] that FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily oral administration." *Id*.

iii. Overview of Budde

Budde discloses a randomized, double-blind, placebo-controlled clinical trial designed to measure safety, single-dose pharmacokinetics, and pharmacodynamics of single oral doses of fingolimod in stable renal transplant patients. Ex. 1008, Abstract. Budde shows that single oral doses of 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, and 3.5 mg of the drug induced decreased lymphocyte counts as compared to placebo with a nadir of 4.7–8 hours after administration. *Id*. at 1078; *see id*. at 1079 ("All FTY-randomized groups manifested a temporal pattern of relative lymphopenia, detected at the latest by 6 h postdose."); *id.* at 1082

("Single oral doses of FTY in doses ranging from 0.5 mg to 3.5 mg caused a dose-dependent, reversible lymphopenia."). According to Budde:

> At FTY doses ranging from 0.5 mg to 3.5 mg, no clear dose response relationship was detected, but the two highest dose groups exhibited a more pronounced decline in lymphocyte numbers. FTY doses of >2.0 mg were associated with a more rapid onset of lymphopenia (31 to 43% decrease after 2 h). The three subjects treated with 3.5 mg FTY manifested the most prolonged and intensive lymphopenia.

Id.

With respect to safety, "single oral doses of FTY were well tolerated with transient asymptomatic bradycardia as the most common adverse event." *Id.* at 1082. "Higher doses of FTY were more frequently associated with bradycardia: 9 out of 12 subjects randomized to >0.75 mg of FTY developed bradycardia; however, only 1 of 12 subjects receiving 0.25 to 0.5 mg of FTY." *Id.* at 1075.

iv. Analysis of Ground 2

Petitioners argue that claims 1–6 would have been obvious "[b]ecause Chiba teaches oral administration of fingolimod hydrochloride for the treatment of multiple sclerosis, with Kappos 2005 confirming its utility in RRMS patients and Budde confirming the efficacy of a 0.5 mg daily dose of FTY720." Pet. 54. In particular, Petitioners state:

> In view of Kappos 2005 and Budde, the skilled artisan would have a reasonable expectation that the 0.5 mg daily dose, a dose within the

> range taught by Chiba and specifically used by Budde, would induce the desired pharmacological effect (lymphopenia) in RR-MS patients. EX1002, ¶¶58, 60-61, 64, 84, 139, citing EX1022 at 309, EX1018 at 237-39, EX1019 at 684, EX1031 at 1081, EX1028 at 440, and identifying lymphopenia as being "often used as a clinical end-point in dose response studies" and "relevant for relating dosage to lymphopenia for MS." Thus, a skilled artisan would have had reason to use the 0.5 mg dose identified in these clinical trials because there was no substantial pharmacological detriment to using the lower 0.5 mg dose and because Budde teaches that the 0.5 mg dose was associated with a decreased risk of adverse effects such as bradycardia when compared to higher doses. EX1008 at 1075-76; EX1002, ¶139.

Id. at 53–54.

In opposing Petitioners' arguments, Patent Owner contends, *inter alia*, that one of ordinary skill in the art would not have been motivated to combine the cited references to arrive at the claimed invention because the art as a whole taught away from administering daily dosages as small as 0.5 mg for the treatment of RR-MS.[18] *See* PO Resp. 33–39; PO Reply 5–8. A reference teaches away "when a person of ordinary skill, upon reading the reference, would be

[18] Patent Owner further provides evidence of unexpected results and skepticism by those of ordinary skill in the relevant field. *See id.* at 39–41. Because our conclusions with respect to teaching away are sufficient to our determination with respect to Petitioners' obviousness grounds, we need not consider this additional evidence.

discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken" in the claim. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). Whether the prior art teaches away from a reference may be dispositive of a challenge set forth in an *inter partes* review. *See generally*, *Meiresonne v. Google, Inc.,* 849 F.3d 1379, 1382 (Fed. Cir. 2017).

Patent Owner's teaching away argument relies primarily on the combination of Webb, Kahan 2003,[19] and the Park references, Park 2003[20] and Park 2005,[21] which we discuss below.

1. Webb, Kahan 2003, and the Park References

Webb, a prior art article published by researchers at Merck in the respected, peer-reviewed Journal of Neuroimmunology, provides the lynchpin of Patent Owner's teaching away argument. *See* Ex. 2014;[22] Ex. 2096 ¶ 26. Webb studied the effects of fingolimod and

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[19] Kahan, et al., Pharmacodynamics, Pharmacokinetics, and Safety of Multiple Doses of FTY720 in Stable Renal Transplant Patients: A Multicenter, Randomized, Placebo-Controlled, Phase I Study, Transplantation, 76(7): 1079-1084 (2003). Ex. 1031.

[20] Park et al. "*Peripheral Blood FTY720 Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling in Renal Transplanted Recipients*," Abstract #707, Kidney: Pharmacogenetics, Kinetics and New Drug, p. 333-334 (2003). Ex. 2048.

[21] Park, et al., Pharmacokinetic/Pharmacodynamic Relationships of FTY720 in Kidney Transplant Patients, Brazilian J. Med. Biol. Res., 38: 683-694 (2005). Ex. 1019.

[22] Webb et al., Sphingosine 1-phosphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice, 153 J. Neuroimmunology 108–21 (2004). Ex. 2014.

its phosphorylated active metabolite, FTY-P, in a mouse model of RR-MS, experimental autoimmune encephalitis, or EAE. Ex. 2014, Abstract, 118. Webb initiated EAE by immunizing SLJ mice with a peptide based on the mouse proteolipid protein, PLP. *Id.* at 109, 110. The mice were then exposed to fingolimod, FTY-P, or control preparations. *Id.* at 110. Noting that "the effects of [fingolimod] are a result of the generation of the metabolite FTY-P," Webb focused on FTY-P "to examine the dose response for clinical efficacy and peripheral lymphopenia, and the relationship between these two phenomena." *Id.* at 114.

In Figure 5B, Webb shows the cumulative clinical scores of mice immunized with the PLP peptide alone, or with increasing amounts of FTP-Y. *Id.* at 115; *see* Ex. 2024 ¶ 73. Although the scores for each of the FTP-Y pools is numerically lower than that of the PLP control, Webb indicates that only the results for the 1 mg/kg and 0.3 mg/kg treatments were statistically significant. *Id.* In Figure 6B, Webb shows that increasing amounts of FTP-Y cause increasing amounts of lymphocyte suppression (lymphopenia), which was considered a marker for therapeutic efficacy. *Id.; see* Ex. 2022 ¶ 41; Ex. 2024 ¶ 74. Figure 6C plots the cumulative clinical scores versus percent lymphopenia for the various pools. *Id.; see Ex. 2024* ¶ 74.

> In discussing these experiments, Webb observed
>
> a dose-dependent and reversible lymphopenia on treatment with FTY720 or FTY-P. This reached a maximum of about 70–80% depletion at the highest doses used. . . . Because EAE is known to be a T cell-dependent disease, such sequestration, by preventing the entry of T cells with specificity for myelin

> components into the CNS, would account for the therapeutic efficacy.
>
> * * *
>
> In dose response experiments, we found that a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy, and thereafter, the dose response relationship between clinical benefit and lymphopenia was very steep.

Id. at 118.

According to Patent Owner, "EAE studies like those in Webb are an important 'predictive index for clinical therapeutic application' for MS treatment and thus useful in establishing dosing." PO Resp. 34 (citing Ex. 2022 ¶¶ 68, 72). Patent Owner further argues that, absent evidence to the contrary, one of ordinary skill in the art would have understood Webb's threshold of about "about 70% depletion of peripheral lymphocytes" to apply across species. *Id.* (citing Ex. 2024 ¶ 75) (further noting that more than 80% lymphocyte suppression was known to be required to achieve a clinical effect in human transplant patients).

Patent Owner further points to Kahan 2003 and the Park references as evidence of the degree of lymphocyte depletion seen in humans dosed with 0.5 mg of fingolimod. *See* PO Resp. 9–14 (citations omitted). Kahan 2003 monitored 65 stable renal transplant patients receiving once-daily doses of 0.125, 0.25, 0.5, 1.0, 2.5, or 5.0 mg fingolimod, or placebo for 28 days. Ex. 1031, Abstract. Kahan 2003 reported that fingolimod "doses greater than or equal to 1.0 mg/day produced a significant reduction in peripheral blood lymphocyte count by up to 85%," with no "major increase in adverse events or a change in renal

function" as compared to placebo. *Id.* Doses less than 1.0 mg/day produced materially lower reductions in peripheral lymphocyte blood counts. *Id*. at 1081-82; Ex. 2022 ¶ 56. As shown in Figure 1 of the reference, at the end of the administration period, the 1.0 mg daily dose resulted in about 70% lymphocyte suppression, whereas the 0.5 mg daily dose resulted in about 50% lymphocyte suppression. *Id.* at 1081; *see* Ex. 2022 ¶ 57.

Park 2003 monitored peripheral blood lymphopenia in 23 kidney transplant patients receiving 0.25, 0.5, 1.0 or 2.5 mg daily doses of fingolimod over the course of 12 weeks. Ex. 2048. Park reports that "EC50 was achieved at FTY720 doses of 0.5 mg and blood concentrations of 0.6 ng/mL. Since FTY720 PK are dose-linear and effective doses of FTY720 are 2.5 and 5 mg/day, the immunosuppressive effect of FTY720 may depend upon induction of high degree of lymphopenia (~80%)." *Id.* According to Dr. Steinmann, this indicates that for fingolimod, "0.5 mg was the 'EC50,' *i.e.*, the 'effective concentration' that reduced lymphocyte counts by half fingolimod's maximum level of about 88%. . . . In other words, 0.5 mg daily suppressed lymphocytes by about 44%." Ex. 2022 ¶ 59.

Dr. Steinmann further points to Park 2005, a follow-on to Park 2003. *Id.* at ¶¶ 61–66, 140–141 (citing Ex. 1019). Figure 7A of Park 2005 plots levels of lymphocyte suppression among patients administered daily doses of fingolimod over the course of 12 weeks. Ex. 1019, 690. Dr. Steinmann testifies that: "Patients in the 0.5 mg group range from less than 20% to less than 60% suppression; the 1.0 mg group range from 40% and 70%; and the 2.5 mg group between 70% and 80%. Thus, dose drove not only the average amount of suppression but also the degree of variation among

patients. Lower doses had far more variation than higher doses." Ex. 2022 ¶ 62. Further interpreting Figure 7, Dr. Steinmann calculates that "the EC50 level—the level that achieves half the maximum effect, or about 44% suppression—is 0.48 mg daily, +/- 0.08 mg." *Id.* ¶ 63; *see also id.* at ¶ 64 (interpreting Park Table 3 as showing that 0.5 mg daily doses result in about 42% lymphocyte suppression with substantially more week-to-week variation than higher dose regimens).

Contrasting Webb's 70% threshold with Kahan 2003's and Park's teachings that 0.5 mg daily doses of fingolimod resulted in 50% or less depletion of lymphocytes, and greater variability than higher doses, Patent Owner argues that the prior art teaches away from administering 0.5 mg daily dosages of fingolimod for the treatment of RR-MS. PO Resp. 33–39; *see* Ex. 2024 ¶¶ 124–127; Ex. 2022 ¶¶ 78, 115, 124–142; Ex. 2003 ¶ 39; Ex. Tr. 35:3–36:21.

Dr. Steinman explains that

> RRMS is a life-long condition. Relapses occur roughly 1.5 times per year. With each relapse (or even without), the disease progresses. More lesions develop on the CNS. Often, baseline function worsens with a relapse; that is, the effects of an attack can linger after the relapse is done. Disability thus accumulates over time. As a result, MS doctors focus on sustained, consistent relapse prevention and slowing progression of the disease. Even with some side-effects, the benefits of such sustained prevention are likely to outweigh the costs.

Ex. 2096 ¶ 43 (citing Ex. 2022 ¶¶ 29–30, 118). Accordingly, Dr. Steinmann testifies, "[s]ubstantial inter-patient variability would be unacceptable in a MS Drug." Ex. 2022 ¶ 144. Moreover, prior art studies showed that fingolimod was generally well tolerated such that any serious "side effects would have been manageable in comparison to the risks associated with submaximal therapeutic efficacy." *Id.* at ¶ 141. Thus, a 0.5 mg daily dosage regimen of fingolimod would have held promise as a treatment for RR-MS only if it could provide consistent, sustained benefits to patients. *See* Ex. 2096 ¶ 43.

With this background, we understand Patent Owner to argue that one of ordinary skill in the art would have been dissuaded from treating patients with doses of fingolimod that were likely to provide ineffective, sub-optimal, or variable clinical efficacy. Whereas Webb teaches that at least about 70% lymphocyte depletion provides a surrogate or marker for optimal efficacy, Kahan 2003 and the Park references show that 0.5 mg daily doses will not provide that level of lymphocyte depletion and, moreover, result in greater variability in this indicia of clinical efficacy.

Responding to Patent Owner's teaching away argument, Petitioners first address Webb's statement that "a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy." Pet. Reply 12– 14. Focusing on Webb's 0.3 mg/kg dose—the lowest dose shown to have statistically significant clinical efficacy—Petitioners argue that the underlying data show that 0.3 mg/kg dose did not achieve at least 70% lymphopenia but "only about 60%, the same level of lymphopenia that 0.5 mg achieved in humans in Kahan 2003 and Park after 4 weeks," thus "suggest[ing] that the 0.5 mg daily dose would be

clinically effective." *Id.* at 12 (citations omitted). Petitioners also contend that one of ordinary skill in the art "would not have been dissuaded from the 0.5 mg dose for RR-MS because of week-to-week or interpatient variability in lymphopenia or because higher lymphopenia (80%) was correlated with 'best efficacy' for preventing transplant rejection." *Id.* (citing Ex. 1047 ¶¶ 56–62).

We do not find Petitioners' arguments persuasive. First, we credit Dr. Steinman's testimony that one of ordinary skill in the art would have read Webb to mean what it says: "In dose response experiments, we found that a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy." *See* Ex. 2096 ¶¶ 26–40; *see also* Ex. 2095 ¶ 10 n.2; Ex. 2024 ¶¶ 65–80. We note for example, Dr. Steinman's testimony that, as compared to the summary data presented in the article, the Webb authors would have had access to more detailed information about their experiments from which to draw their conclusions, and that those conclusions were the result of the authors' collective judgment that had withstood rigorous peer review. *See id.* at ¶¶ 33–40.

