No. 24-

IN THE

Supreme Court of the United States

NORWICH PHARMACEUTICALS INC.,

Petitioner,

v.

SALIX PHARMACEUTICALS, LTD., *et al.*,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

IAN SWAN
AXINN, VELTROP & HARKRIDER LLP
1901 L Street NW
Washington, DC 20036

THOMAS K. HEDEMANN
Counsel of Record
MATTHEW J. BECKER
MATTHEW S. MURPHY
AXINN, VELTROP & HARKRIDER LLP
90 State House Square
Hartford, CT 06103
(860) 275-8100
thedemann@axinn.com

Counsel for Petitioner

332793

COUNSEL PRESS
(800) 274-3321 • (800) 359-6859

QUESTION PRESENTED

Congress created the Hatch-Waxman Act with the purpose of hastening the introduction of less-costly generic drugs while safeguarding the legitimate patent rights of innovator companies. The lower court's interpretation of 35 U.S.C. § 271(e)(4)(A) – the remedy provision in the Hatch-Waxman Act – is contrary to this purpose because it requires blanket injunctions on FDA approval of generic drug applications that may be far broader in scope than the underlying infringement finding. It is also contrary to the general patent-law principle that injunctive relief must be tailored to the infringement and avoid blocking conduct not found infringing.

The question presented is:

Whether 35 U.S.C. § 271(e)(4)(A) requires courts to issue injunctive orders that are broader in scope than the underlying infringement, thereby delaying FDA approval of generic drug applications for indications that have not been found to infringe any valid patent.

PARTIES TO THE PROCEEDING

Petitioner is Norwich Pharmaceuticals, Inc., the defendant-cross-appellant in the court of appeals.

Respondents are Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., Alfasigma S.p.A., and Bausch Health Ireland Ltd., the plaintiffs-appellants in the court of appeals.

CORPORATE DISCLOSURE STATEMENT

Norwich Pharmaceuticals, Inc. is wholly owned by Alvogen Pharma US, Inc. Alvogen Pharma US, Inc. is wholly owned by Alvogen Group, Inc. Alvogen Group, Inc. is wholly owned by Alvogen Holdings (Hungary) LLC. Alvogen Holdings (Hungary) LLC is wholly owned by Alvogen Pharma Ltd. Malta (which is wholly owned by Alvogen Lux Holdings S.à.r.l.)

RELATED PROCEEDINGS

Salix Pharms., Ltd. v. Norwich Pharms., Inc., No. 20-430, U.S. District Court for the District of Delaware. Judgment entered Aug. 10, 2022;

Salix Pharms., Ltd. v. Norwich Pharms., Inc., No. 22-2153, U.S. Court of Appeals for the Federal Circuit. Judgment entered Apr. 11, 2024;

Salix Pharms., Ltd. v. Norwich Pharms., Inc., No. 23-1952, U.S. Court of Appeals for the Federal Circuit. Judgment entered Apr. 11, 2024;

Norwich Pharms., Inc. v. Becerra, No. 23-1611, U.S. District Court for the District of Columbia. Judgment entered Nov. 1, 2023;

Norwich Pharms., Inc. v. Becerra, No. 23-5311, U.S. Court of Appeals for the District of Columbia. Currently held in abeyance.

TABLE OF CONTENTS

Table of Contents

TABLE OF APPENDICES

TABLE OF CITED AUTHORITIES

Page

Federal Cases

Page

Federal Statutes

Regulations

Other Authorities

PETITION FOR A WRIT OF CERTIORARI

Norwich Pharmaceuticals, Inc. respectfully petitions for a writ of certiorari to review the decision of the United States Court of Appeals for the Federal Circuit in this case.

OPINIONS BELOW

The opinion of the Federal Circuit Court of Appeals is reported at *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056 (Fed. Cir. 2024), and reproduced at Pet. App. 1a-33a. The order denying rehearing or rehearing en banc is unreported and reprinted at Pet. App. 94a-95a. The district court's opinion is reported at *Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, No. 20-430, 2022 WL 3225381 (D. Del. Aug. 10, 2022), and reprinted at Pet. App. 34a-93a.

JURISDICTION

The court of appeals entered judgment on April 11, 2024 and denied a timely petition for rehearing or rehearing en banc on June 13, 2024. Pet. App. 95a. This Court has jurisdiction under 28 U.S.C. § 1254.

STATUTORY AND REGULATORY PROVISIONS INVOLVED

35 U.S.C. § 271(e) provides in relevant parts:

(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 . . . for

> a drug claimed in a patent or the use of which is claimed in a patent. . . .
>
> * * *

(4) For an act of infringement described in paragraph (2) –

> (A) the court shall order the effective date of any approval of the drug . . . 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. . . .

21 U.S.C. § 355(j)(2) provides in relevant parts:

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

> * * *
>
> (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).

21 C.F.R. § 314.94(a)(12)(viii) provides in relevant part:

> (A) *After Finding of Infringement.* An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant

> must certify under paragraph (a)(12)(i)(A)(3) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (a)(12)(iii) of this section if the applicant amends its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the ANDA will no longer be considered to contain a paragraph IV certification to the patent. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.

21 C.F.R. § 314.107(b)(1) provides in relevant part

> (ii) Immediately, if the applicant submits an appropriate statement under § 314.50(i) or § 314.94(a)(12) explaining that a method-of-use patent does not claim an indication or other condition of use for which the applicant is seeking approval, except that if the applicant also submits a paragraph IV certification to the patent, then the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(1)(i)(C) of this section.

INTRODUCTION

This year marks the 40th anniversary of the landmark Drug Price Competition and Patent Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. The Act's purpose was to hasten the introduction of inexpensive generic drugs while still ensuring that innovator drug companies retain the profitability required to bring new drugs to market. The Act has largely delivered on this purpose, having paved the way for generic drugs that have saved patients and the health care system more than two trillion dollars in the past decade alone. At the same time, the pharmaceutical industry has maintained high profit margins and continues to introduce new drugs.

The key to the Act's success is its careful balance between provisions that encourage generic entry and provisions that protect innovator drugs. That balance has now been distorted by the lower court's incorrect interpretation of the remedy provision that sits at the heart of the Act. Under that statutory interpretation, courts are required to issue orders that broadly prohibit FDA from approving a proposed generic product for *any* indication even when the underlying infringement finding is limited to a method-of-use patent that covers *only one* of multiple approved indications. Such broad injunctive orders are contrary to Congress' intended balance because the Act explicitly permits approval of generic drugs that seek approval for unpatented indications. They are also contrary to the basic principle of patent law that injunctions must be tailored to the infringement so that they do not bar products and activities that have not been found infringing. Congress could not have intended for

the remedy provision in the Hatch-Waxman Act to have a broader injunctive scope than permitted by ordinary patent law. Indeed, no public interest is served by granting brand companies a monopoly on marketing drugs for unpatented indications.

This Court's intervention is required to correct the lower court's interpretation of the Act and thereby restore the balance that Congress put in place and that is vital to the Act's proper functioning.

STATEMENT OF THE CASE

A. Statutory Background

The Federal Food Drug & Cosmetic Act ("FDCA") establishes the requirements for marketing drugs in the United States. In 1984, Congress amended the FDCA with the Hatch-Waxman Act, a central purpose of which is "to enable competitors to bring cheaper, generic . . . drugs to market as quickly as possible." *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330, 1344 (Fed. Cir. 2007) (quoting 149 Cong. Rec. S15885 (Nov. 25, 2003)).

Before marketing a new drug, a drug company must submit a New Drug Application ("NDA") to FDA, and FDA must approve it. *See* 21 U.S.C. § 355(a), (b). "FDA does not grant across-the-board approval to market a drug [but rather] to make, use, and sell a drug for a specific purpose for which that drug has been demonstrated to be safe and efficacious." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1356 (Fed. Cir. 2003).

"To facilitate the approval of generic drugs as soon as patents allow, the Hatch–Waxman Amendments and FDA regulations direct brand manufacturers to file information about their patents." *Caraco Pharm. Lab'ys, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 405 (2012). Specifically, the NDA applicant must identify each patent that claims the drug or a method of using the drug. *See* 21 U.S.C. § 355(b)(1)(A)(viii); 21 C.F.R. § 314.53. With respect to method-of-use patents, the applicant submits "use codes" that describe the use or indication covered by the patent. Upon approval of the NDA, FDA publishes the patent information in a publication known as the "Orange Book." *See* 21 U.S.C. § 355(b)(1)(A)(viii); 21 C.F.R. § 314.53(e).

Pursuant to the Hatch-Waxman Act, generic drug applicants can submit an Abbreviated New Drug Application ("ANDA") that relies on the safety and efficacy data for the approved brand drug (i.e., the reference-listed drug, or "RLD"). An ANDA applicant must submit one of four patent certifications for each patent listed in the Orange Book for the RLD. The pertinent certification here is the so-called "Paragraph IV certification," which states that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the generic drug. *See* 21 C.F.R. § 314.94(a)(12)(i)(A)(4)(i).

The Hatch-Waxman Act made the submission of an ANDA with a Paragraph IV certification an act of infringement, *see* 35 U.S.C. § 271(e)(2)(A), and further provided a 30-month stay of FDA's ability to approve the ANDA if the patent owner files an infringement suit. *See* 21 U.S.C. § 355(j)(2)(B)(iii), 355(j)(5)(B)(iii). If a court finds that the ANDA submission infringes the patent, the Act requires the court to order that FDA may not approve

"the drug . . . involved in the infringement" before the patent's expiration (a "Section 271(e) order"). 35 U.S.C. § 271(e)(4)(A).

There is one exception to the patent certifications. As discussed, FDA may approve drugs for more than one indication. To avoid delaying the introduction of generic drugs for unpatented indications, the Act permits generic applicants to submit a "section viii statement" rather than a patent certification, which declares that the ANDA is not seeking approval for a patented indication. 21 U.S.C. § 355(j)(2)(A)(viii). FDA may then approve the ANDA product for only the unpatented indication(s). *See Caraco*, 566 U.S. at 415 ("The Hatch-Waxman Amendments authorize the FDA to approve the marketing of a generic drug for particular unpatented uses; and section viii provides the mechanism for a generic company to identify those uses, so that a product with a label matching them can quickly come to market.").

Following a final court decision of infringement for a method of use claimed in an Orange Book-listed patent from which no appeal is or can be taken, FDA regulation provides that an ANDA applicant may either (1) forego approval for the patented method of use until the relevant patent expires, or (2) "amend[] its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent," i.e., convert the Paragraph IV certification to a section viii statement. 21 C.F.R. § 314.94(a)(12)(viii)(A).

B. Proceedings Below

Salix Pharmaceuticals, Inc. ("Salix") is the holder of NDA No. 021361 for rifaximin tablets under the brand name Xifaxan®, which is currently the only rifaximin product available on the market. Xifaxan 550 mg rifaximin tablets are indicated for the treatment of IBS-D in adults (the "IBS-D Indication") and for the reduction of the risk of overt HE recurrence in adults (the "HE Indication").

In February 2020, Norwich submitted ANDA No. 214369 seeking approval to market generic 550 mg rifaximin for both the IBS-D and HE Indications. The ANDA provided Paragraph IV certifications for each of Salix's Orange Book-listed patents. In March 2020, based on the Paragraph IV certifications, Salix filed a patent suit against Norwich in the District of Delaware under 35 U.S.C. § 271(e)(2). Salix's suit triggered a now-expired 30-month stay on FDA approval of the ANDA.

The patents Salix asserted at trial fell into three categories: claims directed to the HE Indication (the "HE Patents"); claims directed to the IBS-D Indication (the "IBS-D Patents"); and claims directed to the crystalline form of rifaximin (the "Polymorph Patents"). After trial, the court ordered the parties to propose a final judgment finding the HE Patents infringed and the Polymorph and IBS-D Patents invalid. Oral Order, No. 20-430 (D. Del. July 28, 2022), ECF No. 189. Norwich proposed a judgment with a Section 271(e) order stating that "any final approval by FDA of Norwich's ANDA with proposed labeling containing the [HE Indication] shall be a date not earlier than the latest expiration of the [HE Patents]." Joint Letter, No. 20-430 (D. Del. Aug. 15, 2022), ECF No. 196

at 3. Salix argued that Norwich's proposal was "improper because under § 271(e)(4)(A), the date of approval is tied to the drug product, not an indication." *Id.* at 1.

On August 10, 2022, the court issued a final judgment finding the IBS-D and Polymorph Patents invalid, and the HE Patents infringed by the ANDA seeking approval for the HE Indication. Accepting Salix's argument that Section 271(e)(4)(A) requires an order tying the date of approval to the drug product, the court ordered "that the effective date of any final approval by [FDA] of Norwich's ANDA No. 214369 is to be a date not earlier than the date of expiration of the last to expire of the [HE Patents] (currently October 2 2029). . . ." Final Judgment, No. 20-430 (D. Del. Aug. 10, 2022), ECF No. 193 at 2.

Norwich subsequently amended the ANDA by removing the HE Indication from the proposed label and providing section viii statements in place of Paragraph IV certifications for the HE Patents. Norwich also filed a motion asking the court to modify the 271(e) order to make it clear that pertains to an ANDA with Paragraph IV certifications to the HE Patents. Motion to Modify Judgment, No. 20-430 (D. Del. Sept. 7, 2022), ECF No. 205. The court denied Norwich's motion. Memorandum Order, No. 20-430 (D. Del. May 17, 2023), ECF No. 222.

On June 2, 2023, FDA granted tentative approval to the amended ANDA but declined to grant final approval. Motion to Expedite, No. 22-2153 (Fed. Cir. June 14, 2023), ECF No. 23, Zaku Decl., Ex. A. Despite acknowledging that Salix's HE Patents "do not claim any indication for which [Norwich is] seeking approval," the agency stated that "final approval cannot be granted until October 2, 2029 as specified in the court order." *Id.* at 3-4.

Norwich appealed the 271(e) order to the Federal Circuit, arguing that the district court's statutory interpretation is contrary to the plain language, the section viii mechanism in the Hatch-Waxman Act, the Act's overall purpose of hastening generic drugs, FDA's implementing regulation, and the basic patent-law principle that injunctions must be tailored to the underlying infringement. The Federal Circuit affirmed the 271(e) order but did so without conducting a substantive review of the district court's statutory interpretation, noting only that the order does not prevent approval of "a new non-infringing ANDA." Pet. App. 23a The parties had never questioned the self-evident fact that the order does not block an ANDA assigned a different ANDA number by FDA, however. But submitting a new ANDA simply to obtain a different ANDA number is not a solution to the district court's erroneous statutory interpretation that requires 271(e) orders that block approval of generic drugs for indications that are not covered by a patent. The Federal Circuit denied Norwich's petition for rehearing or rehearing en banc.