Dr. Steinman's testimony is underscored by that of Dr. Chun, a co-author of Webb, which we likewise find persuasive. Ex. 2098 ¶¶ 2–9, 17– 35. Dr. Chun testifies that:

> Our conclusion that 70% suppression was needed for "any efficacy" was the product of our collective judgment based on a totality of data presented in our paper. The average effect of one dose in one group of mice was just one piece of data. We also assessed the effects of different doses in individual mice; the

> ability of a dose to produce sustained clinical improvement; and other facts to reach our conclusions. As those with experience running EAE experiments know, the model has a subjective aspect that requires judgment-calls when interpreting results.

Id. at ¶ 7; *see also* Ex. 1063, 186:2–25, 275:11–18 (explaining that "any" efficacy in Webb could have been written as "most consistent," "predominant," or "reproducible"). According to Dr. Chun:

> Some mice would respond to lower doses with higher suppression, and vice versa. These differences in how individual mice responded to FTY-P were thus obscured by statistical use of standard error of the mean.
>
> * * *
>
> However, those individual observations did inform our overall conclusion that "a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy[.]" (*Id.* at 118.) It is common in academic papers to report conclusions like this in the Discussion. Practical constraints imposed by journals prevent the publication of all the underlying data, such as data from each individual mouse. We thus highlighted the basic conclusion of "about 70%" in the Discussion to inform the readers.

Id. at ¶¶ 33–34.

Pointing to the testimony of Dr. Steinmann, Patent Owner also contends that Petitioners' expert incorrectly relied on maximum suppression data in Kahan 2003 and Park 2005 to conclude that 0.5 mg daily

doses of fingolimod would have resulted in levels of lymphopenia likely to be effective against RR-MS. PO Sur-Reply 6–7 (citing Ex. 2096 ¶¶ 41–54). According to Dr. Steinmann, Dr. Benet is also "mistaken in arguing that the inter-patient and week-by-week variability for 0.5 mg in Park 2005 would not be of independent concern to a person of skill designing a fingolimod dose." Ex. 2096 ¶¶ 50–52. Having considered the opposing arguments and the respective backgrounds of Drs. Bennet and Steinmann, we credit the testimony of Dr. Steinmann.[23]

2. Kataoka

Patent Owner further contends that Kataoka supports its position that lower doses of fingolimod would have been expected to provide sub-optimal clinical benefits. *See* PO Resp. 15, 19; PO Sur Reply 7–8, 12. Kataoka teaches that:

> Prophylactic administration of FTY720 at 0.1 to 1 mg/kg almost completely prevented the development of EAE, and therapeutic treatment with FTY720 significantly inhibited the progression of EAE and EAE-associated histological change in the spinal cords of LEW rats induced by immunization with myelin basic protein. Consistent with rat EAE, the development of proteolipid protein-induced EAE in SJL/J mice was almost completely prevented and infiltration of CD4+ T cells

[23] Although Dr. Benet presents impressive credentials in drug development and the pharmaceutical sciences generally (*see, e.g.,* Ex. 1047 ¶¶ 1–11; Ex. 1048), Dr. Steinmann's background in researching MS and other autoimmune diseases (*see, e.g.,* Ex. 2022 ¶¶ 1, 12–21) is more pertinent to the issues before us.

> into spinal cord was decreased by prophylactic treatment with FTY720.

Ex. 1029, Abstract. Referencing the rat data in Kataoka Figure 1, Patent Owner argues that "[d]oses of 0.1 and 0.3 mg/kg reduced clinical scores and lymphocyte infiltration, although to a lesser extent than 1.0 mg/kg did. So, like the studies before it, Kataoka pointed to doses of 0.1 mg/kg or higher." PO Resp. 19 (citing Ex. 1029 ¶ 441; Ex. 2022 ¶¶ 86-89; Ex. 2024 ¶¶ 81-82). According to Dr. Steinmann, "Kataoka's lowest dose was more than three times higher than Webb's lowest dose," such that Kataoka "did not explore the boundary between effective and ineffective doses." Ex. 2022 ¶ 89.

We do not find Patent Owner's initial argument persuasive as it relies on rat data without adequately explaining how the dosages of fingolimod in rats correlates to the results reported by Webb using a mouse model.

Petitioners argue that mouse data in Kataoka confirms the efficacy of 0.5 mg fingolimod, thereby negating Patent Owner's teaching away argument. *See* Pet. Reply. 15; Ex. 1047 ¶¶ 64–78. According to Dr. Benet, Kataoka demonstrates that 0.1 mg/kg doses of fingolimod alleviated EAE symptoms in the mouse model. Ex. 1047 ¶¶ 64–65. Then, applying a conversion from the July 2005 FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (Ex. 1049), Dr. Benet calculates that a mouse dose of 0.1 mg/kg translates to approximately 0.5 mg in humans, and would have had substantially the same efficacy as a 1.25 mg dose or 5 mg dose. *Id.* at ¶¶ 67–74; *see also id*. at ¶ 77 (applying conversion factor from FDA Guidelines to Kataoka's rat data).

The FDA Guidance provides "a process (algorithm) for deriving the maximum recommended starting dose (MRSD) for *first-in-human* clinical trials of new molecular entities in adult healthy volunteers . . . . The purpose of this process is to ensure the safety of the human volunteers." Ex. 1049, 1 (italics in original). Fingolimod, however, had already been examined in healthy adult volunteers and, moreover, was used to treat human transplant patients and those suffering from MS. These existing studies provided substantial evidence of fingolimod's safety and side effects profile in humans. *See e.g.,* Ex. 1005, 157 (stating that fingolimod is "[w]ell tolerated. No serious adverse events noted. Most common adverse event is asymptomatic, mild, and transient reduction in heart rate"); Ex. 1006, 317 ("FTY720 is well tolerated and not associated with the side effects commonly observed with immunosuppressant therapy."); Ex. 1007 ("Treatment was generally well tolerated . . . with the most frequently reported (> 15 % patients) being mild headaches and nasopharyngitis."); Ex. 1008, 1075 ("No serious adverse events were reported during or after the administration of FTY. . . . The most common of the 28 reported adverse events were bradycardia (n = 10) and headache."); Ex. 1018, 241 ("Transient, asymptomatic bradycardia was observed after fingolimod administration, but overall the drug was well tolerated with no serious adverse events.").

Accordingly, and notwithstanding Dr. Benet's statement that it was "standard practice for pharmacologists to use the multipliers provided in FDA Guidance to translate animal doses from preclinical studies into doses for use in human clinical studies" (Ex. 1047 ¶ 68), the FDA Guidance on its face, indicates that it is not intended to apply to the dosing of well-established compounds such as fingolimod. Consistent

with the teachings of the FDA Guidance, Patent Owner argues that one of ordinary skill in the art would not have used the FDA Guidance to extrapolate the mouse and rat data in Kataoka to a human dose. PO Sur-Reply 7–8 (citing Ex. 2095).

Consistent with our independent reading of the FDA Guidance, we find Patent Owner's argument persuasive for the reasons set forth in paragraphs 3–18 of Dr. Jusko's Declaration, Exhibit 2095. Summarizing this testimony, Dr. Jusko explains that,

> a person of skill in June 2006 would not have considered extrapolating from animal to human doses because extensive PK/PD data already existed in humans. The FDA Guidance is expressly designed only to identify a safe first-in-human dose before such data exists. But once human PK/PD data exists, that data would provide far more relevant information for estimating a dose's effects than an estimate based on simple animal dose data. Accordingly, a person of skill would not have used the FDA Guidance to extrapolate a human dose from Kataoka's lowest effective mouse dose.

Ex. 2095 ¶ 4.

Extending his analysis, Dr. Jusko argues that applying clearance data gathered from human and animal studies, a pharmacologist would calculate that Kataoka's 0.1 mg/kg effective dose in rats corresponds to about 1.4 mg in a 75 kg human. Ex. 2095 ¶¶ 19–28.[24]

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[24] Petitioners vigorously challenged the bases for Dr. Jusko's calculations at deposition. Petitioners, for example, challenged

In view of the above, Petitioners have not demonstrated that Kataoka detracts from Patent Owner's evidence of teaching away. To the contrary, Dr. Jusko's substantially unrebutted calculations using human and animal clearance data provide some support for Patent Owner's teaching away argument.

Considering all the evidence before us, Patent Owner has established that one of ordinary skill in the art would have been dissuaded from administering 0.5 mg daily dosages of fingolimod for the treatment of RR-MS, and that one of ordinary skill in the art would have had no reason to combine the teachings of Chiba, Kappos 2005 and Budde to arrive at the claimed invention. Accordingly, Petitioners have not demonstrated by a preponderance of evidence that claims 1–6 would have been obvious under 35 U.S.C. § 103(a) as asserted in Ground 2.

F. Ground 3: Obviousness in view of Kappos 2010

Petitioners challenge claims 1–6 under 35 U.S.C. § 102 as anticipated by Kappos 2010. Pet. 21, 57–61; *see* Ex. 1002 ¶¶ 144–146. Petitioners' challenge is predicated on the assertion that Kappos 2010 qualifies as prior art because claims 1–6 are not entitled to a

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Dr. Jusko's decision to use 75 kg as a standard patient weight in his calculation rather than other standard or average patient population weights as low as 60 kg. *See, e.g.*, Paper 74 ¶¶ 13–21; Paper 80, 14. Considering the formula Dr. Jusko used in calculating an equivalent human dose ("0.1 mg/kg from Kataoka x 75 kg human weight x 0.19 Conversion Factor = 1.43 mg"), simple arithmetic indicates that the substitution of 60 kg patient for the 75 kg standard used by Dr. Jusko also results in a dose substantially greater than 0.5 mg, i.e., 0.1 mg/kg from Kataoka x 60 kg human weight x 0.19 Conversion Factor = 1.14 mg. *See* Ex. 2095 ¶ 25.

filing date earlier than the April 21, 2014 filing date of the '342 application. Pet. 17–18, 57. In particular, Petitioners argue that the claim limitation requiring fingolimod administration "absent an immediately preceding loading dose regimen" first appeared in a preliminary amendment to the '342 application, whereas the originally filed '342 application and all prior applications are "silent regarding loading dose regimens." *Id*. at 57–58 (citations omitted).

Patent Owner does not dispute that Kappos 2010 discloses each element of claims 1–6, but argues: first, that Kappos 2010 is not prior art; and second, that in contravention of 35 U.S.C. § 311(b), Petitioners' "anticipation theory is a ruse to unlawfully smuggle a 112 written description argument into an IPR." Prelim. Resp. 5, 45–49. We find no merit in the latter argument.

i. Jurisdiction to address Ground 3

Although § 311(b) permits *inter partes* review "only on a ground that could be raised under section 102 or 103," Petitioners have not challenged the instant claims on any ground other than those that could be raised under sections 102 and 103. *See* Pet. 5–8 (overview of Grounds 1–3). Consistent with the grounds set forth in the Petition, we do not address invalidity on any basis other than under sections 102 and 103. Ascertaining whether an asserted reference qualifies as prior art under these sections, however, is integral to our analysis. *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) (obviousness analysis requires consideration of "the scope and content of the prior art"). Not surprisingly, various panels of the Board have already addressed underlying §112 issues in the context of anticipation and obviousness grounds in *inter partes* reviews. *See, e.g.*, *Bioactive Labs. v.*

BTG Int'l Inc., Case IPR2015-01305 (PTAB Dec. 15, 2015) (Paper 19, 8– 12) (finding that Petitioner failed to demonstrate that parent application having same specification as challenged patent lacked written descriptive support and enablement for the challenged claims); *Dr. Reddy's Labs. Ltd. et al. v. Galderma Labs. Inc.*, Case IPR2015-01778, (PTAB Feb. 16, 2016) (Paper 11, 7-8); *Coalition For Affordable Drugs VIII, LLC v. Trustees of University of Pennsylvania*, Case IPR2015-01835 (PTAB Mar. 7, 2016) (Paper 7, 8-11) (finding that provisional application lacked sufficient written description to support claim of priority).

Consistent with these prior Board decisions, Patent Owner cites no authority precluding us from conducting analyses where, as in the present case, the prior art status of a reference turns on whether one or more applications in the chain of priority of the challenged patent satisfy the written description requirement. Patent Owner, nevertheless, argues that:

> "[C]haracterising this issue as a question of" anticipation or obviousness cannot give the Board authority where it has none. The Board "simply cannot evade Congress's limitation upon its jurisdiction by" using Sections 102 and 103 as a back door to a Section 112 challenge.

PO Resp. 59 (citing *Mayfield v. Nicholson*, 499 F.3d 1317, 1320 (Fed. Cir. 2007); *Widdoss v. Sec'y of Dep't of Health & Human Servs.*, 989 F.2d 1170 (Fed. Cir. 1993)).

Patent Owner's citation to *Mayfield* is inapposite. In *Mayfield*, Appellant attempted to challenge a lower court's finding of fact by characterizing it as a matter of statutory interpretation—a question of law.

Mayfield, 449 F.3d at 1322–23. With respect to Ground 3, however, we address anticipation (resolved on the bases of underlying facts), by ascertaining a factual issue (the scope and content of the prior art) with reference to second factual issue (whether the claims are entitled to a priority date of the '342 application), which necessitates a decision on a third factual issue (whether the '342 application recites sufficient written description to support the claims). *See Martek Biosciences Corp. v. Nutrinova, Inc.,* 579 F.3d 1363, 1369 (Fed. Cir. 2009) (treating as a question of fact whether parent application provided sufficient § 112 support for the challenged claims such that applicants were entitled to an earlier priority date); *see also Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017) (reiterating that anticipation is a question of fact). Nowhere does our analysis invoke the question of law Patent Owner seeks to inject (i.e., whether we have the authority to address a ground of invalidity under § 112). Patent Owner's citation to *Widdoss v. Sec'y of Dep't of Health & Human Servs.*, 989 F.2d 1170 (Fed. Cir. 1993), is also inapplicable insofar as it refers to whether a court may waive a jurisdictional statutory time period and has no bearing on the present case.

In sum, we conclude that the panel is not jurisdictionally barred from addressing the merits of Petitioners' anticipation challenge, including the underlying question of whether Kappos 2010 qualifies as prior art with respect to the '405 patent.

ii. Whether Kappos 2010 qualifies as prior art

Patent Owner relies on the testimony of Drs. Steinman and Jusko in addressing the substance of Petitioners' contention that Kappos 2010 qualifies as prior art because the claim limitation requiring

fingolimod administration "absent an immediately preceding loading dose regimen" is not supported in the text of the '405 patent or any of the substantially identical applications in its chain of priority. PO Resp. 62 (citing Ex. 2022 ¶¶ 10, 182–185; Ex. 2024 ¶¶ 19–21, 171–176). As set forth in the cited testimony, Patent Owner's experts explain why a person of ordinary skill in the art would understand that the specification of the '405 patent and its priority documents show possession of the full scope of the invention claimed. For example, pointing to Clinical Trial section in column 11 of the Specification, Dr. Jusko states:

> An ordinarily skilled person in this art would know that the dosing instructions "daily dosage" in this context are complete and that no loading dose is to be included. Further, a person of skill would know it would be ill-advised to alter the dosing regimen set forth in the instructions because changes in safety and efficacy could result. A person of skill in the art would know not to add in a loading due to the risk of the adverse effect of first-dose bradycardia. Also, MS is a chronic disease and as such would likely not require a loading dose to reach an effective dose quickly in a patient, as was shown in Kappos 2005 using daily doses of 1.25 mg or 5.0 mg. Given these considerations, the recitation in the patent of a daily dosage of 0.5, 1.25, or 2.5 mg p.o. would be understood as clear and complete by a person of ordinary skill in the art, and that the absence of an immediately preceding loading dose would be understood.

Ex. 2024 ¶ 174.

Dr. Jusko further explains that, because the Specification describes intermittent dosing without mentioning a loading dose, "[a] person of skill would understand the daily or intermittent doses to be the full and complete dosing regimen, and thus would understand the patent to mean that there should be no immediately preceding loading dose in the dosing regimen." *Id.* ¶ 175.

Dr. Steinmann sets forth similar opinions (*see* Ex. 2022 ¶¶ 10, 182– 185) emphasizing, for example, that because initial doses of fingolimod were associated with bradycardia, one of ordinary skill in the art would interpret the Specification's silence with respect to loading doses as indicating the administration of only a daily dose. *See* Ex. 2022 ¶¶ 186–187.

Considering their respective backgrounds and experience, Drs. Jusko and Steinman are both well-qualified to testify as to the understanding of one of ordinary skill in the relevant art. *See e.g.*, Ex. 2005 ¶¶ 1, 7–13; Ex. 2006 (Jusko); Ex. 2022 ¶¶ 1, 12–21; Ex. 2023 (Steinman). We find their testimony on this matter credible and substantially unrebutted by Petitioner or Petitioners' experts. *See, e.g.*, Pet. Reply 24–25; Ex. 1002 ¶ 144 (Dr. Giesser stating that she "understood" the Specification lacked support for a loading dose, but evincing no independent analysis from the view point of one of ordinary skill in the art). Their testimony is also consistent with the Specification and comports with our construction of "daily dosage."

"[A] patentee bears the burden of establishing that its claimed invention is entitled to an earlier priority date than an asserted prior art reference." *In re Magnum Oil Tools Int'l, Ltd.,* 829 F.3d 1364, 1376 (Fed. Cir. 2016). Considering the record as a whole,

Patent Owner has demonstrated that the claims of the '405 patent are supported by the '342 application and the substantially similar disclosures of its predecessor applications, such that Kappos 2010 does not qualify as prior art.

Accordingly, we conclude that Petitioners have not demonstrated by a preponderance of evidence that Kappos 2010 anticipates claims 1–6 under 35 U.S.C. § 102(a).

III. MOTIONS

A. Motion to Amend

In its Corrected Contingent Motion to Amend, Patent Owner requests that we consider certain substitute claims if any one of the original claims of the '405 patent are found unpatentable. Paper 61, 1. As Petitioners have not shown by a preponderance of the evidence that any claim of the '405 patent is unpatentable, we deny Patent Owner's motion as moot.

B. Petitioners' Motion to Exclude

Petitioners filed a motion to exclude evidence (Paper 82); Patent Owner opposed (Paper 89); and Petitioners submitted a reply in support of its first motion to exclude (Paper 98).

i. Exhibits 2057 and 2070

Petitioner seeks to exclude Exhibits 2057 and 2070, and expert testimony relying on Exhibit 2057 under F.R.E. 602, 801-803, 805, and 901. Paper 82, 1–5; Paper 98, 1-2. Considering the parties' arguments and evidence, we agree with Patent Owner that Exhibit 2057, together with the signature pages relating to that document (Ex. 2070) comprise a report by

inventors of the '405 patent describing work underlying the claimed invention, and intended to support Patent Owner's unexpected results arguments. *See* Paper 89, 1–5. Nevertheless, because we do not rely on the disputed portions of the record in our Decision, we deny this portion of Petitioners' motion as moot.

ii. Exhibits 2063–2066

Petitioner also seeks to exclude Exhibits 2063–2066 and expert testimony relying thereon under F.R.E. 106, 602, 801-803, 805, and 901. Paper 82, 5–11; Paper 98, 2–4. Patent Owner opposes. Paper 89, 6–11. The disputed exhibits relate to Patent Owner's arguments regarding skepticism in the field. Because, as with Exhibits 2057 and 2070, we have not reached the merits of Patent Owner's evidence of secondary considerations of nonobviousness, we dismiss Petitioners' Motion to exclude regarding those exhibits as moot.

iii. Exhibits 2098 and 2096

Petitioner further seeks to exclude under F.R.E. 702 and 703, Exhibit 2098 and Exhibit 2096, paragraphs 28, 31–34. Paper 82, 11–15; Paper 98, 5. Exhibit 2098 comprises Dr. Chun's testimony regarding the facts and circumstances surrounding the publication of Webb, including that the authors' conclusions reflect detailed, underlying and unpublished experimental data. For example, Dr. Chun states: "We did not report the results from individual mice, nor would the Journal have provided the space needed to do so." Ex. 2098 ¶ 26. "However, those individual observations did inform our overall conclusion that 'a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy[.]'" *Id.* at ¶ 34. Summarizing his testimony, Dr. Chun states that, "our conclusion that about 70% reduction in peripheral

blood lymphocyte levels was required for any efficacy was not a mistake; it was the result of collective judgment based on multiple data sources and an appreciation of the subjective nature of determining clinical scores in this model." *Id.* at ¶ 8.

In the disputed portions of Exhibit 2096, Dr. Steinman testifies that in interpreting Webb, he took into account, for example, that "a person of skill would have understood that the authors had access to data from individual mice too, and that data would have informed their judgment as well." Ex. 2096 ¶ 31; *id.* at ¶ 33 ("Practical constraints on article length would normally preclude the publication of data like this. Instead, I would expect scientists who observe an important trend in disaggregated data to note their observation in summary form in the discussion section, just as the authors did here.").

Petitioner argues that Dr. Chun's testimony is "speculative and unsubstantiated" and his "memory cannot be relied upon." Paper 82, 13–14. Petitioner further contends that Patent Owner's failure to produce "the data underlying the Webb reference and any descriptions or summaries of the data Dr. Chun relied upon . . . renders the testimony cited above both unreliable and entitled to no weight, justifying exclusion of the testimony from consideration." *Id.* at 12.

As an initial matter, Petitioner does not persuasively argue that Dr. Steinmann relies on either Dr. Chun's testimony, or to Webb's unpublished data. *See id.* at 11–12. Nor do we understand Petitioners' complaint that it is not in possession of the underlying unpublished data as having any bearing on Dr. Steinmann's testimony as to how one of ordinary skill in the art would understand Webb. In addition, we

take at face value Patent Owner's explanation that neither it, nor Dr. Chun, is in possession of that data. Paper 89, 13. Rather, "[t]he data belong to Merck, where Dr. Chun was employed while preparing the Webb paper." *Id.* (citing Ex. 2098 ¶ 2). With respect to Dr. Chun's memory and the underlying basis for his testimony, this goes to the weight of his testimony. Assessing the weight of fact and expert testimony is well within the purview of this panel.

Accordingly, and for the reasons set forth at pages 11–15 of Patent Owner's Opposition (Paper 89), which we find persuasive, we deny Petitioners' motion to exclude Exhibit 2098 and paragraphs 28, 31–34 of Exhibit 2096.

C. Patent Owner's First Motion to Exclude

Patent Owner filed a first motion to exclude evidence (Paper 80); Petitioners opposed (Paper 94); and Patent Owner submitted a reply in support of its first motion to exclude (Paper 97).

i. The Testimony of Dr. Giesser

Patent Owner moves to exclude "all or at least the pharmacology opinions" of Dr. Giesser (Ex. 1002), as well as her CV (Ex. 1003). Paper 94, 1. According to Patent Owner, "Dr. Giesser perform[ed] an improper, hindsight-driven analysis" and "strayed far outside her area of expertise." Paper 80 at 1–6. For the reasons set forth in Petitioners' opposition, we do not agree that Dr. Geisser's analysis was improper. *See* Paper 94 at 1–7. Although we recognize the limitations of Dr. Giesser's expertise in pharmacology, Patent Owner's arguments go to the weight we should accord her testimony, not its admissibility. *See e.g.*, Dec. 9–10; Paper 80, 6; Paper 97, 3. Accordingly, Patent Owner's

motion to exclude Ex. 1003 and all or part of Ex. 1002 is denied.

ii. Exhibits relating to IPR2017-01550 and Clinical Trial Protocol

Patent Owner moves to exclude documents relating to IPR2017-01550 (Exs. 1032, 1035, 1037, 1041), and a confidential Novartis clinical trial document obtained during discovery (Ex. 1051). Paper 80, 7–10; Paper 98, 3–4. Petitioners oppose. Paper 94, 7–8. Because we do not rely on Exhibits 1032, 1035, 1037, 1041, or 1051 in our Decision, we deny this portion of Patent Owner's motion as moot.

iii. Dr. Chun's Deposition and Related Exhibits

Patent Owner moves to exclude Exhibits 1055 and 1056, introduced at Dr. Chun's deposition, as well as certain of his responses to questions of fact and opinion Petitioners posed at his deposition. Paper 80, 10–13; Paper 97, 4–5. Petitioners oppose. Ex. 94, 9–13. According to Patent Owner, Exhibits 1055 and 1056 relate to Phase II clinical trials in transplant patients and are thus beyond the scope of Dr. Chun's declaration, which "was limited to reciting facts about his Webb paper." Paper 80, 11. Patent Owner further argues, inter alia, that the introduction of Exhibits 1055 and 1056 was untimely, and that Dr. Chun, by his own admission, lacked the expertise to interpret clinical trial data. *Id.* at 12–13. Although Patent Owner's arguments may have some merit, we do not rely on Exhibits 1055 and 1056 in our Decision. Accordingly, we deny this portion of Patent Owner's motion as moot.

iv. Dr. Jusko's Deposition and Related Exhibits

Patent Owner moves to strike Exhibits 1057–1060, introduced at Dr. Jusko's Deposition, as well as his responses to questions regarding them as "improper impeachment and irrelevant." Paper 80, 13–15; Paper 97, 4–5. As Petitioners' explain, the challenged exhibits were introduced to test Dr. Jusko's opinion that a 75 kg patient would have been used to calculate equivalent human dosages from animal data. Paper 94, 13–15. We agree with Petitioners that this is sufficient reason to introduce Exhibits 1057–1060. Accordingly, we deny Patent Owner's motion with respect to Exhibits 1057–1060 and related testimony, and have considered this information in our analysis.

D. Patent Owner's Supplemental Motion to Exclude

Patent Owner filed a supplemental motion to exclude evidence (Paper 102); Petitioners opposed (Paper 101); and Patent Owner submitted a reply in support of its supplemental motion to exclude (Paper 103). Patent Owner's motion relates to Exhibits 1065–1069, submitted in support of Petitioners' sur-reply to Patent Owner's motion to amend. *See* Paper 102, 1. Because we do not reach the parties' arguments with respect to Patent Owner's motion to amend, or otherwise rely on Exhibits 1065–1069, we deny Patent Owner's motion to exclude these exhibits as moot.

E. Stipulated Protective Order and Motions to Seal

i. Paper 29

In Paper 29, Patent Owner moves for entry of a Stipulated Protective Order (Exhibit 2074), which "differs from the Default Protective Order by addition

of a category of confidential material to be marked "OUTSIDE ATTORNEY'S EYES ONLY – PROTECTIVE ORDER MATERIAL," and that "[a]ccess to such material is restricted to outside counsel, experts, one in-house counsel of a party, and support personnel." Paper 29, 2; *see also* Ex. 2074 (redlined version of the Default Protective Order showing changes). Patent Owner avers that lead Petitioner Apotex agrees to the entry of the stipulated protective order and that "[a]n identical protective order was entered by a similarly constituted panel of the Board in *Torrent Pharms. Ltd. et al v. Novartis AG et al*, IPR2014-00784, Paper 41 (May 7, 2015)." *Id.* at 2–3. The record does not indicate that any other Petitioner objects to the entry of the proposed Stipulated Protective Order. To the contrary, Petitioners collectively submit motions to seal under the Stipulated Protective Order and, thus, acquiesce to its entry. *See* Papers 36, 37, 50, 83, and 99.

Upon review of the motion, we determine that Patent Owner has identified sufficiently how the proposed Stipulated Protective Order departs from the Board's default protective order set forth in the Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48769–71 (Aug. 14, 2012). We further find that good cause exists for the proposed modifications from the Board's default protective order and that the proposed Stipulated Protective Order is warranted. Accordingly, we grant Patent Owner's unopposed motion for entry of a Stipulated Protective Order (Exhibit 2074).

We also address the parties' motions to seal. Papers 29, 37 (by Patent Owner); Papers 36, 50, 83, 99 (by Petitioner). Relevant to these motions, the Office Patent Trial Practice Guide states:

> 3. A party intending a document or thing to be sealed may file a motion to seal concurrent

> with the filing of the document or thing. § 42.14. The document or thing will be provisionally sealed on receipt of the motion and remain so pending the outcome of the decision on motion.
>
> 4. *Protective Orders:* A party may file a motion to seal where the motion contains a proposed protective order, such as the default protective order in Appendix B. § 42.54. Specifically, protective orders may be issued for good cause by the Board to protect a party from disclosing confidential information. § 42.54. Guidelines on proposing a protective order in a motion to seal, including a Standing Protective Order, are provided in Appendix B. The document or thing will be protected on receipt of the motion and remain so, pending the outcome of the decision on motion.

Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012).

"There is a strong public policy for making all information filed in a quasi-judicial administrative proceeding open to the public, especially in an inter partes review which determines the patentability of claims in an issued patent and therefore affects the rights of the public." *Garmin Int'l v. Cuozzo Speed Techs.*, LLC, IPR2012–00001, slip op. at 1–2 (PTAB Mar. 14, 2013) (Paper 34). For this reason, except as otherwise ordered, the record of an *inter partes* review trial shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Motions to seal may be granted for good cause; until the motion is decided, documents filed with the motion shall be sealed provisionally. *See* 37 C.F.R. §§ 42.14, 42.54(a).

The moving party bears the burden of showing that there is good cause to seal the record. *See* 37 C.F.R. § 42.20(c).