REASONS FOR GRANTING THE PETITION

The plain language of Section 271(e)(4)(A) requires that courts issue 271(e) orders that tie the restriction on FDA approval to the indication for which the ANDA seeks approval when that indication is the source of the infringement under Section 271(e)(2)(A). That straightforward application of the statutory language is also necessary to avoid conflict with the section viii mechanism that Congress provided in the Hatch-Waxman Act to permit approval of generic drugs for uses that are not covered by a valid patent. It is further mandated by the basic principle of patent law that injunctive relief may

only encompass the specific infringing conduct and no other conduct.

The district court's 271(e) order here was based on an erroneous interpretation of Section 271(e)(4)(A) under which such orders must be tied to the "drug" regardless of the underlying infringement. The absurd result of this interpretation is that FDA is barred from approving the first generic rifaximin product for IBS-D – an indication that is unquestionably in the public domain following the invalidation of Salix's IBS-D Patents – despite the section viii mechanism that Congress put in place precisely to ensure that generic drugs could be marketed for unpatented indications. With the Federal Circuit having affirmed the order, the district court's interpretation will be the law in all ANDA cases unless this Court grants review.

I. Certiorari Is Required to Prevent 271(e) Orders From Delaying Approval of Generic Drugs for Unpatented Indications

A. The plain statutory language requires courts to tailor 271(e) orders to the underlying infringement

Section 271(e)(4) directs that "[f]or an act of infringement described in paragraph (2) — (A) the court shall order the effective date of any approval of the drug . . . involved in the infringement" to be later than the expiration of the infringed patent. 35 U.S.C. § 271(e)(4)(A). Because the provision explicitly points to the definition of infringement in Section 271(e)(2)(A), it must be read in that context. *See FDA v. Brown & Williamson Tobacco Corp.*,

529 U.S. 120, 133 (2000) ("It is 'a fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme.'") (quoting *Davis v. Michigan Dept. of Treasury*, 489 U.S. 803, 809 (1989)).

Section 271(e)(2)(A) defines "an act of infringement" to be the submission of an ANDA "for a drug claimed in a patent *or* the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A) (emphasis added). Thus, the infringement for which Section 271(e)(4)(A) provides a remedy can refer to infringement of a patent claiming the drug itself *or* infringement of a method patent claiming the applied-for indication. Here, for example, the district court found induced infringement of the HE Patents under Section 271(e)(2)(A) solely because the ANDA sought approval for the HE Indication. *Supra* at 10.

Upon finding an act of infringement, Section 271(e)(4)(A) requires the court to issue an order restricting the approval not merely of "the drug" but of "the drug . . . involved in the infringement." 35 U.S.C. § 271(e)(4)(A). Here, rifaximin – "the drug" – is only "involved in the infringement" when it is used for the HE Indication. Conversely, rifaximin is not "involved in the infringement" when it is sold or used for the IBS-D Indication because the IBS-D Patents covering that indication were held invalid. The term "the drug . . . involved in the infringement" therefore serves to ensure that the scope of the 271(e) order is commensurate with the underlying act of infringement and does not prevent approval of the ANDA product for uses that have not been found infringing.

Rather than adhere to the plain statutory language, the lower court adopted Salix's contention that Section 271(e)(4)(A) ties "the date of approval . . . to the drug product, not an indication." *Supra* at 10. It then implemented this reading by issuing an order that put a blanket ban of approval on "ANDA No. 214369" irrespective of whether it seeks approval for any patented indication. This interpretation reduces the term "involved in the infringement" to serve only to identify the drug to which the order should be directed. As a mere identifier the term is wholly redundant, however, because the infringing drug (and drug application) is already identified in Section 271(e)(2)(A), which itself is explicitly referenced in the first sentence of Section 271(e)(4)(A). An interpretation that renders statutory language redundant or mere surplusage is contrary to the "cardinal principle of statutory construction" of "giv[ing] effect, if possible, to every clause and word of a statute." *Duncan v. Walker*, 533 U.S. 167, 174 (2001) (citation omitted).

B. 271(e) orders must be tailored to the infringement to comport with rather than undermine the purpose of the Hatch-Waxman Act

Correct statutory interpretation seeks to "give effect to congressional purpose so long as the congressional language does not itself bar that result." *Johnson v. United States*, 529 U.S. 694, 710 n.10 (2000). *See also Warner-Lambert*, 316 F.3d at 1355 (Courts interpreting statutory language look to "the objects and policy of the law, as indicated by its various provisions, and give it such a construction as will carry into execution the will of the Legislature.") (quoting *Kokoszka v. Belford*, 417 U.S. 642, 650 (1974)).

Congress enacted the Hatch-Waxman Act with the goal of bringing "'generic … drugs to market as quickly as possible.'" *Teva Pharms. USA*, 482 F.3d at 1344 (quoting Sen. Kennedy Remarks, 149 Cong. Rec. S15885 (Nov. 25, 2003)). *See also In re Barr Lab'ys, Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991) ("Congress sought to get generic drugs into the hands of patients at reasonable prices – fast."). Consistent with that goal, Congress included the section viii mechanism that permits approval of generic drugs for unpatented indications even when other indications for the same drug are covered by patents. As this Court has observed, "[t]he Hatch-Waxman Amendments authorize the FDA to approve the marketing of a generic drug for particular unpatented uses; and section viii provides the mechanism for a generic company to identify those uses, so that a product with a label matching them can quickly come to market." *Caraco Pharm. Lab'ys,*, 566 U.S. at 415.

Reading Section 271(e)(4)(A) as requiring courts to tailor 271(e) orders to the underlying act of infringement gives effect to the overarching purpose of Act and its section viii mechanism because it permits generic applicants to carve out an infringing indication from an ANDA and obtain approval for an unpatented indication. By contrast, the reading applied by the district court requires blanket 271(e) orders that prohibit FDA from approving ANDAs that have section viii statements to a patented indication and only seek approval for an unpatented indication. This means that infringing ANDAs cannot be amended post-judgment to exclude indications covered by valid patents. In this case, for example, FDA declined to approve Norwich's ANDA because of the district court's blanket 271(e) order despite acknowledging the section viii statements to Salix's HE Patents. *Supra* at 10-11.

C. 271(e) orders must be tailored to the infringement to avoid nullifying FDA's implementing regulation

There is no statutory basis for a 271(e) order that precludes the use of the section viii mechanism after a finding of infringement. On the contrary, Congress did not place any temporal limitation on the submission of a section viii statement, and FDA's regulation therefore explicitly permits ANDA applicants to use it to carve out an indication that has been found infringing:

> (A) *After finding of infringement.* An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken. . . . [W]ith respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (a)(12)(iii) of this section if the applicant amends its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the ANDA will no longer be considered to contain a paragraph IV certification to the patent.

21 C.F.R. § 314.94(a)(12)(viii)(A). Other FDA regulation provides that an ANDA with a section viii statement may be approved "immediately." 21 C.F.R. § 314.107(b)(1)(ii). FDA's regulations thus aligns with both the letter and purpose of the Hatch-Waxman Act.

Norwich followed the regulation to the letter. After having undertaken the expense of challenging Salix's Orange-Book listed patents, Norwich succeeded in proving that the Polymorph and IBS-D Patents were invalid but was held to have infringed the HE Patents by seeking approval for the HE Indication. As FDA's regulation prescribes, Norwich then amended the ANDA to remove the infringing HE Indication and submit section viii statements rather than Paragraph IV certifications to the HE Patents. *Supra* at 10. Yet the district court's 271(e) order has denied FDA the ability to follow its own regulation and approve the amended ANDA. The court's interpretation of the Section 271(e)(4)(A) thus effectively nullifies FDA's regulation.

D. 271(e) orders must be tailored to the infringement to comport with patent law

It is a basic principle of patent law that "a court may not enjoin products that have not been found by the jury to infringe the patents-in-suit, and therefore any injunction should be specifically tailored to comport with the jury's findings." *Durel Corp. v. Sylvania, Inc.*, No. 95-1750, 2000 WL 33687212, at *1 (D. Ariz. Apr. 13, 2000) (citing *Square Liner 360, Inc. v. Chisum*, 691 F.2d 362, 378 (8th Cir. 1982*)).* Indeed, the Patent Act only empowers courts to grant injunctions "to prevent the violation of any right secured by patent. . . ." 35 U.S.C. § 283. Thus, "[j]udicial restraint of lawful competitive activities . . . must be avoided. . . ." *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 777 (Fed. Cir. 1993) (vacating injunction and remanding to narrow scope precluding non-infringing activities). *See also Johns Hopkins University v. CellPro, Inc.*, 152 F.3d 1342, 1367-68 (Fed. Cir. 1998*)* (same). By way of

example, no court would countenance an injunction that broadly bars the sale of "F-150" pickup trucks based on infringement of a patent covering intermittent windshield wipers if that injunction would operate to bar F-150 trucks that are redesigned to not have intermittent windshield wipers.

There is nothing in the provisions or legislative history of the Hatch-Waxman Act to suggest that Congress intended it to alter or abrogate any settled principles of patent law, let alone the principle that injunctions should be commensurate in scope with the infringing conduct. Yet the lower court's interpretation places the remedy provision of the Hatch-Waxman Act in the unique position of requiring orders with an injunctive scope that is broader than the infringement they are based on. Congress surely did not intend for the Hatch-Waxman Act to distort this basic tenet of patent law.

II. The Correct Implementation of the Remedy Provision in the Hatch-Waxman Act Is Vital to the Act's Purpose of Incentivizing Generic Drugs and Containing the Cost of Prescription Drugs

The Hatch-Waxman Act constitutes an important part of the legal framework that controls and incentivizes pharmaceutical industry innovation and competition in the United States. Given that the annual expenditure on prescription drugs exceeds half a trillion dollars, it is a matter of national concern that the Act's provisions are correctly interpreted and applied by the courts. Congress intended the Act to strike a balance between enabling the swift introduction of less-costly generic drugs and sufficiently rewarding investment in innovation. The lower

court's erroneous interpretation of Section 271(e)(4)(A) skews that balance away from generic drugs in a way that Congress did not intend. Unless rectified, the effects are unwarranted delay of generic alternatives for unpatented indications and a disincentive for generic companies to challenge the ever-growing patent thickets that protect brand monopolies. *See Comment of the Federal Trade Commission*, FTC, Docket No. PTO-P-2024-0003 (July 9, 2024) ("the Commission . . . shares bipartisan Congressional concerns that patent thickets erected by incumbents can delay and frustrate the entry of new biosimilars and generic drugs, increasing prescription drug costs and limiting patients' access to more affordable options.").

As of today, FDA has approved well over 200 new drugs that have at least two indications, and for which the brand company have listed at least two different use codes (i.e., patented uses) in the Orange Book. The district court's incorrect interpretation of Section 271(e)(4)(A) thus has the potential to delay generic competition for a substantial number of branded drugs. Such unwarranted delay is not limited to the situation where, as here, the generic applicant successfully challenges the patents on one indication but is held to infringe the patents on a second indication. It may also occur when a generic is unsuccessful in challenging both sets of patents where the two sets have different expiration dates. Unless the court fashions a Section 271(e)(4)(A) order that differentiates between the two indications and patent expiration dates, FDA could not approve the indication covered by the earlier-expiring patents until expiration of the later-expiring patents. The result is, again, an unwarranted extension of the brand's monopoly on unpatented indications.

Furthermore, unless the Court grants review, the district court's interpretation requiring blanket 271(e) orders will have a chilling effect on the willingness of generic companies to challenge method-of-use patents covering approved indications. Where there is more than one such approved indication, generics will be strongly incentivized to only seek approval for one, because an adverse infringement finding on any one indication is a death knell for the entire ANDA. This will be true even when the generic perceives the patents for both indications to be equally susceptible to challenge.

The cost of the delay in generic alternatives will be borne by patients and the health care system that will pay monopoly prices for indications that are either not covered by a valid patent or that are covered by patents that would have been proven invalid or not infringed by a generic alternative. And the excess profits enjoyed on the branded side cannot be justified as reward for investment in innovation and intellectual property. Here, for example, Salix's IBS-D Patents were shown to be invalid for obviousness and thus not representative of innovation. Furthermore, 271(e) orders are issued at the end of an ANDA litigation and the brand company has therefore enjoyed the statutory 30-month stay of FDA approval of the ANDA that the Hatch-Waxman Act provides. There is no justification for any further extension of the brand monopoly on an unpatented indication.

III. This Case Is Well-Situated to Address the Question Presented

This case is a good vehicle to address the proper interpretation of the Section 271(e)(4(A) – the remedy

provision in the Hatch-Waxman Act that is invoked in every ANDA litigation after a finding of infringement. The issue is purely one of statutory interpretation with no patent merit disputes remaining. Specifically, Norwich has forgone its right to appeal the district court's infringement finding with respect to the HE Patents, and the Federal Circuit has affirmed that the IBS-D and Polymorph Patents are invalid.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

Ian Swan
Axinn, Veltrop & Harkrider LLP
1901 L Street NW
Washington, DC 20036

Thomas K. Hedemann
Counsel of Record
Matthew J. Becker
Matthew S. Murphy
Axinn, Veltrop & Harkrider LLP
90 State House Square
Hartford, CT 06103
(860) 275-8100
thedemann@axinn.com

Counsel for Petitioner

September 11, 2024

APPENDIX

TABLE OF APPENDICES

APPENDIX A — OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT, FILED APRIL 11, 2024

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2022-2153, 2023-1952

SALIX PHARMACEUTICALS, LTD., SALIX PHARMACEUTICALS, INC., BAUSCH HEALTH IRELAND LTD., ALFASIGMA S.P.A.,

Plaintiffs-Appellants,

v.

NORWICH PHARMACEUTICALS INC.,

Defendant-Cross-Appellant.

April 11, 2024, Decided

Appeals from the United States District Court for the District of Delaware in No. 1:20-cv-00430-RGA, Judge Richard G. Andrews.

Before LOURIE, CHEN, and CUNNINGHAM, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* LOURIE.

Opinion dissenting-in-part filed by *Circuit Judge* CUNNINGHAM.

Appendix A

LOURIE, *Circuit Judge*.

Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., Bausch Health Ireland Ltd., and Alfasigma S.P.A. (collectively, "Salix") appeal from a final judgment of the United States District Court for the District of Delaware holding claim 2 of U.S. Patent 8,309,569, claim 3 of U.S. Patent 10,765,667, claim 4 of U.S. Patent 7,612,199, and claim 36 of U.S. Patent 7,902,206 invalid as obvious. *See Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, No. 20-cv-430, 2022 U.S. Dist. LEXIS 142335, 2022 WL 3225381 (D. Del. Aug. 10, 2022) ("*Decision*").

Norwich Pharmaceuticals Inc. ("Norwich") cross-appeals from an order that issued after the district court concluded that Norwich infringed claim 8 of U.S. Patent 8,624,573, claim 6 of U.S. Patent 9,421,195, and claims 11 and 12 of U.S. Patent 10,335,397 and had failed to prove that those claims were invalid. That order, contained within the final judgment, instructed the FDA that the effective approval date of Norwich's Abbreviated New Drug Application ("ANDA") may not precede the expiration dates of those claims. J.A. 51. Norwich also cross-appeals from a denial of its motion to modify the final judgment. *See Salix Pharms., LTD v. Norwich Pharms., Inc.*, No. 20-430, 2023 U.S. Dist. LEXIS 86257, 2023 WL 3496373 (D. Del. May 17, 2023) ("*Rule 60(b) Order*").

For the following reasons, we affirm.

Appendix A

BACKGROUND

Rifaximin, the active ingredient in Salix's commercial product Xifaxan®, has been widely used as an antibiotic for decades, having been first synthesized in the early 1980s in Italy and approved there as an antibiotic in 1985. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *8; J.A. 2532. The FDA approved Xifaxan nearly 20 years later, in 2004, as 200 mg tablets for the treatment of travelers' diarrhea. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *1. The FDA subsequently approved 550 mg tablets for hepatic encephalopathy ("HE") in 2010 and for irritable bowel syndrome with diarrhea ("IBS-D") in 2015. *Id.*

Norwich sought to market a generic version of rifaximin and, in 2019, filed an ANDA for 550 mg tablets with the same indications as Xifaxan, certifying pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that Salix's rifaximin patents were invalid. Salix timely sued, asserting that Norwich's ANDA infringed dozens of valid, Orange Book-listed patents. By the time of trial, the case had been streamlined to three groups of patents:

- the '573, '195, and '397 patents, directed to treating HE ("the HE patents");
- the '569 and '667 patents, directed to treating IBS-D with 550 mg rifaximin three times a day (1,650 mg/day) for 14 days ("the IBS-D patents"); and,
- the '199 and '206 patents, directed to rifaximin form β ("the polymorph patents").

Appendix A

Following a bench trial, the district court held that Norwich infringed the HE patents' claims and had failed to establish their invalidity. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *10-11. Norwich did not appeal those holdings. The court also held that Norwich's ANDA infringed the IBS-D and polymorph patents, but that those patents' claims would have been obvious over certain prior art. 2022 U.S. Dist. LEXIS 142335, [WL] at *2-3, 16-17. Salix appealed those invalidity holdings.

As part of the entered judgment, the district court ordered that the effective date of a final approval of Norwich's ANDA should not precede October 2029, which is the latest expiration date associated with the HE patents. J.A. 51. Norwich then amended its ANDA in an attempt to remove the infringing HE indication and moved to modify the judgment under Federal Rule of Civil Procedure 60(b), asserting that the amendment negated any possible infringement. The court denied Norwich's motion, and Norwich cross-appealed.

We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Salix first contends that the district court's conclusion that the asserted claims of the IBS-D patents were invalid as obvious was reached in error. Subsumed within that challenge is a question of whether or not a background reference discussed by the court was properly established as prior art. Salix also contends that the court erred in holding that the asserted polymorph patent claims were

invalid as obvious. Norwich's cross-appeal asserts that the court erred in the phrasing of its order precluding final approval of its ANDA until expiration of the HE patents. Norwich further asserts that the court erred in denying its motion to modify after the ANDA was amended in an attempt to avoid infringement. We address each argument in turn.

I

We turn first to Salix's contention that the district court erred in concluding that the asserted claims of the IBS-D patents would have been obvious over the asserted prior art.

Whether or not a claim would have been obvious is a question of law, based on underlying factual determinations. *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1328-29 (Fed. Cir. 2020). We review the ultimate legal question of obviousness *de novo* and the underlying factual determinations for clear error. *Id.* at 1328. A finding is clearly erroneous only if we are "left with a definite and firm conviction that the district court was in error." *Id.* (citations omitted).

The IBS-D patents are directed to treating IBS-D with 550 mg rifaximin, thrice-daily (1,650 mg/day), for 14 days. For example, claim 2 of the '569 patent depends from claim 1 as follows:

> 1. A method of providing acute treatment for diar-rhea-associated Irritable Bowel Syndrome

> (dIBS) comprising: *administering 1650 mg/day* of rifaximin for 14 days to a subject in need thereof, wherein removing the subject from treatment after the 14 days results in a durability of response, wherein the durability of response comprises about 12 weeks of adequate relief of symptoms.
>
> 2. The method of claim 1, wherein *the 1650 mg is administered at 550 mg three times per day*.

'569 patent, col. 30 ll. 4-12 (emphases added); *see also* '667 patent, col. 46 ll. 29-33, 39-40 (claims 1 & 3, similar). The key limitation on appeal is the dosage amount that appears in the claims: 550 mg, three times per day ("TID"), for a total of 1,650 mg/day.

Norwich challenged the IBS-D claims' validity by asserting as prior art references a clinical trial protocol that had been published on the ClinicalTrials.gov website in 2005 ("the Protocol")[1] and a 2006 journal article ("Pimentel").[2] The Protocol describes a Phase II study evaluating twice-daily doses of 550 mg (1,100 mg/

1. ClinicalTrials.gov, *History of Changes for Study: NCT00269412, Randomized, Double Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Three Different Doses of Rifaximin Administered BID either Two or Four Weeks in the Treatment of Patients with Diarrhea-Associated Irritable Bowel Syndrome* (December 22, 2005); J.A. 7047-55.

2. M. Pimentel *et al., The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome*, 145 ANN. INTERN. MED., 557 (2006); J.A. 4639-46.

day) and 1,100 mg (2,200 mg/day) for 14 and 28 days for the treatment of IBSD. *See* J.A. 7051. Pimentel teaches administering 400 mg, TID (1,200 mg/day), for the treatment of IBS,[3] but further opines that the "optimal dosage of rifaximin may, in fact, be higher than that used in our study." J.A. 4644.

The district court found that those two references disclose each and every limitation of the challenged IBS-D claims, and further found that a skilled artisan would have been motivated to combine those two references to arrive at what is claimed with a reasonable expectation of success. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *17, *19-20. The court then concluded that the challenged IBS-D claims were invalid as obvious. 2022 U.S. Dist. LEXIS 142335, [WL] at *17-22. Salix appeals, asserting that the court erred in finding that a skilled artisan would have had a reasonable expectation of success in using the claimed 1,650 mg/day dosage to treat IBS-D. Appellants' Br. at 39-48. Whether or not there would have been a reasonable expectation of success is a question of fact, *IXI IP, LLC v. Samsung Elecs. Co.*, 903 F.3d 1257, 1262 (Fed. Cir. 2018), which we review for clear error, *Hospira*, 946 F.3d at 1328.

Salix does not appear to dispute the district court's finding that the Protocol and Pimentel "disclose all

3. Salix did not argue a difference between a motivation to use rifaximin to treat IBS versus IBS-D. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *19 n.3. It concedes on appeal that "[r]oughly one-third of IBS patients suffer from IBS-D," Appellants' Br. at 6, and has not otherwise suggested that treatments for IBS would not inform treatments of IBS-D.

limitations of the IBS-D claims." *See Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *17. Rather, it contends that even if the asserted combination of references effectively discloses the claimed 1,650 mg/day dosage, there remains insufficient evidence to support a finding of a reasonable expectation of success in using that particular dosage amount. *See, e.g.*, Appellants' Br. at 39-40. According to Salix, the highest prior art dosage amount that could have been supported with a reasonable expectation of success was the 1,200 mg/day dose evaluated by Pimentel. *Id.* at 40. We disagree.

The Protocol provides an outline of a planned Phase II clinical trial in which "three different doses (275, 550 and 1100 mg) of rifaximin" were to be "administered BID [*i.e.*, twice-daily] for either two or four weeks in the treatment of patients with diarrhea-associated irritable bowel syndrome." J.A. 7050 (cleaned up). As an outline of that clinical trial plan, the Protocol provides only that those three specific, twice-daily dosage regimens were to be investigated for either two or four weeks. The Protocol does not include any efficacy or safety data, nor does it mention a 1,650 mg/day dose or TID dosing.

Although we have rejected the idea that "efficacy data [are] always required for a reasonable expectation of success," *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019), we are hesitant to conclude as a general matter that the disclosure of a Phase II clinical trial plan, standing alone, provides an expectation of success sufficient to render obvious a dosage that was not included within the planned clinical trial. *See* Appellants'

Reply Br. at 13?14. But the Protocol was not asserted alone; it was asserted in combination with Pimentel.

Pimentel teaches that administration of 400 mg rifaximin, TID (1,200 mg/day), "resulted in greater improvement in IBS symptoms" and "lower bloating score[s] after treatment." J.A. 4639; *see also id.* at 4642-43 (providing supporting data). Pimentel explains that the 400 mg TID regimen was chosen "on the basis of a previous study that demonstrated the efficacy of rifaximin in bacterial overgrowth." *Id.* at 4640. However, Pimentel does not merely provide that daily rifaximin doses of 1,200 mg were likely to be successful in the treatment of IBS. Pimentel further teaches that "[r]ecent data suggest that the *optimal dosage* of rifaximin *may, in fact, be higher* than that used in our study." J.A. 4644; *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *20 (emphases added).

The district court did not clearly err in finding that a skilled artisan would have looked to both of those references, considered their limits, and had a reasonable expectation of success as to the efficacy of 550 mg TID dosing. The combined message that the skilled artisan would have discerned from the Protocol and Pimentel is that the optimal dosage for treating patients suffering from IBS disorders may be higher than 400 mg TID, and the next higher dosage unit from the Protocol was 550 mg. We see no clear error in the conclusion that there would have been a reasonable expectation of success in administering the claimed 1,650 mg/day to IBS-D patients. Indeed, certainty and absolute predictability are not required to establish a reasonable expectation of success.

See Almirall, LLC v. Amneal Pharms. LLC, 28 F.4th 265, 275 (Fed. Cir. 2022) ("A finding of a reasonable expectation of success does not require absolute predictability of success."); *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018) ("This court has long rejected a requirement of conclusive proof of efficacy for obviousness." (cleaned up)).

Moreover, references establishing the background knowledge of a person of ordinary skill in the art are consistent with the reasonable expectation of success provided by the combination of the Protocol with Pimentel. For example, Cuoco[4] teaches the efficacy of 1,200 mg rifaximin/ day for 14 days for the treatment of small intestinal bacterial overgrowth ("SIBO"). J.A. 4533. Salix has acknowledged that those of ordinary skill in the art identified "bacterial alterations" as a potential underlying cause for IBS, Appellants' Br. at 7, and the literature[5] describes SIBO as a condition that is "highly prevalent in patients with irritable bowel syndrome (IBS)," such that "SIBO decontamination is associated [with] a significant improvement of IBS symptoms." J.A. 4664. We therefore agree with the district court that references describing the treatment of SIBO would have been pertinent to the skilled artisan's considerations as to what treatments

4. L. Cuoco & M. Salvagnini, *Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective study with rifaximin*, 52 MINERVA GASTROENTEROL. DIETOL. (2006) 89; J.A. 4533-39.

5. E. Scarpellini et al., *High dosage rifaximin for the treatment of small intestinal bacterial overgrowth*, 25 ALIMENT. PHARMACOL. THER. 781 (2007); J.A. 4663-67 ("Scarpellini").

would have a potential for success in treating individuals suffering from IBS.

In addition to Cuoco, Lauritano[6] teaches an increase in rifaximin efficacy for the treatment of SIBO as doses were increased from 600 mg/day to 1,200 mg/day, providing the trend that Pimentel described as indicating that doses higher than 1,200 mg/day may be even more optimal for the treatment of IBS. J.A. 7267 ("Higher doses of rifaximin lead to a significant gain in terms of therapeutic efficacy in [SIBO] eradication without increasing the incidence of side-effects."); *see also id.* at 4644. As evidenced by Scarpellini and Lin,[7] those in the art advanced on those findings, and subsequently evaluated higher doses. For example, Scarpellini reported that a 1,600 mg/day dose "showed a significantly higher efficacy" compared with 1,200 mg/day for the treatment of SIBO. J.A. 4663; *see also id.* at 4666 (Table 1, noting study patients included those suffering from IBS-D); *id.* at 4747 (teaching that "[a]bout 400 to about 600 mg of rifaximin may be administered TID for about 10 days" (*i.e.*, 1,200 mg/day to 1,800 mg/day) for the eradication of bacterial overgrowth).

The record further supports the finding that there would have been a reasonable expectation of success in administering higher doses of rifaximin without an intolerable increase in negative side effects. For example,

---

6. E.C. Lauritano et al., *Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth*, 22 ALIMENT. PHARMACOL. THER., 31 (2005); J.A. 7267-71.

7. International Patent Application Publication 2006/102536; J.A. 4721-47.

Cuoco teaches that rifaximin was understood as having "a low risk of causing microbial resistance," J.A. 4533, and that rifaximin was well known for its "profile of tolerability and safety widely described in the literature," *id.* at 4538. Scarpellini further reported that the 1,600 mg/day dose provided a "similar compliance and side-effect profile" compared with the 1,200 mg/day dose. *Id.* at 4663. As the district court noted, the "[w]idespread off-label use" of rifaximin also supported the conclusion that rifaximin was safe and effective "for the treatment of IBS-D with a reasonable expectation of success." *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *19; *see also* Appellants' Br. at 17 ("There is no dispute that skilled artisans knew of the general concept of trying off-label use of rifaximin to treat IBS-D.").

In view of the record before us, we see no clear error in the finding that a skilled artisan would have had a reasonable expectation of success in administering the claimed 1,650 mg/day regimen for the treatment of IBS-D. We therefore affirm the district court's holding that the challenged IBS-D claims would have been obvious over the cited references. *See In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (citation omitted)).