As set forth in the Board's Trial Practice Guide, confidential information that is sealed subject to a protective order ordinarily will become public 45 days after final judgment in a trial. Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,761 (Aug. 14, 2012). A party seeking to maintain confidentiality of information may file a motion to expunge the information before it becomes public; however, if the existence of the information is identified in a final written decision following trial, there is an expectation that the information will be made public. *Id.* This rule "balances the needs of the parties to submit confidential information with the public interest in maintaining a complete and understandable file history for public notice purposes." *Id.*

Under the Board's procedures, there is an expectation that all exhibits, including those filed under seal here, will be made part of the public record. Furthermore, the public's interest in understanding the basis for our decision on patentability means that any good cause alleged in a motion to seal must overcome this heightened public interest. Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. A party seeking to maintain the confidentiality of the information may file a motion to expunge the information from the record prior to the information becoming public. 37 C.F.R. § 42.56.

In Paper 29, Patent Owner moves to seal Exhibits 2057 and 2063– 2066. According to Patent Owner,

> Exhibits 2063-66 represent confidential communications with the FDA and/or disclose proprietary information regarding the design and execution of Novartis clinical trials. Novartis holds the information contained in these exhibits as confidential and takes precaution to prevent their distribution. Additionally, at least Exhibit 2057 contains redactions of specific personal information that is subject to Swiss Privacy Law and may not be distributed outside of Novartis. As a result, public disclosure of these documents could cause competitive business harm and good cause exists to seal them.

Paper 29, 3. We find that Patent Owner has satisfied the good cause requirement with respect to Exhibits 2057 and 2063–2066. Because we do not rely on these exhibits in our Decision, Patent Owner's desire to keep these documents confidential is not outweighed by the public interest in maintaining a complete and understandable record of these proceedings. Accordingly, we grant Patent Owner's motion with respect to Exhibits 2057 and 2063–2066.

Patent Owner further seeks to seal "portions of the Patent Owner's Response [Paper 26] and accompanying declarations of Lawrence Steinman (Ex. 2022), William Jusko (Ex. 2024), Fred Lublin (Ex. 2025), and Christian Schnell (Ex. 2026) containing substantive reference to the above exhibits." Paper 29, 4. Patent Owner does not otherwise identify the portions of those documents subject to its motion. We note, however, that Patent Owner has filed redacted versions of these documents. Accordingly, we grant Patent Owner's request on condition that, within 10 business days of this Decision, Patent Owner certify that the

redacted versions of the documents on file, or in the alternative, replacement copies thereof, comport with the grant or denial of any motion to seal in this proceeding.

ii. Paper 37

In Paper 37, Patent Owner moves to seal Paper 38, the unredacted version of its Brief in Opposition to Additional Discovery and unredacted versions of Exhibits 1042 and 1043, submitted by Petitioners. Considering the nature of these documents, and that we do not rely on this information in our Decision, Patent Owner has sufficiently shown good cause for granting this request.

iii. Paper 36

As we understand Paper 36, Petitioners move to seal the unredacted versions of Exhibits 1042 and 1043 and the entirety of Exhibits 1044 and 1045 because Patent Owner has designated each of these documents confidential subject to the Stipulated Protective Order. We do not discern that Patent Owner joins the motion.

As set forth above, we grant Patent Owner's motion to seal with respect to Exhibits 1042 and 1043, rendering Petitioners' request moot with respect to these Exhibits. With respect to Exhibits 1044 and 1045, because the subject information may be confidential to Patent Owner rather than Petitioner, we deny the request. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

iv. Paper 50

As we understand Paper 50, Petitioners move to seal their Reply to Patent Owner's Response (Paper 49), the unredacted version of Exhibits 1047, and the entirety of Exhibits 1050 and 1051 because Patent Owner has designated such information confidential subject to the Stipulated Protective Order. We do not discern that Patent Owner joins the motion. Because the subject information may be confidential to Patent Owner rather than Petitioner, we deny the request. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

v. Paper 83

As we understand Paper 83, Petitioners move to seal their Motion to Exclude (Paper 82) because Patent Owner has designated such information confidential subject to the Stipulated Protective Order. We do not discern that Patent Owner joins the motion. Because the subject information may be confidential to Patent Owner rather than Petitioner, we deny the request. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

vi. Paper 99

As we understand Paper 83, Petitioners move to seal their Reply in Support of Motion to Exclude (Paper 98) because Patent Owner has designated such information confidential subject to the Stipulated Protective Order. We do not discern that Patent Owner joins the motion. Because the subject information may be

confidential to Patent Owner rather than Petitioner, we deny the request. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

IV. CONCLUSION

Having weighed Petitioners' arguments and evidence as to the challenged claims against Patent Owner's countervailing arguments and evidence, we determine that Petitioners have not established by a preponderance of the evidence the unpatentability of claims 1–6 of the '405 Patent.

V. ORDER

For the above reasons, it is

ORDERED that claims 1–6 of the '405 Patent have not been shown to be unpatentable as obvious under 35 U.S.C. § 103 over Kovarik and Thomson;

FURTHER ORDERED that claims 1–6 of the '405 Patent have not been shown to be unpatentable as obvious under 35 U.S.C. § 103 over Chiba, Kappos 2005, and Budde;

FURTHER ORDERED that claims 1–6 of the '405 Patent have not been shown to be unpatentable as anticipated under 35 U.S.C. § 102 over Kappos 2010;

FURTHER ORDERED that Patent Owner's Corrected Contingent Motion to Amend (Paper 61) is denied as moot;

FURTHER ORDERED that Petitioners' motion to exclude Exhibits 2057 and 2070, and expert testimony relying on Exhibit 2057 (Paper 82) is denied as moot;

FURTHER—ORDERED that Petitioners' motion to exclude Exhibits 2063–2066 and expert testimony relying thereon (Paper 82) is denied as moot;

FURTHER ORDERED that Petitioners' motion to exclude Exhibit 2098 and paragraphs 28, 31–34 of Exhibit 2096 (Paper 82) is denied;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibit 1003 and all or part of Exhibit 1002 (Paper 80) is denied;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1032, 1035, 1037, 1041, 1051 (Paper 80) is denied as moot;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1055, 1056, and portions of Exhibit 1063 (Paper 80) is denied as moot;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1057–1060 and portions of Exhibit 2095 (Paper 80) is denied;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1065–1069 (Paper 102) is denied as moot;

FURTHER ORDERED that Patent Owner's motion for entry of a Stipulated Protective Order (Paper 29) is granted;

FURTHER ORDERED that the Stipulated Protective Order (Exhibit 2074) is hereby entered and shall govern the conduct of this proceeding unless otherwise modified by the Board;

FURTHER ORDERED that Patent Owner's motion to seal Exhibits 2057 and 2063–2066 (Paper 29) is granted. Patent Owner's further request to seal related portions of Paper 26 and Exhibits 2022, 2025 and 2026 is provisionally granted on condition that,

within 10 business days of this Decision, Patent Owner certify that the redacted versions of the documents on file, or in the alternative, replacement copies thereof, comport with the grant or denial of any motion to seal in this proceeding;

FURTHER ORDERED that Patent Owner's motion to seal Paper 38, the unredacted version of its Brief in Opposition to Additional Discovery and unredacted versions of Exhibits 1042 and 1043 (Paper 37) is granted;

FURTHER ORDERED that Petitioners' motion to seal the unredacted versions of Exhibits 1042, 1043, and the entirety of Exhibits 1044 and 1045 (Paper 36) is denied. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

FURTHER ORDERED that Petitioners' motion to seal their Motion to Exclude (Paper 82) is denied. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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APPENDIX E

Trials@uspto.gov
571-272-7822

Paper 10
Entered: August 9, 2017

UNITED STATES PATENT AND
TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND
APPEAL BOARD

Case IPR2017-01550
Patent 9,187,405 B2

ARGENTUM PHARMACEUTICALS LLC.,

Petitioner,

v.

NOVARTIS AG,

Patent Owner.

Before LORA M. GREEN, CHRISTOPHER M. KAISER, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

DECISION

Instituting *Inter Partes* Review and
Granting Motion for Joinder
37 C.F.R. § 42.108; 37 C.F.R. § 42.122(b)

I. INTRODUCTION

Argentum Pharmaceuticals LLC ("Argentum") filed a Petition requesting an *inter partes* review of claims 1–6 of U.S. Patent No. 9,187,405 B2 ("the '405 patent"). Paper 1 ("Pet."). Along with the Petition, Argentum filed a Motion for Joinder to join this proceeding with IPR2017-00854. Paper 3 ("Mot."). Argentum filed the Petition and Motion for Joinder in the present proceeding on June 9, 2017, within one month after we instituted trial in IPR2017-00854. Novartis AG, ("Novartis") has not filed a Preliminary Response to the Petition, and any such response would have been due September 16, 2017.

As explained further below, we institute trial on the same grounds as instituted in IPR2017-00854 and grant Argentum's Motion for Joinder.

II. DISCUSSION

In IPR2017-00854, Apotex, Inc. and Apotex Corp. ("Apotex") challenged claims 1–6 of the '405 Patent on the following grounds:

Ground	Claims	References	Basis
1	1–6	Kovarik[1] and Thomson	§ 103
2	1–6	Chiba,[2] Kappos 2005,[3] and Budde[4]	§ 103
3	1–6	Kappos 2010[5]	§ 102

After considering the Petition and Patent Owner's Preliminary Response, we instituted trial in IPR2017-00854 on each of the three asserted grounds. IPR2017-00854, Paper 11, 27.

Argentum's Petition in the instant matter is substantively identical to Apotex's Petition, challenging the same claims based on the same art and the same grounds. *Compare* IPR2017-01550, Paper 1, *with* IPR2017-00854, Paper 2. For the reasons stated in our Decision on Institution in IPR2017-00854, we institute trial in this proceeding on the same three grounds.

Having determined that institution is appropriate, we now turn to Argentum's Motion for Joinder. 35 U.S.C. § 315(c). Section 315(c) provides, in relevant

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[1] Kovarik and Appel-Dingemanse, WO 2006/058316, published June 1, 2006.

[2] Chiba et al., US 6,004,565, issued Dec. 21, 1999. Ex. 1006.

[3] Kappos et al., "FTY720 in Relapsing MS: Results of a Double-Blind Placebo-Controlled Trial with a Novel Oral Immunomodulator," 252 (Suppl 2) J. NEUROLOGY Abstract O141 (2005).

[4] Budde, et al., "First Human Trial of FTY720, a Novel Immunomodulator, in Stable Renal Transplant Patients," 13 J. AM. SOC. NEPHROLOGY 1073-1083 (2002).

[5] Kappos et al., "A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis," 362(5) N. Engl. J. Med. 387–401.

part, that "[i]f the Director institutes an inter partes review, the Director, in his or her discretion, may join as a party to that inter partes review any person who properly files a petition under section 311." *Id*. When determining whether to grant a motion for joinder we consider factors such as timing and impact of joinder on the trial schedule, cost, discovery, and potential simplification of briefing. *Kyocera Corp. v. SoftView, LLC*, Case IPR2013-00004, slip op. at 4 (PTAB Apr. 24, 2013) (Paper 15).

Under the circumstances of this case, we determine that joinder is appropriate. Argentum raises no new grounds of unpatentability from IPR2017-00854 and contends that there will be no impact on the trial schedule previously set in that case. Mot. 5–6; *see* IPR2017-00854, Paper 12. As Argentum notes, the Petition in IPR2017-00854 is substantively identical to the grounds, analysis, exhibits,[6] and expert declarations relied on in the instant proceeding. Mot. 2, 4, 5. Argentum agrees "to coordinate with Apotex regarding questioning at depositions and at the oral hearing, which will not exceed the time allotted by the rules for one party, or as otherwise agreed between Apotex and Patent Owner or as ordered by the Board," and invites the Board to adopt procedures similar to those used in other joinder cases, such as requiring Petitioners to make consolidated filings, for which Apotex is responsible. *Id*. at 6–7.

Argentum represents that Apotex does not opposed Argentum's Motion for Joinder. *Id*. at 3. By email to

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[6] Argentum notes that it has "added one additional exhibit (EX1041) which is a copy of the Federal Circuit Decision of April 12, 2017 affirming the Final Written Decision in IPR2014-00784, an IPR related to the present proceeding." Mot., 2–3.

the Board dated August 4, 2017, counsel for Novartis represents that, 1) Novartis does not object to the Motion for Joinder; 2) Argentum has agreed not to pursue any arguments or make any filings separate from those made by Apotex; and 3) that Novartis will not submit a Preliminary Response in IPR2017-01550, and "instead will proceed with a Patent Owner Response to the Petitions in both IPRs simultaneously." Ex. 3001.

In view of the foregoing, we find that joinder based upon the conditions stated in Argentum's Motion for Joinder and Novartis' August 4 email will have little or no impact on the timing, cost, or presentation of the trial on the instituted grounds. Moreover, discovery and briefing will be simplified if the proceedings are joined. Thus, without opposition to the Motion for Joinder from any of the parties, the Motion is granted.

III. ORDER

Accordingly, it is

ORDERED that *inter partes* review is instituted in IPR2017-01550 on the following grounds:

> Claims 1–6 under 35 U.S.C. § 103 as unpatentable over the combination of Kovarik and Thomson;
>
> Claims 1–6 under 35 U.S.C. § 103 as unpatentable over the combination of Chiba, Kappos 2005, and Budde;
>
> Claims 1–6 under 35 U.S.C. § 102 as anticipated by Kappos 2010.

FURTHER ORDERED that Argentum's Motion for Joinder with IPR2017-00854 is granted;

FURTHER ORDERED that IPR2017-01550 is terminated and joined to IPR2015-00854, pursuant to 37 C.F.R. §§ 42.72, 42.122, based on the conditions discussed above;

FURTHER ORDERED that the Scheduling Order in place for IPR2017-00854 (Paper 12) shall govern the joined proceedings;

FURTHER ORDERED that all future filings in the joined proceeding shall be made only in IPR2017-00854;

FURTHER ORDERED that the case caption in IPR2017-00854 for all further submissions shall be changed to add Argentum as a named Petitioner after Apotex, and to indicate by footnote the joinder of IPR2017-01550 to that proceeding, as indicated in the attached sample case caption;

FURTHER ORDERED that a copy of this Decision shall be entered into the record of IPR2017-00854.

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IPR2017-01550

Patent 9,187,405 B2

Sample Case Caption

UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE PATENT TRIAL AND APPEAL BOARD

———

APOTEX INC., APOTEX CORP., and ARGENTUM PHARMACEUTICALS LLC,

Petitioners,

v.

NOVARTIS AG.,

Patent Owner.

———

Case IPR2017-00854[7]
Patent 9,187,405 B2

———

[7] Case IPR2017-01550 has been joined with this proceeding.

APPENDIX F

Trials@uspto.gov Paper 11
571-272-7822 Entered: July 18, 2017

UNITED STATES PATENT AND
TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND
APPEAL BOARD

Case IPR2017-00854
Patent US 9,187,405 B2

APOTEX INC. and APOTEX CORP.,

Petitioner,

v.

NOVARTIS AG,

Patent Owner.

Before LORA M. GREEN, CHRISTOPHER M. KAISER, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

DECISION

Instituting *Inter Partes* Review *37 C.F.R. § 42.108*

I. INTRODUCTION

Apotex Inc. and Apotex Corp. ("Apotex" or "Petitioner") filed a Petition requesting an *inter partes* review of claims 1–6 of U.S. Patent No. US 9,187,405 B2 (Ex. 1001, "the '405 patent"). Paper 2 ("Pet."). Novartis AG, ("Novartis" or "Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, we institute an *inter partes* review of claims 1–6 of the '405 patent.

A. Related Proceedings

According to Patent Owner, there are no other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding. Paper 4, 2. Petitioner, however, notes that in IPR2014-00784, the Board issued a Final Written Decision relating to U.S. Patent No. 8,324,283 B2, and that "[a]lthough not from the same patent family as the '405 patent, the '283 patent included claims to pharmaceutical compositions of fingolimod, or a pharmaceutically acceptable salt thereof, that is suitable for oral administration, as well as claims directed to the treatment of multiple sclerosis using S1P receptor agonists." Pet. 20.

B. The '405 Patent and Relevant Background

The '405 Patent, entitled "S1P Receptor Modulators for Treating Relapsing-Remitting Multiple Sclerosis," issued to Peter C. Hiestand and Christian Schnell from U.S. Application No. 14/257,342 ("the '342 application"), filed April 21, 2014. Ex. 1001, at [21], [60], [71], [72]. The '342 application is a divisional of Application No. 13/149,468 ("the '468 application") (now U.S. Pat. No. 8,741,963). *Id.* at [60]. The '468 application, in turn, is a continuation of Application No. 12/303,765 ("the '765 application."), which is the U.S. entry of PCT/EP2007/005597, filed June 25, 2007. *Id.*; Ex. 1009, 21, 40. PCT/EP2007/005597 claims priority to foreign application GB0612721.1 (Ex. 1012), filed on June 27, 2006. Ex. 1001, at [30]; *see* Ex. 1009, 57–58.

The instant "invention relates to the use of an S1P[1] receptor modulator in the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis." Ex. 1001, 1:5-8. "Characteristic pathological features of demyelinating diseases include inflammation, demyelination and axonal and oligodendrocyte loss. In addition[,] lesions can also have a significant vascular component. A firm link has recently been established between chronic inflammation and angiogenesis and neovascularization seems to have a significant role in the progression of disease." *Id.* at 9:6–12. According to the inventors, "[i]t has now been found that S1P receptor modulators have an inhibitory effect on neo-angiogenesis associated with demyelinating diseases, e.g. [multiple sclerosis]." *Id.* at 9:13–15.

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[1] S1P refers to sphingosine-1 phosphate, a natural serum lipid. Ex. 1001, 1:13–14.

"Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with chronic inflammatory demyelination leading to progressive decline of motor and sensory functions and permanent disability." Ex. 1001, 8:61–64. The inventors state that S1P receptor agonists or modulators may be useful in the treatment of MS, including the Relapsing-Remitting MS (RR-MS) form, which accounts for 85% of patients' initial experience with the disease and is the precursor to the more debilitating Secondary-Progressive form (SPMS). *Id.* at 9:64–10:21; *see also id*. at 10:3–5 (noting that within 10 years of onset about half of RR-MS patients will develop SPMS); Ex. 1005,[2] 159–60, Fig. 1 (discussing the pathophysiology, classification, and clinical course of MS).

"S1P receptor agonists or modulators are known as having immunosuppressive properties or anti-angiogenic properties in the treatment of tumors. . . ." Ex. 1001, 8:56–60. Preferred compounds stimulate lymphocyte homing, thereby "elicit[ing] a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression." *Id.* at 2:17–23. "A particularly preferred S1P receptor agonist . . . is FTY720, i.e., 2-amino-2-[2-(4-octyphenyl)ethyl] propane-1,3-diol. . . ." *Id.* at 8:17–30. This compound, also known as fingolimod, is the active ingredient in Novartis's Gilenya product (fingolimod hydrochloride) approved for the treatment of RR-MS. *See id.* at 9:64– 10:16; Pet. 62; Prelim. Resp. 1.

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[2] Thomson, "FTY720 in Multiple Sclerosis: The Emerging Evidence of its Therapeutic Value," 1(3) CORE EVIDENCE 157-167 (2006). Ex. 1005.

C. Challenged Claims

Illustrative claim 3 recites (paragraphing added):

> 3. A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising
>
> orally administering to said subject 2-amino-2-[2-(4- octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form,
>
> at a daily dosage of 0.5 mg,
>
> absent an immediately preceding loading dose regimen.

The remaining independent claims differ only in the language of the preamble, such that the "treating" language of claim 3 is replaced with "reducing or preventing or alleviating relapses" (claim 1) or "slowing progression" of RR-MS (claim 5).

Depending from claims 1, 3, and 5, respectively, claims 2, 4, and 6 specify that the 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol is the hydrochloride salt form—i.e., fingolimod hydrochloride.

C. The Asserted Prior art and Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 21):

Ground	Claims	References	Basis
1	1–6	Kovarik[3] and Thomson	§ 103
2	1–6	Chiba,[4] Kappos 2005,[5] and Budde[6]	§ 103
3	1–6	Kappos 2010[7]	§ 103

Petitioner further relies on the testimony of Barbara S. Giesser, M.D. (Ex. 1002). Patent Owner relies on the testimony of Fred D. Lublin, M.D. (Ex. 2003) and William J. Jusko, Ph.D. (Ex. 2005).

II. ANALYSIS

To anticipate a claim under 35 U.S.C. § 102, "a single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir.

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[3] Kovarik and Appel-Dingemanse, WO 2006/058316, published June 1, 2006. Ex. 1004.

[4] Chiba et al., US 6,004,565, issued Dec. 21, 1999. Ex. 1006.

[5] Kappos et al., "*FTY720 in Relapsing MS: Results of a Double-Blind Placebo-Controlled Trial with a Novel Oral Immunomodulator*," 252 (Suppl 2) J. NEUROLOGY Abstract O141 (2005). Ex. 1007.

[6] Budde, et al., "*First Human Trial of FTY720, a Novel Immunomodulator, in Stable Renal Transplant Patients,*" 13 J. AM. SOC. NEPHROLOGY 1073-1083 (2002). Ex. 1008.

[7] Kappos et al., "*A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis*," 362(5) N. Engl. J. Med. 387–401.

2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art to combine the elements in the way the claimed invention does. *Id.*

A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Warsaw Orthopedic, Inc.*, 832 F.3d 1327, 1333 (Fed. Cir. 2016) ("As part of the obviousness inquiry, we consider 'whether a [PHOSITA] would have been motivated to combine the prior art to achieve the claimed invention and whether there would have been

a reasonable expectation of success in doing so.'" (quoting *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006)).

A. Person of Ordinary Skill in the Art.

Petitioner contends that a person of ordinary skill in the art as of the date of the invention

> would typically include a person with a medical degree (M.D.) and several years of experience treating multiple sclerosis patients. . . . would be familiar with administering therapeutic agents for the treatment of multiple sclerosis, including RR-MS, and dosing regimens of the various therapeutic agents available for treating RR-MS. . . . [and] would be knowledgeable about the multiple sclerosis medical literature available at the relevant time.

Pet. 18–19 (citations to Ex. 1002 ¶¶ 39–40 omitted). This is consistent with the definition offered during prosecution that, "[t]he relative skill of those in the art is high, generally that of an M.D. or Ph.D. with expertise in the area of neurology." Ex. 1009, 13. Further, in focusing on the MS disease state and the conduct of a prophetic clinical trial of fingolimod ("Compound A") in treating RR-MS, the Specification suggests that one of ordinary skill in the art would possess a medical or related doctoral degree and have experience in the field of MS treatment and clinical research. *See, e.g.*, Ex. 1001, 8:61–9:12, 9:64–10:16, 11:4–12:13.

In the Preliminary Response, however, Patent Owner contends that Apotex's proposed definition "is plainly incorrect" because "a person of skill in other

dosing patent cases almost always includes a pharmacologist," the '405 Patent and relevant references include pharmacologists as "essential contributing authors," and "[p]harmacologists would have to interpret that data before reaching any conclusions about the obviousness of a 0.5 mg daily dose." Prelim. Resp. 39–43.

In the context of the '405 patent and prior art, we agree with Patent Owner that expertise in pharmacology may be useful in determining obviousness, particularly in light of the prior art proffered in the Preliminarily Response. *See id*. at 41–43; *see also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the level of ordinary skill in the art may be evident from the prior art). This is not to say that a person of ordinary skill in the art would lack an M.D. degree, other related doctoral degree, or expertise in the treatment of multiple sclerosis. Accordingly, we do not consider this a binary choice. To the contrary, courts and tribunals have frequently identified the hypothetical person of ordinary skill as a composite or team of individuals with complementary backgrounds and skills. *See, e.g.*, *AstraZeneca Pharm. LP v. Anchen Pharm., Inc.,* No. 10 CV-1835 JAP TJB, 2012 WL 1065458, at *19, *22 (D.N.J. Mar. 29, 2012), *aff'd*, 498 F. App'x 999 (Fed. Cir. 2013) (collecting cases); *Merial, Inc. v. Fidopharm Inc.*, IPR2016-01182, Paper 11 at 9 (PTAB Nov. 7, 2016). Indeed, Patent Owner relies on one such case in which "a person of skill would be a 'multi-member drug development team' including in the 'pertinent art[s]' of 'pharmaceutical science,' 'clinical medicine,' and formulation pharmaceuticals.'" Prelim. Resp. 51 (citing *Helsinn Healthcare S.A. v. Dr. Reddy's Labs. Ltd.*, No. CV 11-3962 (MLC), 2016 WL 832089, at *72 (D.N.J. Mar. 3, 2016) (reversed on other grounds by *Helsinn Healthcare S.A. v. Teva Pharm.*

USA, Inc., No. 2016-1284, 2017 WL 1541518 (Fed. Cir. May 1, 2017)).

On the record before us, we find that one of ordinary skill in the art may be part of a multi-disciplinary research team including 1) a Ph.D. with expertise in the area of neurology and/or an M.D. having several years of clinical experience treating multiple sclerosis patients, and who would be knowledgeable about the multiple sclerosis medical literature, and 2) a pharmacologist with experience in drug development.

Patent Owner addresses the definition of one of ordinary skill in the art, at least in part, by asserting that Petitioner's expert, Dr. Giesser, is "a physician without the necessary expertise to opine on what a person of skill would have inferred from the prior art as fingolimod's dosing." Prelim. Resp. 36. Although Dr. Giesser appears to lack a formal degree in pharmacology, she does have extensive experience in the field of medicine, particularly with respect to MS treatment and clinical research. *See generally* Ex. 1002 ¶¶ 1–4; Ex. 1003. In light of Dr. Giesser's background and experience in these areas, which would necessitate at least some familiarity with pharmacological principles, we decline to dismiss her opinions on the '405 Patent and relevant literature. *See SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010), aff'd sub nom. *Glob.-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754 (2011) (expert testimony admissible where testimony established an "adequate relationship" between witness's experience and the claimed invention). In determining the evidentiary weight to be accorded to Dr. Giesser's testimony, we are cognizant of the fact that she lacks a formal degree in pharmacology.

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

The preambles of the independent claims recite methods for "reducing or preventing or alleviating relapses in" (claim 1), "treating" (claim 3), and "slowing progression of" (claim 5) RR-MS "in a subject in need thereof." This "subject in need thereof" is then reflected in the body of each claim as it recites the step of orally administering fingolimod "to said subject."

Petitioner argues that the preambles of the independent claims should be accorded no patentable weight as they "at most merely describe[] the intended purpose of the method and that the subject receiving fingolimod is a subject with RR-MS." Pet. 24–25; Ex. 1002 ¶¶ 43–45. As we understand the argument, Petitioner proposes that "said subject" is any subject with RR-MS, as such persons inherently are, or will be, "in need of a treatment that reduces, prevents or alleviates relapses and slows the progression of RR-MS." *Id.* at 22–23; Ex. 1002 ¶¶ 43–45. Petitioner's argument, however, conflates the etiology and progression of multiple sclerosis with the plain language of the claims. Thus, for example, Petitioner may be

correct that because patients accrue neurologic disability with each relapse episode "an RR-MS patient is in need of a treatment that reduces, prevents or alleviates relapses and slows the progression of RR-MS." *See* Pet. 23. But Petitioner does not present evidence that "reduc[ing], prevent[ing] or alleviat[ing] relapses," as set forth in claim 1, is necessarily the same as the arguably broader language, "treating," recited in claim 3. *See CAE Screen Plates, Inc. v. Heinrich Fiedler GMBH & Co. KG*, 224 F.3d 1308, 1317 (Fed. Cir. 2000) ("In the absence of any evidence to the contrary, we must presume that the use of these different terms in the claims connotes different meanings.").

In contrast to Petitioner's position, Patent Owner contends that the preambles of independent claims 1, 3, and 5, limit the scope the challenged claims. Prelim Resp. 29–35. Relying on the testimony of its expert, Dr. Lublin, Patent Owner presents evidence that "a person of skill would not understand reducing relapses, treating the disease, and slowing its progression to mean the same thing." *Id*. at. 32–33 (relying on Ex. 2003 ¶¶ 5–7, 43–55). As noted above, we do not ascertain where Petitioner or Petitioner's expert, Dr. Giesser, argues that these terms are synonymous.

Patent Owner also points out that failing to accord meaning to the differences in the preambles "would eliminate any differences among claims 1–2, 3–4, and 5–6." *Id.* at 30–31. On balance, we agree with Patent Owner that the presumption against claim redundancy weighs against Petitioner's proposed construction.

We also find persuasive Patent Owner's argument that the words in the preambles inform the scope of "said subject" in the body of each claim. Prelim. Resp.

29–35. In particular, the preambles of claims 1, 3 and 5:

> provide[] an antecedent basis for terms used in the body of each claim, specifying the needs of the "subject" alluded to later. This is a classic example of the preamble defining a term—the "subject in need" of certain effects—which then is subsequently used in the body of the claim—"to said subject."