Salix further contends that a Press Release[8] issued by Salix in a filing with the Securities and Exchange

8. Salix Pharms., Ltd., Current Report (Form 8-K) (Sept. 5, 2007); J.A. 7477-82.

Commission less than a year before the patents' priority date was not prior art because Norwich failed to establish that it was "by others" as required by pre-AIA 35 U.S.C. § 102(a). Appellants' Br. at 30-39. According to Salix, the district court's inclusion of that allegedly non-prior art reference in its discussion of the skilled artisan's expectation of success was harmful error. *Id.*

Although the district court cited the Press Release in its discussion of the skilled artisan's expectations, it ultimately held that the "Protocol and Pimentel [] disclose all limitations of the IBS-D claims" and that a skilled artisan "would have been motivated to combine the . . . Protocol and Pimentel [] with a reasonable expectation of success." *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *17. We therefore need not decide whether or not the Press Release was prior art because, even assuming that it was not, the Protocol and Pimentel alone established the obviousness of the claims.

We accordingly affirm the district court's determination that Norwich established that the IBS-D claims would have been obvious in view of the Protocol and Pimentel.

II

We next turn to Salix's contention that the district court clearly erred in finding that there would have been a reasonable expectation of success in obtaining the rifaximin form β recited in the polymorph patents' claims.

Whether or not there would have been a reasonable expectation of success is a question of fact, *IXI IP, LLC*

v. Samsung Elecs. Co., 903 F.3d 1257, 1262 (Fed. Cir. 2018), which we review for clear error, *Hospira*, 946 F.3d at 1328. We review the ultimate conclusion of obviousness *de novo. Id.*

The polymorph patents are directed to rifaximin form β. For example, claim 4 of the '199 patent recites:

> 4. Rifaximin in polymorphic form β, wherein the rifaximin has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9°2θ and wherein the rifaximin has a water content of greater than 5%.

'199 patent, col. 10 ll. 24-27; *see also* '206 patent, col. 11 ll. 33-37, 41-43 (claims 34 & 36, similar).

Norwich challenged the polymorph claims' validity by asserting, *inter alia*, Cannata,[9] which discloses that rifaximin exists in crystalline form with "outstanding antibacterial properties." J.A. 4528; *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *6. Cannata does not discuss rifaximin's crystal structure in detail, but it does disclose several preparation protocols for rifaximin that include solvents used for crystallization. J.A. 4529-31; *see also id.* at 3408.

The district court held that expert testimony supported a conclusion that, in view of the prior art, (1) a skilled artisan would have had good reason to characterize

9. U.S. Patent 4,557,866; J.A. 4526-32.

the crystalline rifaximin obtained by following the Cannata protocols, (2) that such characterization was routine and could have been performed "in one day," and (3) that doing so would have led the skilled artisan to have "detected rifaximin β." *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *6-7. The district court subsequently concluded that the challenged polymorph claims would have been obvious over the asserted prior art in view of the common knowledge of the skilled artisan. 2022 U.S. Dist. LEXIS 142335, [WL] at *7-8.

Salix first challenges the district court's conclusion of obviousness by asserting that *Grunenthal GMBH v. Alkem Laboratories Ltd.*, 919 F.3d 1333 (Fed. Cir. 2019) and *Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 U.S. App. LEXIS 31479, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022) compel the opposite result. Appellants' Br. at 49-51. Salix further contends that the court "applied the wrong test" by not following a rationale provided in the district court opinion from *Pharmacyclics*. *Id.* at 55-57. We disagree.

In *Grunenthal*, we held that it was not clear error for the district court to find that the record failed to establish by clear and convincing evidence a reasonable expectation of success in preparing the claimed polymorphic Form A of tapentadol hydrochloride. *See* 919 F.3d at 1341. In that case, the synthesis of tapentadol hydrochloride known in the prior art produced a particular form—Form B. *Id.* The district court found that there was a lack of evidence that a prior art synthesis would have resulted in the claimed Form A and that no prior art guidance existed to establish

"what particular solvents, temperatures, agitation rates, etc., were likely to result" in the claimed polymorph. *Id.* at 1343. We found no clear error in that analysis. *Id.* at 1344-45.

We also affirmed a conclusion of non-obviousness of a claimed polymorph in our non-precedential *Pharmacyclics* decision, which issued after the district court released its decision in this case. *See* 2022 U.S. App. LEXIS 31479, 2022 WL 16943006, at *10-11. But the court here acted within its discretion when it declined to follow the district court decision in *Pharmacyclics* as though it was binding precedent. *See Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *7 n.1 ("Plaintiffs call to my attention [the district court's decision in] *Pharmacyclics LLC v. Alvogen Pine Brook LLC*. I have considered that case but I do not agree with it on this point."). And our later affirmance of the factual findings in *Pharmacyclics* did not retroactively override the district court's analysis here.

Moreover, a lack of clear error in *Grunenthal* and *Pharmacyclics* does not compel a conclusion of non-obviousness here. Indeed, *Grunenthal* underscored the factual nature of these types of inquiries and expressly held that it did "not rule out the possibility that polymorph patents could be found obvious." 919 F.3d at 1344-45. "The determination of obviousness is dependent on the facts of each case." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1089 (Fed. Cir. 2008); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007). In *Grunenthal* and *Pharmacyclics*, the issue was whether a skilled artisan would have had a reasonable expectation

of success in *producing* a crystalline form of a compound. *See* 919 F.3d at 1341-43; 2022 U.S. App. LEXIS 31479, 2022 WL 16943006, at *10-11. Here, the prior art included a process to produce a crystalline form of rifaximin, and the dispute centered around *characterizing* the crystalline form resulting from that process. *See Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *13-14. These distinct factual predicates support the district courts' factual findings in each of these three cases under the clear error standard of review.

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966), the Supreme Court set forth the background against which obviousness is to be assessed: "Under § 103, the scope and content of the prior art are to be determined" and "differences between the prior art and the claims at issue are to be ascertained." *Id.* at 17. The scope and content of the prior art here includes preparations of crystalline rifaximin, which expert testimony supports would have yielded the β form of rifaximin. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *7; J.A. 3391-92 ("[T]he as-synthesized form of rifaximin reported by Examples 1, 6, 7, and 9 [of Cannata] were necessarily rifaximin form Beta, because of the methods used, the solvent system used, and it was later confirmed by later work, including work from the named inventors."); *id.* at 3408-09 (similar testimony); *id.* at 3393-3404 (discussing the evidence of record that supports that conclusion); *id.* at 4700-07, 4846-47, 5007-14 (providing supporting evidence for that conclusion). And the parties do not dispute that the methods for characterizing the resulting crystalline rifaximin were

well known and readily available to the skilled artisan. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *3. The difference between the prior art and the claims is thus effectively nothing more than the performance of routine characterization to identify the polymorphic forms that result from the known Cannata processes.

In this regard, Salix does not appear to dispute that there would have been a motivation to explore potential polymorphic forms of rifaximin. Appellants' Br. at 48-49. Rifaximin was, after all, a known compound with a known, useful activity. Salix further refers to the district court's finding that "polymorph β is a commonly produced polymorph and the most stable form of rifaximin" as an "undisputed" fact. *Id.*; *see also Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *7. There thus appears to be no dispute that the claimed polymorph can be readily produced from the crystallization conditions disclosed in Cannata and that it would have been well within the abilities of the skilled artisan to procure and characterize the β form of rifaximin.

According to Salix, however, rifaximin's β form constituted a non-obvious invention because, although skilled artisans "actually succeed[ed]" in producing and characterizing it, they would not have "*expect*[*ed*] to succeed" because, as of the critical date, the polymorphic nature of rifaximin had not yet been reported and the identity of the β form remained undisclosed. Appellants' Br. at 49. Salix further argues that there could have been no expectation of success because the skilled artisan would not have been able to predict what polymorphic forms

might result from following the preparation protocols disclosed in the prior art. *Id.* at 20-21, 50-53. Salix's framing of the issue suggests that no unknown entity could ever be obvious, as one cannot reasonably expect what was hitherto unknown, which is incorrect.

Here, the district court found a reasonable expectation of success in characterizing the crystalline product of Cannata for potential polymorphism using routine, conventional methods and skill. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *6-7. We see no clear error in that conclusion. Indeed, Salix has done no more than combine known elements of the prior art to verify readily accessible information concerning a compound already in the hands of those of ordinary skill in the art, and such routine efforts do not justify removing this polymorph from the public domain. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007); *see also Pfizer*, 480 F.3d at 1367-68. To be sure, we do not hold that there is always a reasonable expectation of success in accessing or characterizing polymorphs. We are simply reviewing the district court's decision before us as to its factual finding of a reasonable expectation of success, and in so doing, have not been left with a definite and firm conviction that a mistake was made in reaching that finding. *See Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1374 (Fed. Cir. 2008).

Having found no clear error in the district court's fact findings as to the existence of a reasonable expectation of success, we affirm the court's conclusion that the polymorph patent claims were invalid as obvious. Because

we affirm the court's holding that the polymorph patent claims would have been obvious over the asserted prior art, we need not consider Norwich's separate argument that the polymorph claims would have also been invalid as inherently anticipated.

III

On cross-appeal, Norwich raises two related but distinct arguments that arose after the district court held that Norwich infringed the HE patents and failed to establish invalidity. *See Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *10-16. Norwich first argues that, in issuing its final decision, the district court misinterpreted 35 U.S.C. § 271(e)(4)(A), which directs a court, following a finding of infringement, to order the FDA to defer final approval of an ANDA until the expiration of the infringed patent. According to Norwich, that statute precludes delaying final approval of an entire ANDA, and instead requires delaying only the approval of the infringing use.

Norwich's second argument arises from its decision to amend its ANDA to carve out the infringing HE use after final judgment. Following that amendment, Norwich filed a motion to modify the final judgment to allow for prompt approval of the amended ANDA that purportedly no longer sought approval for the infringing HE use. The district court denied that motion, and Norwich cross-appealed.

We address both of Norwich's concerns in turn.

Appendix A

A.

We first address Norwich's arguments regarding the district court's interpretation of 35 U.S.C. § 271(e)(4)(A) in ordering that a final approval of Norwich's ANDA could not be effective before the HE patents expired. J.A. 50-51.

We review issues of statutory interpretation without deference to the district court's interpretation. *Waymark Corp. v. Porta Sys. Corp.*, 245 F.3d 1364, 1366 (Fed. Cir. 2001). "The starting point in every case involving construction of a statute is the language itself." *Blue Chip Stamps v. Manor Drug Stores*, 421 U.S. 723, 756, 95 S. Ct. 1917, 44 L. Ed. 2d 539 (1975) (Powell, J., concurring). Moreover, we "give effect, if possible, to every clause and word of [the] statute." *United States v. Menasche*, 348 U.S. 528, 538-39, 75 S. Ct. 513, 99 L. Ed. 615 (1955) (citation omitted). When a statute does not define a given word or phrase, we presume that Congress intended the word or phrase to have its ordinary meaning. *Asgrow Seed Co. v. Winterboer*, 513 U.S. 179, 187, 115 S. Ct. 788, 130 L. Ed. 2d 682 (1995). However, "[i]n expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law, and to its object and policy." *U.S. Nat'l Bank of Or. v. Indep. Ins. Agents of Am. Inc.*, 508 U.S. 439, 455, 113 S. Ct. 2173, 124 L. Ed. 2d 402 (1993) (citation omitted).

Section 271(e)(4)(A) instructs that, following a finding of infringement, "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." The order here instructed the FDA that "the effective date of any final approval . . . of Norwich's ANDA No. 214369 is to be a date not earlier than the date of expiration of the last to expire of [the HE patents] (currently October 2, 2029)." J.A. 51.

Norwich argues that the language of § 271(e)(4) requires courts to tie the restriction on FDA approval to the *indication* for which the ANDA seeks approval when that indication was the source of infringement. Cross-Appellants' Br. at 14. Norwich's ANDA originally sought approval for the treatment of both IBS-D and HE. Although only the HE indication was found to infringe a valid patent, the order restricted final approval of the entire ANDA, including the non-infringing indication, until 2029. Norwich argues that the statute requires the district court's order "to specify that the approval date pertains to Norwich's ANDA seeking approval for the infringing HE Indication." *Id.* at 18. But the district court order concerned only the specific ANDA in question that included an infringing use, referred to the ANDA by its number, and enjoined the approval of that ANDA. J.A. 51. Norwich suggests that the district court order unfairly precludes it from receiving final approval of a new non-infringing ANDA.[10] The district court did no such thing.

10. Norwich notes that on June 2, 2023, FDA tentatively approved its amended ANDA, which purportedly lacks the HE indication. Cross-Appellant's Br. at 6. The tentative approval letter noted, however, that "final approval cannot be granted until October 2, 2029 as specified in the court order." *Id.*

Section 271(e)(4)(A) describes delaying the approval of "the drug . . . involved in the infringement." Since the FDA does not approve drugs in the abstract, but rather approves drugs for particular uses (indications) of that drug, the statute is appropriately construed as directed to approval of particular infringing uses of the drug, not all uses of the drug including non-infringing uses. The statutory scheme makes clear that it is not the potential use of Norwich's rifaximin for HE that constitutes the relevant infringement here, nor is it the unpatented drug compound itself, but rather it is the submission of the ANDA that included an infringing use. *See* 35 U.S.C. § 271(e)(2)(A) (making it an "act of infringement to submit" an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent"). That the ANDA further recited a non-patent-protected indication does not negate the infringement resulting from the ANDA's submission. The order thus appropriately delayed the effective final approval date of "this infringing ANDA" submission. J.A. 48. The order appropriately said nothing that would prevent approval of a new non-infringing ANDA.

We therefore affirm the district court's order setting the effective approval date of Norwich's ANDA No. 214369 to be no earlier than the date of expiration of the last to expire of the HE patents.

B.

Following entry of the final judgment, which included the resetting order barring final approval of Norwich's ANDA until 2029, Norwich amended its ANDA in an

attempt to remove the infringing HE indication. Norwich then moved to modify the judgment under Federal Rule of Civil Procedure 60(b), asserting that the amendment negated any possible infringement, and that the final approval date of the ANDA, as amended, should not be tied to the HE patents. *See* Cross-Appellant's Br. at 27. The district court denied that motion, holding that Norwich "fully litigated the merits of its non-infringement and invalidity case, lost, and now seeks a way around the final judgment through Rule 60(b)." *Rule 60(b) Order*, 2023 U.S. Dist. LEXIS 86257, [WL] at *2. Norwich cross-appealed.