Id. at 34.

In accord with the above, at least for the purpose of deciding whether to institute review, we find the preambles of claims 1, 3, and 5 limiting, and accord the ordinary and customary meaning to the claim language "reducing or preventing or alleviating relapses in," "treating," and "slowing progression of" RR-MS "in a subject in need thereof." We further construe the terms "reducing or preventing or alleviating relapses" and "slowing progression" as subsumed within the genus of "treating" RR-MS. No other claim term requires express construction for purposes of this Decision. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

C. Ground I: Obviousness of Claims 1–6 Over Kovarik and Thomson

1. 35 U.S.C. § 325(d)

Petitioner challenges claims 1–6 under 35 U.S.C. § 103 as obvious in view of Kovarik and Thomson. Pet. 21, 32–48. Patent Owner opposes on the merits and further requests that we reject this challenge under § 325(d). Prelim. Resp. 2–3, 21–36. With respect to the latter, Patent Owner argues that the Board should not "rehash" prosecution in this IPR because Applicants

overcame a rejection based on Kovarik and Virley (a reference allegedly interchangeable with Thomson). *See id*. at 21–23.

Anticipating the § 325(d) argument, Petitioner admits that Kovarik was substantively discussed during prosecution but argues that, "Ground 1 provides new evidence and argument regarding the obviousness of the challenged claims," including Dr. Giesser's testimony that "several assertions made by Applicants' attorneys during prosecution to overcome the rejection are incorrect." Pet. 5–6; *see* Ex. 1002 ¶¶ 27–30. Dr. Giesser testifies, for example, that

> applicants state that the maintenance dose is "dependent on the immediately preceding loading dose." EX1011 at 0034. However, this is incorrect. As discussed more fully below in Section VIII.E, maintenance doses are not dependent on loading dose regimens. Rather maintenance doses are dependent on the desired steady state plasma concentration and the clearance rate of the drug.

Ex. 1002 ¶ 28 (citations omitted).

Patent Owner attempts to provide context to those statements, stating, for example, that Applicant's attorney, Dr. Holmes, "summarized Kovarik as teaching 'that the daily dosage administered after the initial period can vary substantially relative to the standard daily dosage and is dependent on the immediately preceding loading dose administered during the initial phase.'" *See, e.g.*, Prelim Resp. 25–26 (quoting Ex. 1001 ¶ 33). Nevertheless, on the present record, we find Petitioner's argument persuasive. Accordingly, we decline to exercise our discretion to deny institution under § 325(d).

2. Overview of Kovarik

Kovarik relates to an improved dosage regimen of S1P receptor modulators or agonists for the treatment of transplant patients suffering from autoimmune diseases or disorders, including multiple sclerosis. Ex. 1004, 1, 14. Preferred S1P receptor modulators or agonists "elicit a lymphopenia resulting from a redistribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression." *Id.* at 2. In a particularly preferred embodiment, the S1P receptor agonist is FTY720 (i.e., fingolimod). *Id.* at 13.

Kovarik teaches that S1P receptor modulators or agonists are used in combination with cyclosporine A and everolimus in transplantation experiments and "[d]ue to their immune-modulating potency . . . are also useful for the treatment of inflammatory and autoimmune diseases." *Id.* at 1. According to Kovarik, "[i]t has now surprisingly been found that a specific dosage regimen, e.g. a loading dose, will provide further unexpected benefits." *Id.* In particular, an "S1P receptor modulator or agonist . . . is administered in such a way that during the initial 3 to 6 days . . . of treatment the dosage of said S1P receptor modulator or agonist is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage of said S1P receptor modulator or agonist is administered and thereafter the treatment is continued with the standard or a lower daily dosage. . . ." *Id.* at 13–14. "[T]he standard daily dosage (also called maintenance dose) refers to the dosage of an S1P receptor modulator or agonist necessary for a steady-state trough blood level of the medication or its active metabolite(s) providing effective treatment." *Id.* at 14.

In one embodiment of the invention, a loading dose of, e.g., 0.5 mg, 1 mg, 1.5 mg, or 2 mg fingolimod per day is administered "during the initial period of four days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 0[.]5 mg." *Id.* at 15.

3. Overview of Thomson

Thomson teaches that "[fingolimod] elicits lymphocyte sequestration by facilitating a reversible redistribution of lymphocytes from the circulation to secondary lymphoid tissues. This is a unique immunomodulation mechanism whereby T lymphocytes are effectively directed away from inflammatory sites toward the lymphatic system." Ex. 1005, 162; *see also id*. at Abstract ("There is good evidence that FTY720 achieves immunomodulation as shown by a reversible redistribution of peripheral blood lymphocytes after oral administration."). According to Thomson:

> FTY720 has shown promising results in preclinical models of EAE, which in part has led to its clinical evaluation in multiple sclerosis. There is moderate evidence from two meeting abstracts of a phase II study that FTY720 (administered orally once daily for up to 12 months) improved the patient-oriented outcomes of relapse rate and the likelihood of remaining relapse-free. In addition, there is moderate evidence that disease-oriented outcomes were also improved by FTY720 in that inflammatory disease activity (both new and existing) was reduced as determined by MRI.

Id. at 166–167.

In reviewing the emerging clinical evidence for fingolimod as a treatment for multiple sclerosis, Thomson reports that "[t]wo meeting abstracts have been published showing results obtained with FTY720 in a 12-month phase II clinical trial in patients with active relapsing multiple sclerosis." Ex. 1005, Abstract. These publications disclosed the benefits of fingolimod as compared to placebo at doses of 1.25 and 5 mg per day.[8] *See id*. at 164–65, Table 4.

Thomson also reviews a number of shorter-term clinical trials relating to pharmacodynamic and pharmacokinetic outcomes of fingolimod administration. *Id.* at 162–164, Table 3. In one multi-dose study, Thomson notes that "[p]eripheral blood lymphocyte counts decreased from baseline to nadir (range 3–7 d after first dose) by 80 and 88% in subjects receiving FTY720 1.25 and 5 mg, respectively." *Id.* at Table 3.

With respect to another study involving single doses of 0.25, 0.5, 0.75, 1, 2, or 3.5 milligrams of FTY720, Thomson states that "All FTY720 groups showed a temporal pattern of relative lymphocyte sequestration, seen at the latest 6 h postdose. No clear dose response, but the highest doses showed a more pronounced reduction in lymphocyte numbers." *Id.* (referencing, in part, Budde 2002 (Ex. 1008)); *see also id.* at 163 ("Although the higher doses of FTY720 produced a more rapid and sustained lymphocyte sequestration, the actual degree of this property was similar across the range of doses used in the study and no clear dose–response relationship was detected.").

With respect to yet another study involving renal transplant patients co-administered cyclosporine and

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[8] We note that one of the referenced studies is Kappos 2005 (Ex. 1007).

0.25, 0.5, 1, or 2.5 mg doses of fingolimod for twelve weeks, Thomson reports that "lymphocyte sequestration was seen as early as w 1, nadir was reached at w 4 and was fully reversed 4-8 w after cessation of treatment. The pharmacodynamics were not dose-linear over the 10-fold dose range." *Id.* at Table 3; *see id*. at 164.

4. Analysis of Ground I

In arguing that the challenged claims would have been obvious over Kovarik and Thomson, Petitioner states that "Kovarik discloses that the oral administration of a 0.5 mg daily dose of FTY720 provides effective treatment of multiple sclerosis. . . ." Pet. 36; *see* Ex. 1002 ¶¶ 119, 126. According to Petitioner:

> A person of skill in that art would have read Kovarik's teachings as readily applicable to a patient with the RR-MS form of the disease because RR-MS is by far the most common form of the disease at onset and accounts for approximately 85% of cases. Also, a skilled artisan would have known that inflammation is the driver of relapses in RR-MS and that fingolimod hydrochloride was taught to treat MS by reducing inflammation through the accelerated lymphocyte homing mechanism taught by Kovarik.

Pet. 41–42 (internal citations omitted). Petitioner further argues that, "Thomson provides additional motivation to administer 0.5 mg FTY720 to a patient with RR-MS . . . [by] present[ing] an array of evidence supporting the efficacy of FTY720 in treating RR-MS by reducing relapse rates and slowing progression of RR-MS associated with inflammation." Pet. 42 (citing Ex. 1002, ¶ 109). According to Petitioner,

> [t]he skilled artisan would have had a reasonable expectation that the daily oral dose of 0.5 mg FTY720 taught by Kovarik would be therapeutically effective for patients suffering from RR-MS because Thomson describes clinical trials of FTY720 that tested doses in the range of 0.25 mg to 3.5 mg, in which it was found that "the actual degree of this property [lymphopenia] was similar across the range of doses used."

Pet. 43 (citing Ex. 1005, 162–63; Ex. 1002 ¶¶ 112–13).

In response, Patent Owner contends that Kovarik "indisputably mandates a loading dose, without exception," and therefore teaches away from a method that excludes a loading dose as required by the challenged claims. *See* Prelim. Resp. 23–28. However, as noted above, Kovarik teaches one embodiment in which 0.5 mg of fingolimod, nominally administered as a "loading dose" for four days, is followed by "maintenance therapy" at the same daily dose. Ex. 1004, 15. Further, based on the evidence of record, we accept the testimony of Petitioner's expert that "a person of ordinary skill would recognize that the loading dose regimen taught by Kovarik is not necessary to obtain therapeutic efficacy," but is merely a means to achieve rapid, steady-state drug concentrations, which may be beneficial in organ transplantation, but was not standard practice in the treatment of MS. *See* Ex. 1002 ¶¶ 67, 72, 119, 121–22. We further note that Kovarik teaches that, whereas, a standard daily dose (i.e., "maintenance dose") provides a steady-state trough blood level of the drug or its active metabolites for "effective treatment," the addition of a loading dose provides "*further* unexpected benefits." *See* Ex. 1004, 1, 14 (italics added). Kovarik, thus,

teaches the addition of a loading dose as an improvement to fingolimod dosage regimes known in the art. It, therefore, stands to reason that one of ordinary skill in the art would understand that a standard daily dose (e.g., the 0.5 mg daily dose recited at page 15 of Kovarik) will provide therapeutic benefits absent a loading dose. *See* Ex. 1002 ¶ 120.

Patent Owner further argues that Ground I should fail because Kovarik and Thomson do not provide "any reason to believe that 0.5 mg daily doses of fingolimod would actually be of use to a subject in need of "reducing or preventing or alleviating relapses in" RR-MS (claims 1 and 2); "treating" RR-MS (claims 3 and 4); or "slowing progression" of RR-MS (claims 5 and 6)." Prelim. Resp. 29; *see id*. at 35–36.

As an initial matter, in section II(B), above, we construe "reducing or preventing or alleviating relapses" and "slowing progression" as subsumed within the genus of "treating" RRMS. *See* Ex. 1002 ¶ 47 (testifying that the goals of treating RRMS "include (1) the reduction of, alleviation of, or relief from the relapses that characterize RR-MS; and (2) providing some delay, even if short, in disease progression"). Patent Owner provides no reasonable explanation or evidence as to why one of ordinary skill in the art would have believed that "treating" RRMS with fingolimod would not be expected to reduce, prevent, or alleviate relapses, or slow the progression of the disease.

Second, as discussed in sections II(C)(1) and II(C)(2), above, Kovarik teaches a daily dose of 0.5 mg and Thomson teaches a range of doses including 0.5 mg, which result in the lymphocyte homing effect then thought to underlie fingolimod's efficacy in treating RR-MS. According to Dr. Giesser, one of ordinary skill

in the art would recognize that 0.5 mg/day of fingolimod would likely be efficacious in treating RR-MS—and less likely to result in side effects than higher doses. *See* Ex. 1002 ¶¶ 60–62, 116–118, 125.

In contrast to Dr. Giesser's testimony, we note with interest Patent Owner's argument, supported by its experts Drs. Lublin and Jusko, that pharmacokinetic data evidenced by Webb, Kahan 2003, and Park would have indicated to those of ordinary skill in the art that 0.5mg/day of fingolimod would not result in sufficient lymphopenia to successfully treat RR-MS.[9] *See, e.g.*, Prelim. Resp. 41–43; Ex. 2003 ¶¶ 39; Ex. 2005 ¶¶ 36–39. Although we do not find Patent Owner's argument unreasonable, at this stage of the proceedings, "a general issue of material fact created by [Patent Owner's] testimonial evidence will be viewed in the light most favorable to the petitioner." *See* 37 C.F.R. § 42.108(c).

Responding to Patent Owner's argument that Petitioner should have addressed Patent Owner's pharmacokinetic argument in the Petition, we do not discern where this argument was raised during the course of prosecution, nor are we convinced that this argument is self-evident based on the art of record. *See* Prelim. Resp. 43–45. Accordingly, and contrary to Patent Owner's contention, we see nothing unfair or improper in the lack of discussion in the Petition of the pharmacokinetic data in Webb, Kahan 2003, and/or Park. We, nevertheless, look forward to further development of this issue at trial.

On the present record, we find that Petitioner's arguments and evidence establish a reasonable

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[9] Although Patent Owner directs the argument to Ground II, we find it equally applicable here.

likelihood that Petitioner would prevail in demonstrating the unpatentability of claims 1–6 over the combination of Kovarik and Thomson.

D Ground II: Obviousness of Claims 1–6 Over Chiba, Kappos 2005, and Budde

1. Overview of Chiba

Chiba discloses that fingolimod hydrochloride and related compounds are capable of suppressing the immune response of mammals through accelerated lymphocyte homing ("ALH-immunosuppression"). Ex. 1006, Abstract, 2:35–44, 4:63–5:7. "For example, the compound FTY720 specifically directs lymphocytes to the peripheral lymph nodes, mesenteric lymph nodes, and Peyer's patches. By reversibly sequestering lymphocytes in these tissues, the compounds can inhibit an immune response in a mammal." *Id.* at Abstract; *see id.* at 2:38–40, 17:38–40. Such ALH-immunosuppressive compounds "are useful in for the prevention or treatment of resistance to transplantation or transplantation rejection . . . [and] autoimmune diseases such as . . . multiple sclerosis" (*id.* at 6:26–49) and may be administered "to an adult daily by 0.01-10 mg (potency) in a single dose or in several divided doses . . ." (*id*. at 8:28–34).

2. Overview of Kappos 2005

According to Kappos 2005, "FTY720 is an oral immunomodulator (sphingosine-1 phosphate receptor (S1P) modulator) that reversibly sequesters tissue damaging T and B cells away from blood and the central nervous system to peripheral lymph nodes. FTY720 has demonstrated both preventive and therapeutic efficacy in several animal models of MS." Ex. 1007, O141. Kappos discloses the clinical and MRI

results of a double-blind, placebo-controlled study to evaluate efficacy, safety and tolerability of 1.25 mg and 5.0 mg daily doses of FTY720 in the treatment of RR-MS. *Id.* According to Kappos 2005, the study "demonstrated efficacy of FTY720 on MRI and relapse-related endpoints" and "strongly suggest[s] that FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily oral administration." *Id*.

3. Overview of Budde

Budde discloses a "randomized, double-blind, placebo-controlled [study] that explored single oral doses of FTY720 from 0.25 to 3.5 mg" in renal transplant patients. Ex. 1008, Abstract. Budde shows that single oral doses of 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, and 3.5 mg induced decreased lymphocyte counts as compared to placebo with a nadir of 4.7–8 hours after administration. *Id*. at 1078; *see id*. at 1079 ("All FTY-randomized groups manifested a temporal pattern of relative lymphopenia, detected at the latest by 6 h postdose."). Moreover,

> At FTY doses ranging from 0.5 mg to 3.5 mg, no clear dose response relationship was detected, but the two highest dose groups exhibited a more pronounced decline in lymphocyte numbers. FTY doses of >2.0 mg were associated with a more rapid onset of lymphopenia (31 to 43% decrease after 2 h). The three subjects treated with 3.5 mg FTY manifested the most prolonged and intensive lymphopenia.

Id.; *but see id.* at 1082 ("Single oral doses of FTY in doses ranging from 0.5 mg to 3.5 mg caused a dose-dependent, reversible lymphopenia.").

With respect to safety, "single oral doses of FTY were well tolerated with transient asymptomatic bradycardia as the most common adverse event." *Id.* at 1082. "Higher doses of FTY were more frequently associated with bradycardia: 9 out of 12 subjects randomized to >0.75 mg of FTY developed bradycardia; however, only 1 of 12 subjects receiving 0.25 to 0.5 mg of FTY." *Id.* at 1075.

4. Analysis of Ground II

Petitioner argues that claims 1–6 would have been obvious "[b]ecause Chiba teaches oral administration of fingolimod hydrochloride for the treatment of multiple sclerosis, with Kappos 2005 confirming its utility in RRMS patients and Budde confirming the efficacy of a 0.5 mg daily dose of FTY720." Pet. 54. In particular,

> In view of Kappos 2005 and Budde, the skilled artisan would have a reasonable expectation that the 0.5 mg daily dose, a dose within the range taught by Chiba and specifically used by Budde, would induce the desired pharmacological effect (lymphopenia) in RR-MS patients. EX1002, ¶¶58, 60-61, 64, 84, 139, citing EX1022 at 309, EX1018 at 237-39, EX1019 at 684, EX1031 at 1081, EX1028 at 440, and identifying lymphopenia as being "often used as a clinical end-point in dose response studies" and "relevant for relating dosage to lymphopenia for MS." Thus, a skilled artisan would have had reason to use the 0.5 mg dose identified in these clinical

> trials because there was no substantial pharmacological detriment to using the lower 0.5 mg dose and because Budde teaches that the 0.5 mg dose was associated with a decreased risk of adverse effects such as bradycardia when compared to higher doses. EX1008 at 1075-76; EX1002, ¶139.

Id. at 53–54.

In response, and as discussed above in section II(C)(3), Patent Owner relies on the testimony of its experts to argue that pharmacokinetic data evidenced by Webb, Kahan 2003, and Park would have indicated to those of ordinary skill in the art that 0.5 mg/day of fingolimod would not result in sufficient lymphopenia to successfully treat RR-MS. *See, e.g.*, Prelim. Resp. 41–43; Ex. 2003 ¶¶ 39; Ex. 2005 ¶¶ 36–39. Again, though we may find Patent Owner's argument reasonable on its face, at this stage of the proceedings, we are bound to consider disputed facts created by testimonial evidence "in the light most favorable to the petitioner." *See* 37 C.F.R. § 42.108(c). Accordingly, on the present record, we find that Petitioner's arguments and evidence establish a reasonable likelihood that Petitioner would prevail in demonstrating the unpatentability of claims 1–6 in view of Chiba, Kappos 2005, and Budde.

E. Ground III: Anticipation of Claims 1–6 by Kappos 2010.

Petitioner challenges claims 1–6 under 35 U.S.C. § 102 as anticipated by Kappos 2010. Pet. 21, 57–61; *see* Ex. 1002 ¶¶ 144–146. Petitioner's challenge is predicated on the assertion that Kappos 2010 qualifies as prior art because claims 1–6 are not entitled to a filing date earlier than the April 21, 2014 filing date of

the '342 application. Pet. 17–18, 57. In particular, Petitioner argues that the claim limitation requiring fingolimod administration "absent an immediately preceding loading dose regimen" first appeared in the '342 application in a preliminary amendment, whereas the originally filed '342 application and all prior applications are "silent regarding loading dose regimens." *Id*. at 57–58 (citations omitted).

Patent Owner does not presently dispute that Kappos 2010 discloses each element of claims 1–6, but argues first, that Kappos 2010 is not prior art; and second, that in contravention of 35 U.S.C. § 311(b), Petitioner's "anticipation theory is a ruse to unlawfully smuggle a 112 written description argument into an IPR." Prelim. Resp. 5, 45–49. We find no merit in the latter argument.

Although § 311(b) permits *inter partes* review "only on a ground that could be raised under section 102 or 103," Petitioner has not challenged the instant claims on any ground other than those that could be raised under sections 102 and 103. Moreover, ascertaining whether an asserted reference qualifies as prior art is integral to our analysis under these sections. Patent Owner cites no authority precluding the Board from conducting such analysis where, as in the present case, the prior art status of a reference turns on whether applications in the chain of priority of the challenged patent satisfy the written description requirement of § 112. *Cf. Bioactive Labs. v. BTG Int'l Inc*., Case IPR2015-01305 (PTAB Dec. 15, 2015) (Paper 19) (finding that Petitioner failed to demonstrate that parent application having same specification as challenged patent lacked written descriptive support and enablement for the challenged claims).

In addressing the substance of Petitioner's contention that Kappos 2010 qualifies as prior art, Patent Owner contends that the '405 patent (and presumably each of the applications in its chain of priority) supports excluding a loading dose because "the specification says that doses administered as infrequently as once per week can treat RRMS." Prelim. Resp. 47; *see* Ex. 1001 ("[Fingolimod], may alternatively be administered intermittently, e.g. at a dose of 0.5 to 30 mg every other day or once a week."). Relying on the testimony of Petitioner's expert that it was standard practice to treat multiple sclerosis without using a loading dose, Patent Owner further contends that because the Specification did not expressly prescribe a loading dose, "a person of skill reading the specification would understand that it excluded a loading dose." Prelim. Resp. 48.

On the current record, we do not find Patent Owner's argument persuasive. First, at this stage of the proceeding, Patent Owner's contention that one of ordinary skill in the art would have understood the specification to categorically exclude a loading dose is attorney argument entitled to little weight. *See In re Geisler,* 116 F.3d 1465, 1470 (Fed. Cir. 1997).

Second, although the Specification's recitation of once per week administration may encompass a daily dosage "absent an immediately preceding loading dose regimen," the claim language is directed to a broader genus that requires no immediately preceding loading dose under any circumstances. It is well settled that under § 112, "[s]uch description need not recite the claimed invention in haec verba but must do more than merely disclose that which would render the claimed invention obvious." *See ICU Med., Inc. v. Alaris Medical Systems, Inc*. 558 F.3d 1368, 1377 (Fed.

Cir. 2009). In this case, the disclosure of only a single species relating to once weekly administration fails to show possession of the full scope of the invention. *See LizardTech, Inc. v. Earth Res. Mapping, Inc.,* 424 F.3d 1336, 1345 (Fed. Cir. 2005) (holding that "[a]fter reading the patent, a person of skill in the art would not understand" the patentee to have invented a generic method where the patent only disclosed one embodiment of it).

"[A] patentee bears the burden of establishing that its claimed invention is entitled to an earlier priority date than an asserted prior art reference." *In re Magnum Oil Tools Int'l, Ltd.,* 829 F.3d 1364, 1376 (Fed. Cir. 2016). On the present record, we agree with Petitioner that the '405 patent is not entitled to a filing date earlier than April 21, 2014, such that Kappos 2010 qualifies as prior art. The parties will have the opportunity to further address this issue at trial.

On the present record, we find that Petitioner's arguments and evidence establish a reasonable likelihood that Petitioner would prevail in demonstrating the unpatentability of claims 1–6 as anticipated by Kappos 2010.

III. CONCLUSION

For the foregoing reasons, we find that the information presented in the Petition establishes a reasonable likelihood that the Petitioner would prevail in showing that claims 1–6 of the '405 Patent are anticipated by Kappos 2010, and would have been obvious in view of (1) Kovarik and Thomson, and (2) Chiba, Kappos 2005, and Budda.

IV. ORDER

For the reasons given, it is

ORDERED that *inter partes* review is instituted with regard to the following asserted grounds:

> Claims 1–6 under 35 U.S.C. § 103 as unpatentable over the combination of Kovarik and Thomson;
>
> Claims 1–6 under 35 U.S.C. § 103 as unpatentable over the combination of Chiba, Kappos 2005, and Budde;
>
> Claims 1–6 under 35 U.S.C. § 102 as anticipated by Kappos 2010.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '405 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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APPENDIX G

STATUTES AND REGULATIONS

U.S. Const. art. III, § 2

The judicial power shall extend to all cases, in law and equity, arising under this Constitution, the laws of the United States, and treaties made, or which shall be made, under their authority;—to all cases affecting ambassadors, other public ministers and consuls;—to all cases of admiralty and maritime jurisdiction;—to controversies to which the United States shall be a party;—to controversies between two or more states;—between a state and citizens of another state;—between citizens of different states;—between citizens of the same state claiming lands under grants of different states, and between a state, or the citizens thereof, and foreign states, citizens or subjects.

In all cases affecting ambassadors, other public ministers and consuls, and those in which a state shall be party, the Supreme Court shall have original jurisdiction. In all the other cases before mentioned, the Supreme Court shall have appellate jurisdiction, both as to law and fact, with such exceptions, and under such regulations as the Congress shall make.

The trial of all crimes, except in cases of impeachment, shall be by jury; and such trial shall be held in the state where the said crimes shall have been committed; but when not committed within any state, the trial shall be at such place or places as the Congress may by law have directed.

21 U.S.C. § 355 (b), (j)
New drugs

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation

with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section—

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or

subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed.—

(A) Agreement to give notice.—An applicant that 89shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of notice.—An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph—

(i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of notice.—An applicant required under this paragraph to give notice shall give notice to—

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed

by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of notice.—A notice required under this paragraph shall—

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) of this section prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards,

and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim or, with respect to an applicant for approval of a biological product under section 262(k) of title 42, any necessary clinical study or studies. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall

provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(6) An application submitted under this subsection shall be accompanied by the certification required under section 282(j)(5)(B) of title 42. Such certification shall not be considered an element of such application.

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)(A) An abbreviated application for a new drug shall contain—

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been

previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed

under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1);

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c)—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B) Notice of opinion that patent is invalid or will not be infringed.—

(i) Agreement to give notice.—An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give notice as required by this subparagraph.

(ii) Timing of notice.—An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice as required under this subparagraph-

(I) if the certification is in the application, not later than 20 days after the date of the

postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(II) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(iii) Recipients of notice.—An applicant required under this subparagraph to give notice shall give notice to—

(I) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(II) the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(iv) Contents of notice.—A notice required under this subparagraph shall—

(I) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(II) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds—

(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(D)(i) An applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary.

(ii) With respect to the drug for which an application is submitted, nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(iii) Within 60 days after December 8, 2003, the Secretary shall issue guidance defining the term "listed drug" for purposes of this subparagraph.

(3)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).

(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds—

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and

packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C)(i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show—

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321(p) of this title,

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

(D)(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration,

dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the

listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e), the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) for grounds described in the first sentence of subsection (e), the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

(5)(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or

within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined by applying the following to each certification made under paragraph (2)(A)(vii):

(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B) is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter

or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(I) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on-

(aa) the date on which the court enters judgment reflecting the decision; or

(bb) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(II) if before the expiration of such period the district court decides that the patent has been infringed-

(aa) if the judgment of the district court is appealed, the approval shall be made effective on—

(AA) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(BB) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(bb) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of title 35;

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in subclause (I); or

(IV) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in subclause (II).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(iv) 180-day exclusivity period.—

(I) Effectiveness of application.—Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the

date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

(II) Definitions.—In this paragraph:

(aa) 180-day exclusivity period.—The term "180-day exclusivity period" means the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause.

(bb) First applicant.—As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug.

(cc) Substantially complete application.—As used in this subsection, the term "substantially complete application" means an application under this subsection that on its face is sufficiently complete to permit a substantive review and contains all the information required by paragraph (2)(A).

(dd) Tentative approval.—

(AA) In general.—The term "tentative approval" means notification to an applicant by the Secretary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective

approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section 355a of this title, or there is a 7-year period of exclusivity for the listed drug under section 360cc of this title.

(BB) Limitation.—A drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application.

(v) 180-day exclusivity period for competitive generic therapies.—

(I) Effectiveness of application.—Subject to subparagraph (D)(iv), if the application is for a drug that is the same as a competitive generic therapy for which any first approved applicant has commenced commercial marketing, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the competitive generic therapy (including the commercial marketing of the listed drug) by any first approved applicant.

(II) Limitation.—The exclusivity period under subclause (I) shall not apply with respect to a competitive generic therapy that has previously received an exclusivity period under subclause (I).

(III) Definitions.—In this clause and subparagraph (D)(iv):

(aa) The term "competitive generic therapy" means a drug—

(AA) that is designated as a competitive generic therapy under section 356h of this title; and

(BB) for which there are no unexpired patents or exclusivities on the list of products described in section 355(j)(7)(A) of this title at the time of submission.

(bb) The term "first approved applicant" means any applicant that has submitted an application that—

(AA) is for a competitive generic therapy that is approved on the first day on which any application for such competitive generic therapy is approved;

(BB) is not eligible for a 180-day exclusivity period under clause (iv) for the drug that is the subject of the application for the competitive generic therapy; and

(CC) is not for a drug for which all drug versions have forfeited eligibility for a 180-day exclusivity period under clause (iv) pursuant to subparagraph (D).