"Because denial of a Rule 60(b) motion is a procedural issue not unique to patent law, we apply the rule of the regional circuit where appeals from the district court would normally lie," *Amstar Corp. v. Envirotech Corp.*, 823 F.2d 1538, 1550 (Fed. Cir. 1987), which, here, is the Third Circuit. The Third Circuit "review[s] the denial of Rule 60(b) relief for an abuse of discretion." *Coltec Indus., Inc. v. Hobgood*, 280 F.3d 262, 269 (3d Cir. 2002); *see also Bohus v. Beloff*, 950 F.2d 919, 930 (3d Cir. 1991) (noting that Rule 60(b) motions are "extraordinary relief which should be granted only where extraordinary justifying circumstances are present" (citation omitted)).

"A district court may reconsider its own finding of infringement in light of an amended ANDA," but the court need not do so. *Ferring B.V. v. Watson Lab'ys, Inc. Fla.*, 764 F.3d 1382, 1391 (Fed. Cir. 2014). Rather, "[a]llowing an amendment is within the discretion of the district court, guided by principles of fairness and prejudice to the patent-holder." *Id.* Here, the court reasonably

held that consideration of the amended ANDA would be inequitable and inappropriate. *Rule 60(b) Order*, 2023 U.S. Dist. LEXIS 86257, [WL] at *2. The court noted that "[i]t is not a simple matter to determine whether an ANDA applicant has successfully carved out language from a label to turn infringement into non-infringement" and that what Norwich sought in its Rule 60(b) motion "would essentially be a second litigation" following final judgment. *Id.* (noting also that, other than simply asserting that it carved out the HE indication and providing the court with the amended label, Norwich "ha[d] presented no evidence in support of its assertion" that the amended ANDA would no longer infringe the HE patents).

Norwich nevertheless argues that the amended ANDA satisfies the judgment by not seeking approval for the infringing use and that, in view of the amendment, it is no longer equitable to apply the judgment prospectively. But Rule 60(b) is permissive, holding only that the court "*may* relieve a party or its legal representative from a final judgment, order, or proceeding" under various circumstances. That is—a district court has the discretion, not the obligation, to modify a final judgment in view of a post-judgment ANDA amendment. And as the district court held, simply asserting that a patented indication has been carved out of an ANDA application does not necessarily satisfy the judgment or entitle the applicant to direct entry to the market. *See Rule 60(b) Order*, 2023 U.S. Dist. LEXIS 86257, [WL] at *2. We see no abuse of discretion in the district court reaching that conclusion or in subsequently denying the motion.

Norwich further argues that the district court erred by not explicitly discussing Rule 60(b)(6), which provides that a court may relieve a party from a final judgment for "any other reason that justifies relief." We disagree that the district court so erred. The court's Memorandum Order thoroughly discussed the law, the equities, the record, and the arguments before it. In so doing, the court implicitly found no additional reason that justified the relief that Norwich sought.

We therefore affirm the district court's denial of the motion to modify the final judgment.

Conclusion

We have considered both parties remaining arguments and find them unpersuasive. For the foregoing reasons, we affirm (1) the district court's holding that claim 2 of the '569 patent, claim 3 of the '667 patent, claim 4 of the '199 patent, and claim 36 of the '206 patent would have been invalid as obvious, (2) the district court's order setting the effective approval date of Norwich's ANDA to be no earlier than the date of expiration of the last to expire of the HE patents, and (3) the district court's denial of the motion to modify the final judgment.

AFFIRMED

costs

No costs.

Appendix A

CUNNINGHAM, *Circuit Judge*, dissenting in part.

I join most of the majority's opinion, but I respectfully dissent from the majority's opinion concerning U.S. Patent Nos. 8,309,569 and 10,765,667 (the "IBS-D patents"). I would vacate the district court's judgment that the asserted claims of the IBS-D patents are obvious and remand for further proceedings.

I

The district court found that "[t]he asserted IBS-D claims describe a dosing regimen within the known range" and that "[a] POSA would have been motivated to combine the RFIB 2001 Protocol[1] and Pimentel 2006[2] with a reasonable expectation of success." *Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, No. 20-430-RGA, 2022 U.S. Dist. LEXIS 142335, 2022 WL 3225381, at *17 (D. Del. Aug. 10, 2022) ("*Decision*") (footnotes added). Based on these findings of fact, the court concluded that "Pimentel 2006 in light of the RFIB 2001 Protocol renders the asserted claims of the IBS-D patents obvious." 2022 U.S. Dist.

1. ClinicalTrials.gov, *History of Changes for Study: NCT00269412, Randomized, Double Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Three Different Doses of Rifaximin Administered BID Either Two or Four Weeks in the Treatment of Patients with Diarrhea-Associated Irritable Bowel Syndrome* (December 22, 2005); J.A. 7048-55.

2. M. Pimentel et al., *The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome*, 145 ANNALS INTERN. MED. 557 (2006); J.A. 4639-46. The majority refers to this reference as Pimentel.

LEXIS 142335, [WL] at *18. After reviewing the evidence relied on by the district court, applying a clear error standard, I am "left with the definite and firm conviction that a mistake has been committed" regarding these findings. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007) (quoting *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395, 68 S. Ct. 525, 92 L. Ed. 746 (1948)).

The evidence cited by the district court does not support its finding that a skilled artisan would have a reasonable expectation of success for the claimed dosage. *See Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *17, *19. "The reasonable-expectation-of-success analysis must be tied to the scope of the claimed invention"—here, the claimed 1,650 mg/day (550 mg TID[3]) dosage for treating IBS-D. *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021). The district court mainly relied on the results of the RFIB 2001 trial disclosed in the RFIB 2001 Press Release[4] in arriving at this conclusion. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *19. However, there is no reason that a skilled artisan "would have known about the successful RFIB 2001 Protocol results," *id.*, as to the claimed 1,650 mg/day (550 mg TID) dosage because the RFIB 2001 Press Release only discloses an improvement in the *550 mg twice-a-day* group. J.A. 7480; *see Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *19. In fact, evidence in the record suggests the opposite—that a skilled artisan

3. TID stands for three times per day.

4. Salix Pharms., Ltd., Current Report (Form 8-K) (Sept. 5, 2007); J.A. 7477-82.

might have understood the absence of discussions of the *1,100 mg twice-a-day* group to imply that higher dosage *did not* lead to similar successful results. *See* J.A. 3313-14. Indeed, the 2,200 mg/day dosage "did not achieve more responders compared to the placebo for adequate relief."[5] J.A. 3042. Thus, the court's reliance on the RFIB 2001 Press Release to establish a reasonable expectation of success was erroneous.[6]

The district court's citations to other references do not cure this error. Cuoco[7] discloses a total dose of *1,200 mg/day* for 14 days, and Barrett[8] similarly discloses 400 mg TID for a total dosage of *1,200 mg/day. Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *19; *see also* J.A. 4536;

---

5. Although the evidence that the 2,200 mg/day dosage did not achieve adequate relief post-dates the priority date of the patent, it clarifies what a skilled artisan would have understood from the RFIB 2001 Press Release. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1379 (Fed. Cir. 2005) (holding district court erred in not considering a reference that post-dates the priority date when it is relevant to what "was known in the art at the relevant time").

6. Salix also challenges the district court's finding that the RFIB 2001 Press Release was prior art. Appellant's Br. 30-39; *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *20. I agree with the majority that we do not need to reach this issue.

7. L. Cuoco & M. Salvagnini, *Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective study with rifaximin*, 52 Minerva Gastroenterol. Dietol. 89 (2006); J.A. 4533-39.

8. G. Barrett, Abstract, *Benefits of the Antibiotic Rifaximin as Empiric Therapy in Patients with Irritable Bowel Syndrome*, 101 Am. J. Gastroenterol. S479 (2006); J.A. 4799-4800.

J.A. 4800. The district court did not explain why these references would give rise to a reasonable expectation of success for a dosage that is almost 40% higher. The reference by the district court to the "[w]idespread off-label use" of rifaximin was also unaccompanied by any discussion of dosages or citations to the record. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *19. Likewise, it discussed market research that shows many physicians prescribe rifaximin for IBS without discussing their prescribed dosages. *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *20 (citing J.A. 7186). The cited research does not show that physicians prescribe at the 1,650 mg/day (550 mg/TID) dosage. J.A. 7186.

Although "efficacy data is [not] always required for a reasonable expectation of success," *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019), the analysis must still be tied to the scope of the claims—here, the 1,650 mg/day dosage. *See Teva*, 18 F.4th at 1381; *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1070-72 (Fed. Cir. 2012) (finding no reasonable expectation of success when the court "cited no evidence specifically indicating that a [drug with a pK profile disclosed in the prior art] would be expected to yield the same therapeutic effect as [a different pK profile as claimed]"); *Ferring B.V. v. Watson Lab'ys, Inc.-Fla.*, 764 F.3d 1401, 1407 (Fed. Cir. 2014) (finding asserted claims not to be invalid for obviousness when prior art references "disclose 500 mg [] formulations, but no higher tablet strengths, and particularly not the claimed 650 mg formulation"). Aside from its erroneous reliance on the RFIB 2001 Press Release, the district

court failed to tie its reasonable expectation of success analysis to the claimed dosage. Therefore, I would find that it clearly erred in its reasonable expectation of success analysis.

In sum, the district court clearly erred in relying on the RFIB 2001 Press Release and other references that do not teach the claimed dosage. For these reasons, I would have found the district court's finding to be clearly erroneous and would vacate the district court's judgment that the IBS-D claims were invalid as obvious.

II

In affirming the district court's judgment of obviousness, the majority relies on one additional sentence in Pimentel 2006 regarding the reasonable expectation of success analysis: "Recent data suggest that the optimal dosage of rifaximin may, in fact, be higher than that used in our study." J.A. 4644; *see* Maj. Op. 8. But the lack of discussion of any actual dosage that may be optimal, the use of the word "may," and the fact that the RFIB 2001 Protocol discloses a specific dosing regimen of 2,200 mg/day rather than 1,650 mg/day all call into question the majority's finding. Indeed, the district court only relied on this sentence in its motivation to combine analysis and did not rely on this sentence in its reasonable expectation of success analysis. *See Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *18-20. The parties never made this argument before us. Therefore, I disagree that this additional sentence, when considered together with the RFIB 2001 Protocol, would give rise to a reasonable expectation of success for the claimed dosage.

The majority also discusses references not relied on by the district court in its reasonable expectation of success analysis, including Lauritano[9], Scarpellini[10], and Lin.[11] Maj. Op. 9-10. But the district court did not make any findings on what these references teach, other than finding that the references were prior art. *See Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *17-22. Nor are the majority's conclusions regarding these references uncontested. For example, Salix argues that Scarpellini and Lauritano are both directed to the treatment of small intestinal bacterial overgrowth (SIBO), not to the treatment of IBS or IBS-D, and therefore cannot establish a reasonable expectation of success. Appellant's Reply Br. 18. Although the majority may be right that Lauritano's and Scarpellini's disclosures on treating SIBO also support finding a reasonable expectation of success for treating IBS-D, *see* Maj. Op. 9-10, the district court never made this finding. *See Golden Bridge Tech., Inc. v. Nokia, Inc.*, 527 F.3d 1318, 1323 (Fed. Cir. 2008) (declining to find what a prior art reference teaches in the first instance). It merely found that "[t]he relationship between IBS and SIBO was actively being explored," and that certain prior art references "do not teach away from using rifaximin

9. E.C. Lauritano et al., *Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth*, 22 ALIMENT. PHARMACOL. THER. 31 (2005); J.A. 7267-71.

10. E. Scarpellini et al., *High dosage rifaximin for the treatment of small intestinal bacterial overgrowth*, 25 ALIMENT. PHARMACOL. THER. 781 (2007); J.A. 4663-67.

11. International Patent Application Publication No. WO 2006/102536; J.A. 4721-47.

to treat IBS." *Decision*, 2022 U.S. Dist. LEXIS 142335, [WL] at *21. I would not make such fact-findings about Scarpellini and Lauritano in the first instance.

In summary, I would vacate the district court's judgment that the asserted claims of the IBS-D patents were obvious and remand for further proceedings. On remand, I would order the district court to consider in the first instance the teachings in the additional prior art references. *See ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1578 (Fed. Cir. 1984) ("Where the trial court fails to make findings, the judgment will normally be vacated and the action remanded for appropriate findings to be made."). Accordingly, I respectfully dissent in part.

APPENDIX B — TRIAL OPINION OF THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE, FILED AUGUST 10, 2022

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civil Action No. 20-430-RGA

SALIX PHARMACEUTICALS, LTD.; SALIX PHARMACEUTICALS, INC.; BAUSCH HEALTH IRELAND LTD.; ALFASIGMA S.P.A.,

Plaintiffs,

v.

NORWICH PHARMACEUTICALS, INC.,

Defendant.

August 10, 2022, Decided
August 10, 2022, Filed

Signed August 10, 2022

TRIAL OPINION

ANDREWS, U.S. DISTRICT JUDGE:

Salix sued Norwich for infringement of twenty-six patents that cover Salix's branded Xifaxan (rifaximin) 550 mg tablets. (D.I. 59 ¶¶ 12, 41). Before trial, Salix narrowed

its case to U.S. Patent Nos. 7,612,199, 7,902,206 ("the Polymorph Patents"), 8,642,573, 9,421,195, 10,335,397 ("the HE Patents"), 8,309,569, and 10,765,667 ("the IBS-D Patents"). In March 2022, I held a four-day bench trial. (D.I. 168-172, hereinafter "Tr.").

I. BACKGROUND

Norwich submitted an Abbreviated New Drug Application (ANDA) to the Food and Drug Administration (FDA) for approval to market a generic version of Xifaxan. Salix alleges infringement under § 271(e)(2)(A) of the Patent Act. 35 U.S.C. §271(e)(2)(A). Norwich counters that the asserted patents are invalid.

In 2004, the FDA approved Xifaxan (rifaximin) 200 mg tablets to treat travelers' diarrhea. (D.I. 155 ¶ 9). On March 24, 2010, the FDA approved Xifaxan (rifaximin) 550 mg tablets to reduce the risk of overt hepatic encephalopathy ("HE") recurrence in adults. *(Id.* ¶10). On May 27, 2015, the 550 mg tablets were approved to treat irritable bowel syndrome with diarrhea ("IBS-D") in adults. *(Id.* ¶11). The asserted patents cover a polymorphic form of rifaximin and methods of treating HE and IBS-D in adults.

II. LEGAL STANDARD

A. Infringement

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented

invention, within the United States . . . during the term of the patent . . . ." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370, 116 S. Ct. 1384, 134 L. Ed. 2d 577 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Under § 271(b), whoever actively induces infringement of a patent shall be liable as an infringer." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). To prevail on a theory of induced infringement, a plaintiff must prove (1) direct infringement and (2) "that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute infringement." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2019) (quoting *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006)).

In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted patent]." *Vanda*, 887 F.3d at 1130. For method-of-treatment patents, if an ANDA applicant's "proposed label instructs users to perform the patented method . . . , the proposed label may

provide evidence of [the ANDA applicant's] affirmative intent to induce infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). "When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, the label must encourage, recommend, or promote infringement" *Vanda*, 887 F.3d at 1129 (cleaned up).

B. Obviousness

A patent is invalid as obvious under 35 U.S.C. § 103 if "the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made." *Kahn v. GMC*, 135 F.3d 1472, 1479 (Fed. Cir. 1998). "Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." *In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013) (citations omitted).

To show a patent is obvious, a party "must demonstrate by clear and convincing evidence 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." *InTouch Techs., Inc. v. VGo Communs., Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) (cleaned up). The overall inquiry into obviousness, though, must be "expansive and flexible." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007). In conducting the obviousness analysis, "a court

can take account of the inferences and creative steps that a of skill in the art would *Id.* at 418.

C. Written Description

The written description "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed.Cir.2010) (en banc) (cleaned up). The test is whether the disclosure "conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* This requires an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.*

D. Indefiniteness

35 U.S.C. § 112 requires that claims "particularly point[] out and distinctly claim[] the subject matter." The claims, viewed in light of the specification and prosecution history, must "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments*, Inc., 572 U.S. 898, 910, 134 S. Ct. 2120, 189 L. Ed. 2d 37 (2014). "While a claim employing a term of degree may be definite where it provides enough certainty to one of skill in the art when read in the context of the invention, a term of degree that is purely subjective and depends on the unpredictable vagaries of any one person's opinion is indefinite." *Intell. Ventures I LLC v. T-Mobile USA Inc.*, 902 F.3d 1372, 1381 (Fed. Cir 2018) (cleaned up)

Appendix B

III. THE POLYMORPH PATENTS

The Polymorph Patents claim polymorphic forms of rifaximin. Plaintiffs assert two such claims. Asserted Claim 4 of the '199 patent states:

> 4. Rifaximin in polymorphic form β, wherein the rifaximin has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 20 and wherein the rifaximin has a water content of greater than 5%.

Asserted Claim 36 of the '206 patent depends on claim 34:

> 34. A solid pharmaceutical composition comprising rifaximin in polymorphic Form β and a pharmaceutically acceptable excipient or carrier, wherein the rifaximin Form β has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2-0.
>
> 36. The pharmaceutical composition of claim 34, wherein the rifaximin Form β has a water content of between about 4.5% to about 40%.

A. Findings of Fact

1. If approved, Norwich's ANDA product will infringe the asserted claims of the Polymorph Patents.

2. The priority date of the asserted polymorph claims is November 7, 2003.

3. A person of skill in the art (a "POSA") would have had a B.S. in chemistry, chemical engineering, or a related discipline with at least 3 years' experience in the pharmaceutical industry related to API manufacturing, crystallization, characterization, or evaluation of solid state forms. Or a POSA would have had an advanced degree with less or no experience.

4. The '199 patent is a continuation of, and contains substantially the same disclosures as, the '206 patent.

5. Rifaximin exists in polymorphic forms. Norwich's ANDA product comprises polymorphic form β.

6. X-ray powder diffraction (XRPD) peaks are an inherent characteristic of a polymorph. Each peak in an XRPD diffractogram is a structural element of that form. XRPD was routine as of the priority date.

7. A crystalline form of a known compound can be characterized by a subset of XRPD peaks. The subset of XRPD peaks at about 5.4°, 9.0°, and 20.9° 28 was sufficient as of the priority date to distinguish rifaximin β from the other known rifaximin polymorphs.

8. Water content is an inherent characteristic of a crystal form that can be determined by routine testing methods such as Karl Fischer (KF) or thermogravimetric analysis (TGA).

9. Cannata, Marchi, and the Normix Label are prior art.

10. Cannata disclosed crystalline rifaximin, methods of making it, and that it had antibacterial properties.

11. The four post-filing references relied upon by Defendant's expert, Dr. Zaworotko, do not show that any of the Cannata methods produces rifaximin β every time.

12. Cannata does not inherently anticipate the asserted polymorph claims.

13. Marchi disclosed methods of preparing crystalline rifaximin, rifaximin's antibacterial properties, and that it could be used in pharmaceutical compositions with conventional pharmaceutically acceptable excipients or carriers.

14. The Normix Label describes the use of rifaximin as a pharmaceutical.

15. Cannata in view of common knowledge discloses each and every limitation of claim 4 of the '199 patent.

16. A POSA would have had a motivation to combine Cannata with commonly known testing techniques XRPD and KF or TGA because regulatory bodies instructed applicants to characterize the solubility, stability, and bioavailability of drug candidates.

17. A POSA would have had a reasonable expectation of success at characterizing the rifaximin β polymorph and arriving at the claimed XRPD peaks at about 5.4°, 9.0°, and 20.9° 20 and water content of greater than 5%.

18. Marchi in view of Cannata and common knowledge discloses each and every limitation of claim 36 of the '206 patent.

19. A POSA would have had a motivation to combine Cannata with Marchi in light of common knowledge.

20. A POSA would have had a reasonable expectation of success at achieving a pharmaceutical composition comprising rifaximin β and a pharmaceutically acceptable excipient or carrier.

21. All rifaximin β claim limitations are expressly disclosed in the specifications of the Polymorph Patents..

B. Infringement

Norwich admits that its ANDA Product, if approved, will infringe claim 4 of the '199 patent and claim 36 of the '206 patent. (DJ. 148, Ex. 1, ¶¶ 126, 127).

C. Invalidity

1. Inherent Anticipation

Each expert asserts that his validity analysis is not impacted by which definition of a POSA I use. (Tr. 860:7-861:8; Tr. 936:21-937:13). In view of Defendant's burden to prove invalidity by clear and convincing evidence, I will adopt Plaintiffs' definition of a POSA.

Norwich argues that U.S. Patent No. 4,557,866 (the "Cannata" reference) (JTX-37) inherently anticipates claim 4 of the '199 patent because it discloses a process that necessarily produces the claimed rifaximin β. (D.I. 176 at 32). "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). A disclosed process may anticipate "if it discloses in an enabling manner the production" of the claimed polymorph. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1344 (Fed. Cir. 2005).

Here, the issue is whether the process disclosed by Cannata invariably produces rifaximin β Norwich has presented the following evidence in support:

- The "Viscomi Declaration," a declaration to the PTO stating that samples of batches produced according to Cannata "are composed either of mixture of polymorph (alpha and beta, and in some case alpha and epsilon) or different polymorphs." (JTX 80 ¶ 7).

- The "Viscomi 2008" article, which Norwich's expert Dr. Zaworotko testified shows that rifaximin β is a necessary precursor to the formation of rifaximin α, δ, and ϵ. (JTX 65; Tr. 880:20-881:1, 921:24-922:6).

- The "Braga 2012" article, which describes the inherent properties of rifaximin β (JTX 105).

- The "Bacchi 2008" article, which described rifaximin beta 4 ("RX4"), a substance the author concluded was "the so-called beta rifaximin of the literature." (DTX 43; Tr. 882:14-24). The article describes slow evaporation as the method of preparation. From this article, Dr. Zaworotko concluded, "Examples 1 and 7, at the very least, of Cannata would have . . . necessarily afforded rifaximin Beta because of the solvent system used, the method used of controlled crystallization, and the lack of drying or lack of aggressive drying." (Tr. 883:6-10).

According to this evidence, Norwich argues, "Cannata inherently produced rifaximin β every time, either directly *or as a necessary precursor* to the α, δ, and ϵ forms and mixtures disclosed in the Viscomi Declaration." **(D.I.** 185 at 9).

I do not think this evidence amounts to clear and convincing evidence that Claim 4 is inherently anticipated by Cannata. Norwich could have shown anticipation either because (1) as a law of nature, rifaximin α, δ, and ϵ cannot exist without having been derived from rifaximin β, or (2) a method disclosed in Cannata produces rifaximin β each and every time it is practiced. Dr. Zaworotko's testimony did not prove either.

Dr. Zaworotko's opinion does not clearly support the conclusion that, as a law of nature, rifaximin β is a necessary precursor to rifaximin α, δ, and ϵ. For one thing, had that been his opinion, he could have clearly stated that, and I do not think he did. (*See* Tr. at 870-884). I think Dr. Zaworotko's opinion was relying upon the Viscomi 2008 article:

> Q: Would rifaximin Beta form as a precursor to any polymorph listed in the Viscomi declaration listed at paragraph 7?
>
> A: Yes, based upon the Viscomi 2008 article, where the effect of moisture on rifaximin crystal forms was studied and based upon the diagram [derived from Viscomi 2008] it's clear that Beta has to be the precursor for any of the other crystal forms with lower water content.

(Tr. 921:25-922:1). This opinion appears to be based on Dr. Zaworotko's reading of Viscomi 2008, and not a conclusion that rifaximin α, δ, and ϵ cannot exist in the world without having first been rifaximin β. I think Dr.

Zaworotko stated his opinion the way he did because the "diagram" to which Dr. Zawortko refers, which is based on Figure 4 ("The relationship between the various crystal forms of rifaximin"), was not the main point of the article. The article's purpose, consistent with its title ("Crystal forms of rifaximin and their effect on pharmaceutical properties") was to report on a "study [] to identify the presence of crystal forms of rifaximin and to assess their impact on parameters such as solubility, intrinsic dissolution and bioavailability." (JTX-65 at 1074). The paper concluded, "The unexpected outcome of this study is that we have found that some crystal forms of rifaximin are significantly absorbed, while it was previously considered a non-absorbable drug. These finding[s] indicate the need of putting appropriate manufacturing and analytical procedures in place to consistently yield rifaximin of the appropriate crystalline structure." *(Id*. at 1080). Thus, to the extent Dr. Zaworotko was offering an opinion that Viscomi 2008 is conclusive proof that rifaximin α, δ, and ϵ are necessarily derived from rifaximin β, I do not find that conclusion to be well-supported. It is not clear and convincing proof

Thus, to show that Cannata inherently anticipates Claim 4, Norwich would need to show that every time Cannata is performed, rifaximin β is produced. Norwich has not done so.

The Viscomi Declaration does not help Norwich. It stated that among "samples of batches" produced according to Cannata, when retested in 2006, there were four batches with no rifaximin β. The four batches

consisted of (1) only the "delta polymorph," (2) only of the "epsilon form," (3) a mixture of "the alpha and epsilon form," and (4) a mixture of the "alpha and delta forms," respectively. (JTX-80, ¶7; *see* Tr. 949:8-12).

Although Viscomi 2008 states that the "method of production of rifaximin" was disclosed in European Patent No. 161534, the counterpart to Cannata, Salix has persuasively argued that Viscomi 2008 discloses steps that are more specific than what Cannata describes. *(See* JTX 105 at 6404 n.3; JTX 65 at 1074 & 1074 n.29; Tr. 874:16-25).

In Viscomi 2008, the reaction step for preparing wet rifaximin describes (1) heating the reaction mixture to 50°C for 5 hours, then cooling it to 20°C; (2) adding a mixture of 0.1 moles of ascorbic acid and 2.5 moles of concentrated hydrochloric acid in 220 mL of 58% ethyl alcohol in water over 30 minutes; and (3) adding concentrated hydrochloric acid dropwise until pH 2.0 is reached. (Tr. 951:8-13; JTX 65 at 1074). Cannata has none of these details. (Tr. 951:13-17). The crystallization step in Viscomi is also described with more precision than in Cannata. (Tr. 951:18-952:2).

Similarly, Bacchi 2008 discloses a process that does not precisely match Cannata's examples 1 and 7. Bacchi describes using a "slow evaporation" process while Cannata does not mention evaporation. (DTX 43 at 1734; Tr. 949:20-22). Furthermore, the Cannata examples crystallize rifaximin from a 7:3 ethanol to water mixture, whereas Bacchi does not disclose any ethanol to water ratio. (Tr. 949:15-23; Tr. 953:2-954:3).

Ultimately, it appears that Cannata left certain steps up to the discretion of the chemist preparing the rifaximin. To show that Cannata invariably produces rifaximin β, Norwich would have needed to show that, no matter how the chemist exercised his or her discretion, rifaximin β would be produced. I do not think Norwich has done so. "Experiments that do not follow the prior art procedure alleged to inherently anticipate cannot show inherent anticipation." *Merck & Cie v. Watson Lab'ys, Inc.*, 125 F. Supp. 3d 503, 513 (D. Del. 2015) (cleaned up), *rev'd on other grounds*, 822 F.3d 1347 (Fed. Cir. 2016).

Thus, I find that Norwich has not shown by clear and convincing evidence that claim 4 of the '199 patent is inherently anticipated by Cannata.

2. Obviousness

Norwich contends that claim 4 of the '199 patent is obvious over Cannata in view of common knowledge. (DI 176 at 34-35). Norwich contends that claim 36 of the '206 patent is obvious over Cannata in view of the Normix Label and common knowledge or over Marchi in view of Cannata and common knowledge. *(Id.* at 35).

A POSA would have understood from Cannata that rifaximin exists in crystalline form and that rifaximin has "outstanding antibacterial properties." (JTX 37 at 3:10-16, 5:21-36). Norwich argues this knowledge would motivate a POSA to "identify the characteristics of the obtained rifaximin" using "routine methods." (D.I. 176 at 35). Furthermore, Norwich argues that a POSA

would recognize "that the crystallization solvent used by Cannata included water, which could lead to hydrate formation, and thus [the POSA] would have been motivated to analyze the effect of water on the crystalline form using conventional methods." (*Id.*). A POSA could have performed a "routine humidity experiment . . . in one day and detected rifaximin β." (*Id.*).

The Court of Appeals considered the obviousness of a polymorph patent in *Grunenthal GmbH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1336 (Fed. Cir. 2019). The *Grunenthal* patent claimed Form A of tapentadol hydrochloride characterized by its XRPD peaks. *Id.* The *Grunenthal* defendant, Alkem, argued that the claim was obvious in light of prior art that disclosed a Form B of tapentadol hydrochloride. *Id.* at 1337.