(C) Civil action to obtain patent certainty.—

(i) Declaratory judgment absent infringement action.—

(I) In general.—No action may be brought under section 2201 of title 28 by an applicant under paragraph (2) for a declaratory judgment with respect to a patent which is the subject of

the certification referred to in subparagraph (B)(iii) unless-

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to non-infringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action.—If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where

the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application.—For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant under paragraph (2) for the purpose of determining whether an action referred to in subparagraph (B)(iii) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the

applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action.—

(I) In general.—If an owner of the patent or the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) on the ground that the patent does not claim either-

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action.—Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages.—An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(D) Forfeiture of 180-day exclusivity period.—

(i) Definition of forfeiture event.—In this subparagraph, the term "forfeiture event", with respect to an application under this subsection, means the occurrence of any of the following:

(I) Failure to market.—The first applicant fails to market the drug by the later of-

(aa) the earlier of the date that is—

(AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or

(BB) 30 months after the date of submission of the application of the first applicant; or

(bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:

(AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.

(BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a fording that the patent is invalid or not infringed.

(CC) The patent information submitted under subsection (b) or (c) is withdrawn by

the holder of the application approved under subsection (b).

(II) Withdrawal of application.—The first applicant withdraws the application or the Secretary considers the application to have been withdrawn as a result of a determination by the Secretary that the application does not meet the requirements for approval under paragraph (4).

(III) Amendment of certification.—The first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period.

(IV) Failure to obtain tentative approval.—The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

(V) Agreement with another applicant, the listed drug application holder, or a patent owner.—The first applicant enters into an agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for

a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 12 of title 15, except that the term includes section 45 of title 15 to the extent that that section applies to unfair methods of competition).

(VI) Expiration of all patents.—All of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.

(ii) Forfeiture.—The 180-day exclusivity period described in subparagraph (B)(iv) shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant.

(iii) Subsequent applicant.—If all first applicants forfeit the 180-day exclusivity period under clause (ii)—

(I) approval of any application containing a certification described in paragraph (2)(A)(vii)(IV) shall be made effective in accordance with subparagraph (B)(iii); and

(II) no applicant shall be eligible for a 180-day exclusivity period.

(iv) Special forfeiture rule for competitive generic therapy.—The 180-day exclusivity period described in subparagraph (B)(v) shall be forfeited by a first approved applicant if the applicant fails to market the competitive generic therapy within 75 days after the date on which the approval of the first approved applicant's application for the competitive generic therapy is made effective.

(E) If the Secretary decides to disapprove an application, the Secretary shall give the applicant

notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(F)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b).

(ii) If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b),

except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) for such drug.

(iv) If a supplement to an application approved under subsection (b) is approved after September

24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

(v) If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.

(6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended—

(A) for the same period as the withdrawal or suspension under subsection (e) or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(7)(A)(i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public—

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(B) A drug approved for safety and effectiveness under subsection (c) or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or September 24, 1984, whichever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list—

(i) for the same period as the withdrawal or suspension under subsection (e) or paragraph (6), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(8) For purposes of this subsection:

(A)(i) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid

measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.

(B) A drug shall be considered to be bioequivalent to a listed drug if—

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

(9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of—

(A) the name of the applicant,

(B) the name of the drug covered by the application,

(C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and

(D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(10)(A) If the proposed labeling of a drug that is the subject of an application under this subsection differs from the listed drug due to a labeling revision described under clause (i), the drug that is the subject of such application shall, notwithstanding any other provision of this chapter, be eligible for approval and shall not be considered misbranded under section 352 of this title if—

(i) the application is otherwise eligible for approval under this subsection but for expiration of patent, an exclusivity period, or of a delay in approval described in paragraph (5)(B)(iii), and a revision to the labeling of the listed drug has been approved by the Secretary within 60 days of such expiration;

(ii) the labeling revision described under clause (i) does not include a change to the "Warnings" section of the labeling;

(iii) the sponsor of the application under this subsection agrees to submit revised labeling of the

drug that is the subject of such application not later than 60 days after the notification of any changes to such labeling required by the Secretary; and

(iv) such application otherwise meets the applicable requirements for approval under this subsection.

(B) If, after a labeling revision described in subparagraph (A)(i), the Secretary determines that the continued presence in interstate commerce of the labeling of the listed drug (as in effect before the revision described in subparagraph (A)(i)) adversely impacts the safe use of the drug, no application under this subsection shall be eligible for approval with such labeling.

(11)(A) Subject to subparagraph (B), the Secretary shall prioritize the review of, and act within 8 months of the date of the submission of, an original abbreviated new drug application submitted for review under this subsection that is for a drug—

(i) for which there are not more than 3 approved drug products listed under paragraph (7) and for which there are no blocking patents and exclusivities; or

(ii) that has been included on the list under section 356e of this title.

(B) To qualify for priority review under this paragraph, not later than 60 days prior to the submission of an application described in subparagraph (A) or that the Secretary may prioritize pursuant to subparagraph (D), the applicant shall provide complete, accurate information regarding facilities involved in manufacturing processes and testing of the drug

that is the subject of the application, including facilities in corresponding Type II active pharmaceutical ingredients drug master files referenced in an application and sites or organizations involved in bioequivalence and clinical studies used to support the application, to enable the Secretary to make a determination regarding whether an inspection of a facility is necessary. Such information shall include the relevant (as determined by the Secretary) sections of such application, which shall be unchanged relative to the date of the submission of such application, except to the extent that a change is made to such information to exclude a facility that was not used to generate data to meet any application requirements for such submission and that is not the only facility intended to conduct one or more unit operations in commercial production. Information provided by an applicant under this subparagraph shall not be considered the submission of an application under this subsection.

(C) The Secretary may expedite an inspection or reinspection under section 374 of this title of an establishment that proposes to manufacture a drug described in subparagraph (A).

(D) Nothing in this paragraph shall prevent the Secretary from prioritizing the review of other applications as the Secretary determines appropriate.

(12) The Secretary shall publish on the internet website of the Food and Drug Administration, and update at least once every 6 months, a list of all drugs approved under subsection (c) for which all patents and periods of exclusivity under this chapter have expired and for which no application has been approved under this subsection.

(13) Upon the request of an applicant regarding one or more specified pending applications under this subsection, the Secretary shall, as appropriate, provide review status updates indicating the categorical status of the applications by each relevant review discipline.

28 U.S.C. § 2201

Creation of remedy

(a) In a case of actual controversy within its jurisdiction, except with respect to Federal taxes other than actions brought under section 7428 of the Internal Revenue Code of 1986, a proceeding under section 505 or 1146 of title 11, or in any civil action involving an antidumping or countervailing duty proceeding regarding a class or kind of merchandise of a free trade area country (as defined in section 516A(f)(10) of the Tariff Act of 1930), as determined by the administering authority, any court of the United States, upon the filing of an appropriate pleading, may declare the rights and other legal relations of any interested party seeking such declaration, whether or not further relief is or could be sought. Any such declaration shall have the force and effect of a final judgment or decree and shall be reviewable as such.

(b) For limitations on actions brought with respect to drug patents see section 505 or 512 of the Federal Food, Drug, and Cosmetic Act, or section 351 of the Public Health Service Act.

35 U.S.C. § 271

Infringement of patent

(a) Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.

(b) Whoever actively induces infringement of a patent shall be liable as an infringer.

(c) Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

(d) No patent owner otherwise entitled to relief for infringement or contributory infringement of a patent shall be denied relief or deemed guilty of misuse or illegal extension of the patent right by reason of his having done one or more of the following: (1) derived revenue from acts which if performed by another without his consent would constitute contributory infringement of the patent; (2) licensed or authorized another to perform acts which if performed without his consent would constitute contributory infringement of the patent; (3) sought to enforce his patent rights against infringement or contributory infringement; (4) refused to license or use any rights to the patent; or (5) conditioned the license of any rights to the patent or

the sale of the patented product on the acquisition of a license to rights in another patent or purchase of a separate product, unless, in view of the circumstances, the patent owner has market power in the relevant market for the patent or patented product on which the license or sale is conditioned.

(e)(1) It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

(2) It shall be an act of infringement to submit—

(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent,

(B) an application under section 512 of such Act or under the Act of March 4, 1913 (21 U.S.C. 151–158) for a drug or veterinary biological product which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques and which is claimed in a patent or the use of which is claimed in a patent, or

(C)(i) with respect to a patent that is identified in the list of patents described in section 351(*l*)(3) of

the Public Health Service Act (including as provided under section 351(*l*)(7) of such Act), an application seeking approval of a biological product, or

(ii) if the applicant for the application fails to provide the application and information required under section 351(*l*)(2)(A) of such Act, an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(*l*)(3)(A)(i) of such Act,

if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

(3) In any action for patent infringement brought under this section, no injunctive or other relief may be granted which would prohibit the making, using, offering to sell, or selling within the United States or importing into the United States of a patented invention under paragraph (1).

(4) For an act of infringement described in paragraph (2)—

(A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,

(B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved

drug, veterinary biological product, or biological product,

(C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product, and

(D) the court shall order a permanent injunction prohibiting any infringement of the patent by the biological product involved in the infringement until a date which is not earlier than the date of the expiration of the patent that has been infringed under paragraph (2)(C), provided the patent is the subject of a final court decision, as defined in section 351(k)(6) of the Public Health Service Act, in an action for infringement of the patent under section 351(*l*)(6) of such Act, and the biological product has not yet been approved because of section 351(k)(7) of such Act.

The remedies prescribed by subparagraphs (A), (B), (C), and (D) are the only remedies which may be granted by a court for an act of infringement described in paragraph (2), except that a court may award attorney fees under section 285.

(5) Where a person has filed an application described in paragraph (2) that includes a certification under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), and neither the owner of the patent that is the subject of the certification nor the holder of the approved application under subsection (b) of such section for the drug that is claimed by the patent or a use of which is claimed by the patent brought an action

for infringement of such patent before the expiration of 45 days after the date on which the notice given under subsection (b)(3) or (j)(2)(B) of such section was received, the courts of the United States shall, to the extent consistent with the Constitution, have subject matter jurisdiction in any action brought by such person under section 2201 of title 28 for a declaratory judgment that such patent is invalid or not infringed.

(6)(A) Subparagraph (B) applies, in lieu of paragraph (4), in the case of a patent—

(i) that is identified, as applicable, in the list of patents described in section 351(*l*)(4) of the Public Health Service Act or the lists of patents described in section 351(*l*)(5)(B) of such Act with respect to a biological product; and

(ii) for which an action for infringement of the patent with respect to the biological product—

(I) was brought after the expiration of the 30-day period described in subparagraph (A) or (B), as applicable, of section 351(*l*)(6) of such Act; or

(II) was brought before the expiration of the 30-day period described in subclause (I), but which was dismissed without prejudice or was not prosecuted to judgment in good faith.

(B) In an action for infringement of a patent described in subparagraph (A), the sole and exclusive remedy that may be granted by a court, upon a finding that the making, using, offering to sell, selling, or importation into the United States of the biological product that is the subject of the action infringed the patent, shall be a reasonable royalty.

(C) The owner of a patent that should have been included in the list described in section 351(*l*)(3)(A) of

the Public Health Service Act, including as provided under section 351(*l*)(7) of such Act for a biological product, but was not timely included in such list, may not bring an action under this section for infringement of the patent with respect to the biological product.

(f)(1) Whoever without authority supplies or causes to be supplied in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(2) Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(g) Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a

product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after—

(1) it is materially changed by subsequent processes; or

(2) it becomes a trivial and nonessential component of another product.

(h) As used in this section, the term "whoever" includes any State, any instrumentality of a State, and any officer or employee of a State or instrumentality of a State acting in his official capacity. Any State, and any such instrumentality, officer, or employee, shall be subject to the provisions of this title in the same manner and to the same extent as any nongovernmental entity.

(i) As used in this section, an "offer for sale" or an "offer to sell" by a person other than the patentee, or any designee of the patentee, is that in which the sale will occur before the expiration of the term of the patent.

35 U.S.C. § 311

Inter partes review

(a) In General.—Subject to the provisions of this chapter, a person who is not the owner of a patent may file with the Office a petition to institute an inter partes review of the patent. The Director shall establish, by regulation, fees to be paid by the person requesting the review, in such amounts as the Director determines to be reasonable, considering the aggregate costs of the review.

(b) Scope.—A petitioner in an inter partes review may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications.

(c) Filing Deadline.—A petition for inter partes review shall be filed after the later of either—

(1) the date that is 9 months after the grant of a patent; or

(2) if a post-grant review is instituted under chapter 32, the date of the termination of such post-grant review.

35 U.S.C. § 315(e)

Relation to other proceedings or actions

(e) Estoppel.—

(1) Proceedings before the office.—The petitioner in an *inter partes* review of a claim in a patent under this chapter that results in a final written decision under section 318(a), or the real party in interest or privy of the petitioner, may not request or maintain a proceeding before the Office with respect to that claim on any ground that the petitioner raised or reasonably could have raised during that *inter partes* review.

(2) Civil actions and other proceedings.—The petitioner in an *inter partes* review of a claim in a patent under this chapter that results in a final written decision under section 318(a), or the real party in interest or privy of the petitioner, may not assert either in a civil action arising in whole or in part under section 1338 of title 28 or in a proceeding before the International Trade Commission under section 337 of the Tariff Act of 1930 that the claim is invalid on any ground that the petitioner raised or reasonably could have raised during that *inter partes* review.

35 U.S.C. § 319

Appeal

A party dissatisfied with the final written decision of the Patent Trial and Appeal Board under section 318(a) may appeal the decision pursuant to sections 141 through 144. Any party to the *inter partes* review shall have the right to be a party to the appeal.

37 C.F.R. § 42.73(d)

Judgment

(d) *Estoppel.* (1) *Petitioner other than in derivation proceeding.* A petitioner, or the real party in interest or privy of the petitioner, is estopped in the Office from requesting or maintaining a proceeding with respect to a claim for which it has obtained a final written decision on patentability in an *inter partes* review, post-grant review, or a covered business method patent review, on any ground that the petitioner raised or reasonably could have raised during the trial, except that estoppel shall not apply to a petitioner, or to the real party in interest or privy of the petitioner who has settled under 35 U.S.C. 317 or 327.

(2) *In a derivation,* the losing party who could have properly moved for relief on an issue, but did not so move, may not take action in the Office after the judgment that is inconsistent with that party's failure to move, except that a losing party shall not be estopped with respect to any contested subject matter for which that party was awarded a favorable judgment.

(3) *Patent applicant or owner.* A patent applicant or owner is precluded from taking action inconsistent with the adverse judgment, including obtaining in any patent:

(i) A claim that is not patentably distinct from a finally refused or canceled claim; or

(ii) An amendment of a specification or of a drawing that was denied during the trial proceeding, but this provision does not apply to an application or patent that has a different written description.