Alkem's prior art references included (1) the prior art patent that described a crystalline form of tapentadol hydrochloride (later called "Form B") and (2) an article that "outlines a number of variables that may be adjusted during the recrystallization process to determine whether polymorphism occurs in a compound." *Id.* at 1337, 1341. The "polymorphism of tapentadol hydrochloride was unknown at the time of filing the [asserted patent]," and "Form B was the only crystal structure . . . known in the art at the time." *Id.* at 1341.

The Court of Appeals found that the article did not provide "guidelines regarding which [variables] are likely to result in polymorphs of particular compounds." *Id.* at 1342. Thus, the article did little more than tell a

POSA to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result," which does not provide a reasonable expectation of success. *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348,1365 (Fed. Cir. 2007)).

Here, the prior art includes Cannata, which discloses processes for preparing a crystalline form of rifaximin. As in *Grunenthal*, rifaximin's polymorphism was unknown as of the priority date. In *Grunenthal*, however, the prior art patent was known to produce a particular form—Form B—of tapentadol hydrochloride. Here, by contrast, no rifaximin had been publicly characterized as a particular form as of the priority date.

I think the evidence is clear and convincing that a POSA would have been motivated to characterize the rifaximin produced by the Cannata processes. Cannata disclosed that rifaximin had strong antibacterial properties and low bioavailability, motivating a POSA to evaluate the substance as a potential drug candidate. (JTX 37 at 3:10-16; JTX 94 at 6-7; Tr. 869:16-870:4; Tr. 891:16-892:12). The FDA encouraged, if not required, that the solid forms of a drug substance be well-characterized during drug development, including as to the properties of solubility, stability, and bioavailability. (DTX 315-35; Tr. 892:13-894:7). XRPD profiling was the predominant method for identifying crystalline materials. (DTX 315-38; Tr. 894:23-895:12). FDA guidance required "appropriate manufacturing and control procedures" when manufacturing and storing the drug substance could result in a hydrated drug substance. (DTX 315-39; Tr.

895:13-24). Because the Cannata process for preparing rifaximin used water, a POSA would know about the potential for a hydrate to form, and be motivated to perform routine testing (e.g., KF or TGA) for water content and hydration formation. (DTX 317-19; JTX 54 at 182; Tr. 888:3-890:5; DTX 315-39).

I think the evidence shows that a POSA would have a reasonable expectation of success in characterizing the polymorph β, as opposed to the other forms of rifaximin. Although Norwich's evidence failed to show that β was produced each and every time rifaximin was prepared according to Cannata, it did strongly suggest that polymorph β is a commonly produced polymorph and the most stable form of rifaximin.

The Viscomi Declaration stated that rifaximin prepared according to Cannata yielded β along with other polymorphs. (JTX 80 at ¶ 7). Dr. Zaworotko explained that β is the most stable form. Tr. 877:17-18. ("[B]eta is the winner in terms of stability under normal conditions of temperature and humidity."). Dr. Myerson's critiques of Dr. Zaworotko's testimony do not have the same force in the context of obviousness as they did in the context of inherent anticipation. While Viscomi 2008's increased specificity in the method of preparation suffices to suggest that Cannata may not produce rifaximin β each and every time (as would be required for inherent anticipation), the standard for obviousness is a reasonable expectation of success. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a certainty of success.").

I reject Salix's argument that a POSA would not have been able to predict the precise peaks that characterize rifaximin β, and accordingly a POSA would not have had a reasonable expectation of success. The Federal Circuit has held, "[A] rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt . . . would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). I think the same is true in this context. I credit the testimony of Dr. Zaworotko that the XRPD peaks and water content are "inherent" properties of a crystal form that can be tested using routine methods. (Tr. 871:20-872:5; 884:2-13; 895:8-12). Thus, a POSA would have a reasonable expectation of success at characterizing the polymorph and arriving at the claimed XRPD peaks and water contents.[1]

There is no evidence of secondary considerations of nonobviousness for the Polymorph Patents. (*See* D.I. 174 at 15-18).

Thus, I find by clear and convincing evidence that claim 4 of the '199 patent is obvious in light of Cannata in view of common knowledge.

---

1. Plaintiffs call to my attention *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 412 (D. Del. 2021), *app. filed*, No. 21-2270 (Fed. Cir. Aug. 31, 2021). (D.I. 181 at 37). I have considered that case but I do not agree with it on this point.

Appendix B

Claim 36 of the '206 patent claims a pharmaceutical composition comprising (1) rifaximin β with the claimed XRPD peaks and a water content between about 4.5% to 40% and (2) a pharmaceutically acceptable excipient or carrier.

Norwich argues that rifaximin had previously been formulated as a pharmaceutical composition comprising pharmaceutically acceptable excipients or carriers. (D.I. 176 at 37). Marchi in 1982 and the Normix Label in 2001 each taught "pharmaceutical compositions" comprising rifaximin. (*Id.*). Marchi disclosed that rifaximin can be used as an "antibacterial agent[]" in pharmaceutical compositions with conventional pharmaceutically acceptable excipients or carriers. (JTX 48 at 4:27-33, 4:67-5:4, 5:14-40, 60-62, 6:6-31, Cls. 10-11; Tr. 865:10-866:12, 868:20-869:3). The Normix Label disclosed that rifaximin was an approved antibacterial drug in Italy in 1985 as a coated tablet comprising 200 mg of rifaximin and pharmaceutically acceptable excipients. (JTX 94 at 5, 7-8; Tr. 867:13-17, 869:10-870:4, 903:3-9).

Norwich further argues that rifaximin's antibacterial properties were known. Cannata taught that rifaximin has outstanding antibiotic properties and has poor absorption, which indicates to a POSA that it could be used for GI treatments. (Tr. 862:22-24; 863:14-18). Marchi also disclosed "remarkable" antibacterial properties. (JTX 48 at 4:27-33, 4:67-5:4, 5:14-40, 5:60-62, 6:6-31, Cls. 10-11; Tr. 865:10-866:12, 868:20-869:3).

Salix did not respond to these arguments. (*See* D.I. 181 at 37-39).

The only difference between the previous pharmaceutical compositions of rifaximin and claim 36 is that claim 36 characterizes rifaximin as polymorphic form β Rifaximin β is obvious over Cannata in view of common knowledge, for the same reasons as previously stated in connection with asserted claim 4 of the '199 patent. Accordingly, I find that a POSA would have had the motivation to combine the prior art references of Cannata, the Normix Label, or Marchi and Cannata, in view of the commonly known testing techniques, with a reasonable expectation of success in doing so. Salix offers no evidence or arguments to the contrary. Thus, Norwich has proved by clear and convincing evidence that claim 36 of the '206 patent is invalid as obvious.

3. Written Description

The asserted claims describe rifaximin β as having XRPD peaks "at about 5.4°, 9.0°, and 20.9° 20."'199 Patent, Cl. 4, '206 Patent, Cl. 36. The specification states that rifaximin β is "characterized . . . by a powder X-ray diffractogram (reported in FIG. 2) which shows peaks at the values of the diffraction angles 20 of 5.4°; 6.4°; 7.0°; 7.8°; 9.0°; 10.4°; 13.1°; 14.4°; 17.1°; 17.90°; 18.30°; 20.9°."'199 Patent 5:64-6:3. Norwich argues that the polymorph patents improperly claim a genus, whereas the specification recites only a species. (D.I. 176 at 37-38).

Salix responds that (1) the claims, on their face, are limited to the specific polymorphic form rifaximin β,

rendering Norwich's genus characterization inaccurate, and (2) even if Norwich is right, the claims identify structural features common to the genus as required by the caselaw. (D.I. 181 at 39-42). I agree with Salix on the first point, and accordingly will not address Salix's second argument.

The evidence shows that a subset of XRPD peaks can identify the polymorph. The "normal practice at the USPTO" is to claim a polymorphic form using "at least three powder diffraction pattern peaks." (Tr. 965:11-17; JTX 28 at XIFAX_NOR_0002208). Dr. Zaworotko's own patent explains, "For XRPD data herein, each composition of the present invention[, a new crystalline form of a known compound,] may be characterized by any one, any two, any three, any four, any five, any six, any seven, or any eight or more the 20 angle peaks." (Tr. 916:17-917:18, PTX 707 at 15:36-39). I do not think the asserted claims claim a genus. They claim only rifaximin β, a polymorphic form which can be identified using the three peaks recited in the claims.

Thus, I reject Norwich's written description challenge.

IV. THE METHOD PATENTS

A. Inducement

1. Findings of Fact

1. At least some physicians will review Norwich's label.

2. Physicians will instruct patients to take rifaximin according to the instructions on the label.

2. Infringement

Before turning to a limitation-by-limitation infringement analysis for the method patents, I will address an underlying dispute regarding induced infringement when the patient is the one performing the patented method. Inducement requires direct infringement. Salix argues that either (1) the patients, in taking rifaximin, will directly infringe "because patients will read and follow the instructions in Norwich's Label (with or without the help of their physician)," or (2) physicians and patients will jointly infringe based on the label. (D.I. 174 at 4). I do not think there is joint infringement. I find that Plaintiffs have not shown that doctors condition the patient's receipt of a rifaximin prescription on the performance of particular steps in the way contemplated by *Akamai. See Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1023 (Fed. Cir. 2015) (en banc). Rather, the patients directly infringe.

According to Norwich, "Because patients will not take rifaximin correctly without physician instruction, the Norwich Label does not induce patients and cannot be the basis for finding specific intent." (D.I. 183 at 3-4 (citation omitted)). Essentially, because there is another party involved in the inducement (physicians), the "chain of events leading to infringement is . . . too attenuated to prove specific intent." (D.I. 183 at 6-7). I disagree. The Court of Appeals has long held, "the sale of a

product specifically labeled for use in a patented method constitutes inducement to infringe that patent[.]" *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011). In the context of a prescription medication, physicians have a particularly important role in conveying essential information to patients. The evidence in this case bears this out. (*See* Tr. 66:22-69:20; Tr. 119:5-120:16 (describing the process of prescribing rifaximin to patients)). Other areas of law, such as the learned intermediary doctrine, recognize the physician's essential role in communicating information about a medication to the patient. *See Reyes v. Wyeth Laboratories*, 498 F.2d 1264, 1276 (5th Cir. 1974). A pharmaceutical company, such as Norwich, is well aware of how doctors prescribe medications to patients. Thus, if there will be direct infringement, then Norwich will have the specific intent to induce patients' direct infringement.

B. The HE Patents

HE is a liver disease that affects the brain. (Tr. 41:15-21; 48:10-16). For patients with HE, the liver does not properly filter toxins from the blood. These toxins can cause changes to the patient's mental state. (*Id.*) Physicians grade HE severity using the Conn score, which ranges from 0 to 4. (Tr. 45:14-47:4). Conn scores of 0 or 1 reflect a normal or near-normal mental state. A Conn score of 2 or higher reflects more serious symptoms, from obvious personality changes to stupor or even coma. (Tr. 46:6-11, 14-15). Conn scores of 0 and 1 cannot be detected in a routine physical exam. (Tr. 45:20-21; 46:4-5). Physicians also assess HE severity using an asterixis score. (Tr.

346:5-8). Asterixis occurs when a patient cycles between lower and higher levels of consciousness and can be measured by tremors in a patient's outstretched hand. (Tr. 46:16-47:4).+++ HE can be either episodic or persistent. (Tr. 44:13-25). Persistent HE is characterized by a Conn score that remains at 2 or above. (Tr. 44:24-25). Patients with episodic HE have periods of remission punctuated by episodes of breakthrough overt HE. (Tr. 44:13-25; 45:14-46:15). An episode of "breakthrough overt HE" is an increase in the patient's Conn score to grade 2 or higher (e.g., going from 0 or 1 to 2 or more), or an increase in the patient's Conn and asterixis scores of one grade each with a baseline Conn Score of 0. (D.I. 149, Ex. 1 ¶ 81). Patients with a history of overt HE who are not currently having an overt HE episode are in "remission of HE." (*Id.* ¶ 81; Tr. 48:2-6). Thus, patients with a Conn score of 0 or 1 and no asterixis are in remission. (Tr. 48:2-6). After a first overt HE episode, only about half of patients will live one year. (Tr. 50:6-19).

Plaintiff asserts four method claims in connection with the HE patents.

Asserted Claim 6 of the '195 patent is a dependent claim with three elements: (1) reducing the risk of HE recurrence, (2) by orally administering about 550 mg of rifaximin twice daily (BID) to the adult subject, (3) for a period of 12 months or longer.

Asserted Claim 8 of the '573 patent is a dependent claim with three elements: (1) maintaining remission of HE, wherein remission is defined as a Conn score of 0 or

1, (2) by administering 550 mg of rifaximin to the subject BID, (3) for a period of 12 months or longer.

Asserted Claim 11 of the '397 patent is a dependent claim with four elements: (1) reducing a subject's risk of experiencing a breakthrough overt HE episode, (2) by orally administering to the subject 550 mg of rifaximin BID, (3) for a period of about 12 months or longer, (4) to a subject with a Conn score of 0 or 1.

Asserted Claim 12 of the '397 patent is a dependent claim with five elements: (1) reducing a subject's risk of experiencing a breakthrough overt HE episode, (2) by orally administering to the subject between about 1000 mg to about 1200 mg of rifaximin daily, (3) for a period of about 12 months or longer, (4) to a subject with a Conn score of 0 or 1, (5) "further comprising administering lactulose."

1. Findings of Fact

1. Norwich has knowledge of the HE patents.

2. Norwich's label will encourage administration of rifaximin for 12 months or longer.

3. Norwich's label will encourage administration of rifaximin for the "reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults."

4. Norwich's label will encourage administration in patients having a Conn score of 0 or 1.

5. Norwich's label will encourage at least some physicians to co-administer rifaximin and lactulose.

6. Patients will take rifaximin according to the instructions on the label and will directly infringe the asserted HE claims.

7. Norwich's label will induce infringement of the asserted HE claims.

8. The priority date of the asserted claims is October 2, 2008.

9. A POSA would have had a Ph.D. in pharmacology, biology, biomedical sciences, microbiology and/or an M.D. with board certification in gastroenterology. He or she would have had training in or experience with liver and GI disorder research. If needed, a POSA would have collaborated with others having ordinary skill in areas relevant to the claimed subject matter, including infectious diseases and microbiology.

10. The Salix Presentation was not publicly accessible as of the priority date and is not prior art.

11. Leevy 2007 does not disclose a method of administering rifaximin to maintain remission.

12. As of the priority date, a 12-month duration for the administration of rifaximin was not within the common knowledge of a POSA.

13. The claimed method met a long-felt need of reducing the risk of HE recurrence and maintaining remission.

14. There was skepticism in the industry regarding the long-term use of antibiotics to maintain remission in HE patients.

15. The HE patents are not invalid as obvious.

16. The specification describes using rifaximin with or without lactulose.

17. A POSA would recognize that the inventors had possession of the claimed method.

2. Infringement

i. Administering for 12 Months or Longer (All Claims)

It is more likely than not that Norwich's Label will encourage administration of the ANDA product for 12 months or longer in at least some patients, and that Norwich knows and specifically intends for this period of administration. Norwich's product is indicated for reducing overt HE recurrence. (JTX 73 § 1.2). HE is chronic. It must be managed until the patient gets a liver transplant or dies. I credit the testimony of Drs. Mahl and Brown that they have had HE patients maintain remission of HE for 12 months while on rifaximin 550 mg BID. (Tr. 120:21-24; Tr. 55:3-11). The label has no recommendation

as to duration of administration. The label further describes a study in which some patients used the product for 12 months or longer. Taken together, this evidence demonstrates by a preponderance of the evidence that Norwich's label would encourage administering rifaximin for at least 12 months.

ii. Maintaining Remission ('573 patent, Claim 8)

I find that Salix has proved by a preponderance of the evidence that Norwich's label instructs as to "maintaining remission of HE" as required by the asserted claims. Norwich's label is indicated for the "reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults." (JTX 73 § 1.2). The experts described "reducing the risk of overt HE recurrence" and "maintaining remission of HE" as "basically synonymous" or a "continuum of the same thing." (Tr. 249:23-250:18, 252:9-18; Tr. 51:21-52:19). Remission is binary—either a patient is in remission or the patient is not. An overt HE recurrence ends remission. Thus, to maintain remission, a patient must avoid overt HE recurrence.

iii. Conn Score of 0 or 1 ('397 patent, Claims 11 and 12)

Norwich's label will more likely than not induce use of rifaximin in patients with a Conn score of 0 or 1. The label encourages use to prevent an overt HE recurrence, which as I have found, means maintaining remission. The evidence shows that patients in remission of HE have a

Conn score of 0 or 1. Thus, the label will encourage the use of rifaximin in patients who have a Conn score of 0 or 1. This conclusion is bolstered by the Clinical Studies section, which describes a clinical study in which the patients were "defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy." (JTX 73 § 14.2).

Norwich argues that (1) doctors do not calculate a Conn score for their patients before prescribing rifaximin, and (2) the Indications section does not reference the Clinical Studies section and thus it "merely describe[es] a parameter of the study, rather than actually encouraging, recommending, or promoting" the infringing use. (D.I. 183 at 10). I find these arguments unpersuasive.

The expert testimony shows that at least some physicians use Conn scores in clinical practice. (Tr. 154:2-22; 264:6-7). Defendant's expert, Dr. Mahl, testified that he does not calculate Conn scores but does record the "elements that might go into a Conn score." (Tr. 114:16-20). The patents do not require the calculation of a Conn score. Rather, they require use in patients with a Conn score of 0 or 1, which can be present regardless of whether it has been calculated. On this testimony, it seems likely that Norwich's ANDA product will be used in at least some patients who have a calculated Conn score of 0 or 1 as well as patients whose Conn scores would be a 0 or 1, if calculated, based on the symptoms observed by their physicians.

Regarding the Clinical Studies section, the law does not require the indication section of a label to specifically

direct the reader to look at other sections in order for those other sections to be considered. The Court of Appeals has held, "The jury was entitled to credit expert testimony regarding the label's instructions on who should take what drug, when, why, and how, and to reject the argument that certain portions of the label were disjointed from others." *GlaxoSmithKline LLC v. Teva Pharms. USA Inc.*, 7 F.4th 1320, 1329 (Fed. Cir. 2021), *petition for cert. filed*, No. 22-37 (July 11, 2022). I credit the testimony of Dr. Brown that physicians commonly read the Clinical Studies section. (Tr. 67:24-68:8). The "Hepatic Encephalopathy" subsection starts with the sentence: "The efficacy of rifaximin tablets 550 mg taken orally two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult subjects from the U.S., Canada, and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE)." (JTX 73 § 14.2). Accordingly, I find that the label will induce use in patients with a Conn score of 0 or 1.

iv. Administration with Lactulose ('397 patent, Claim 12)

Norwich's label will encourage co-administration with lactulose. In the Indications and the Clinical Studies section, the label notes that 91% of patients took rifaximin and lactulose concomitantly, and that lactulose did not alter the treatment effect of rifaximin. (JTX 73 §§ 1.2, 14.2). This strongly suggests that taking lactulose concomitantly is safe and effective, and it will likely encourage some physicians to administer rifaximin in conjunction with

lactulose as required by the claims. I reject Norwich's comparison to *Shire LLC v. Amneal Pharmaceuticals*, which held that label indicating that a drug could be taken "with or without" food was "indifferent" as to which option was select and thus not an instruction to infringe. 2014 U.S. Dist. LEXIS 85369, 2014 WL 2861430, at *5 (D.N.J. June 23, 2014), *aff'd in part, rev'd on other grounds*, 802 F.3d 1301 (Fed. Cir. 2015). The high percentage of patients who took lactulose concomitantly, and the fact that this information was included in the Indications section, encourages physicians to prescribe the two concomitantly.

I credit the testimony of Dr. Brown, who stated that the label, by citing the 91 percent figure, "makes clear that you can — you can and probably should use Lactulose in the majority of your subjects." (Tr. 76: 5-7). I further credit Dr. Brown's testimony, "Whenever possible, I use the combination of Lactulose and rifaximin because that's where the bulk of the data is." (Tr. at 76:12-13). I find that a physician reading the Norwich label and considering a study in which 91% of the patients were administered lactulose concomitantly will be inclined to do so likewise "because that's where the bulk of the data" showing the efficacy of rifaximin is.

v. Substantial Noninfringing Use (All Claims)

Norwich argues that its ANDA product has substantial noninfringing uses, which is relevant to intent to induce. (D.I. 183 at 11-12). Most HE patients live less than 12 months after their first overt HE episode. Thus, a

substantial number of patients taking Norwich's ANDA as directed will not take rifaximin for 12 months or more, and these uses will not meet the 12-month-or-more claim limitation. Norwich points to *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363-66 (Fed. Cir. 2003) in support of this argument.

The Federal Circuit has distinguished *Warner-Lambert*, where the infringing use would be off-label use of the defendant's ANDA product and encompass only a small number of sales, and cases where "the proposed label itself recommends infringing acts." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1132-33 (Fed. Cir. 2018). Here, since I find that the label itself recommends infringement, the potential for substantial non-infringing uses does not negate Norwich's intent to induce infringement.

3. Invalidity

The parties agree that the definition of a POSA is not outcome determinative. (D.I. 176 at 2; D.I. 181 at 1). I adopt Plaintiffs' definition of a POSA.

Norwich argues that as of 2008, it was widely known that rifaximin was safe and effective for treating HE. (D.I. 176 at 3). Rifaximin was indicated abroad for HE in 2000. (JTX 94 at 5, 9). In 2004, the FDA approved Salix's Xifaxan for traveler's diarrhea. From that time, there is evidence of widespread off-label use of Xifaxan by physicians to treat patients with HE. Market research conducted by Salix shows that, by January 2007, 77% of physicians

who treated HE patients had prescribed Xifaxan for HE. (DTX 349-16).

The prior art described the use of rifaximin in HE patients. For instance, a 1993 article ("Festi") described one open study and two randomized, controlled, comparative studies. The three studies "confirm[ed] the usefulness of rifaximin in the management of cirrhotic patients with mild HE." (JTX 42 at 607; Tr. 165:11-166:5). A 2000 article ("Williams 2000") described a study confirming that 1200 and 2400 mg doses of rifaximin showed significant improvement "in reducing objective parameters of HE in cirrhotic patients," and "treatment with rifaximin 1200 mg/day may be considered as an adjuvant or an alternative" to lactulose, with no adverse effects. (JTX 66 at 203-4, 207). Lactulose was the "mainstay" for HE therapy at the time. (*See* Tr. 203:17-204:5). In 2004, doctors at a Salix-hosted conference on hepatology reported being "very happy with [rifaximin's] results" and that rifaximin had "excellent" tolerability with "no significant side effects." (Tr. 172:10-18; 174:8-22; DTX 584-1, 3). A 2007 retrospective chart review ("Leevy 2007") showed better treatment outcomes for patients on rifaximin than on lactulose. (DTX 390-3; Tr. 204:6-16).

Norwich also points to retrospective chart reviews published after the priority date that show use of rifaximin for HE before the priority date. (*See* D.I. 176 at 9-10 (citing JTX 111, JTX 109)). I do not think these uses are in the prior art because there is no evidence that a POSA would have known about them. They do provide evidence of a POSA's state of mind, since the physicians

prescribing Xifaxan off-label meet both parties' definition of a POSA. (*See* D.I. 182 ¶ 121; D.I. 177 ¶ 1). *See In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1025 (Fed. Cir. 2018) (holding, "The district court . . . properly relied on [a reference] not as statutory prior art, but for the fact that [POSAs] were interested in pursuing less frequent dosing regimens.").

i. Prior Art Combinations

Norwich presents two obviousness combinations for the asserted HE claims: the Bausch HE Study in light of the Salix Presentation, and Leevy 2007 in light of common knowledge. I will consider each in turn.

The Bausch HE Study is the protocol for the clinical trial that ultimately led to the approval of rifaximin for HE. It disclosed the method, dosage, lactulose, and Conn score limitations of the asserted claims. The Salix Presentation was a presentation given by Dr. Leevy at a Salix shareholder's meeting in which Dr. Leevy described using rifaximin to treat HE. (DTX 52-4). Dr. Leevy described the duration limitation. Between the two, all claim limitations are disclosed.

Salix argues that the Salix Presentation was not in the prior art because it was not accessible. (D.I. 181 at 4). Salix tried to exclude the evidence before trial. (D.I. 150). I denied Salix's motion without prejudice to evaluating its prior art status based on a complete understanding of the record. (D.I. 161 at 28:9-18). Norwich's response to the motion in limine relied on evidence that Norwich did not

present at trial. (*See* D.I. 150 at 9 of 18 (describing a Salix press release announcing the conference)). Accordingly, I will reconsider the question in light of the evidence presented at trial.

At trial, Defendant offered the transcript of the Salix Presentation and expert testimony regarding the presentation. (DTX 660; Tr. 175:20-176:22). Defendant's expert, Dr. Berg, testified that the Salix presentation was publicly available online at the SEC and that a POSA would be motivated to find it because Salix was the only company selling rifaximin in the United States at the time. (Tr. 175:22-24; 176:15-22). Salix responds that this testimony is unsupported by explanation or evidence. (D.I. 181 at 4-5). While I credit Dr. Berg's assertions regarding a POSA's motivation to look for and methods of finding such a document, I do not credit his testimony regarding the availability of the Salix Presentation online before the priority date. I do not think a medical doctor's expertise is a basis for opining on what the SEC had available online more than a decade ago. Dr. Berg's opinion is not supported by independent evidence. "At this critical point in the determination of obviousness, there must be factual support for an expert's conclusory opinion." *Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1311 (Fed. Cir. 2000). Without evidence of online accessibility, and without evidence that the meeting was attended by interested POSAs (or even directed to POSAs, rather than investors), I find that Defendant has not shown by clear and convincing evidence that the Salix Presentation is prior art.

Appendix B

Norwich's second prior art combination is Leevy 2007 and common knowledge. Norwich argues, "Leevy 2007 disclosed the method, dosage, and Conn score limitations." (D.I. 176 at 8). Norwich argues that common knowledge supplies the missing limitations of duration (of 12 months or more) and lactulose. (*Id.* at 9).

Upon review of the evidence, I find that Leevy 2007 does not describe the method limitation. Independently, common knowledge cannot supply the duration limitation. I will address each in turn.

The claims are directed to maintaining remission or reducing the risk of breakthrough overt HE. Leevy 2007 concluded that HE hospitalizations were less frequent and shorter for patients on rifaximin than for patients on lactulose. Norwich argues that these hospitalizations are a metric for breakthrough overt HE and therefore Leevy 2007 discloses the method limitation. (D.I. 176 at 8). But Norwich's argument is not supported by the record. Norwich's expert, Dr. Berg, testified as to Leevy 2007's disclosure of rifaximin's ability "to treat HE" or as "therapy for HE." (*E.g.*, Tr. 181:9-18; 206:2-10). He did not characterize it as disclosing prevention or the like. I see no testimony linking Leevy's reduction in hospitalizations with the claimed method of preventing breakthrough overt HE.

Furthermore, Leevy 2007 did not track Conn scores throughout the study. As Salix argues, "a POSA would not have been able to determine whether subjects who had a Conn score of 1 at the beginning of the rifaximin phase

maintained that Conn score throughout the 6 months." (D.I. 181 at 5). I credit Dr. Brown's testimony, "You cannot interpret the natural course of these patients' HE through the six-month period based on the data provided." (Tr. 393:4 6). Leevy 2007 does not teach the maintaining remission limitation.

Thus, Leevy 2007 cannot supply the limitations required for the asserted claims, whether it is maintaining remission of HE or reducing the risk for breakthrough overt HE. On that basis alone, Defendant fails to prove obviousness.

There is a second, independent basis to reject the prior art combination of Leevy 2007 and common knowledge. I do not think that a POSA would have a reasoned basis to resort to the "common sense" that rifaximin could be used for 12 months or longer. Common sense can supply a limitation missing from the prior art if a "searching" review of the prior art provides a "reasoned basis for resort to common sense." *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1363 (Fed. Cir. 2016).

Many of the sources Norwich relies upon to show long-term administration are not prior art. (*See* D.I. 176 at 9-10 (citing retrospectives published after the priority date and the Salix Presentation)). They were not, at that point, in the common knowledge of the field.

Administration of rifaximin for 12 months or more suggests prevention (i.e., maintaining remission or reducing the risk of overt HE recurrence), not mere

treatment. Norwich argues, "[T]he record is replete with prior art disclosing the use of rifaximin in patients in remission from HE (i.e., having a Conn score of 0 or 1)." (D.I. 185 at 5-6). It is true that some of the studies included patients with Conn scores of 0 or 1. (JTX 66 at 205; JTX 42 at 607.) Many of these patients would have been in remission, but the sources discuss HE "treatment," not prevention or maintenance of remission. The Bausch HE study was the first prior art source to clearly articulate a desire to prevent hepatic encephalopathy. (DTX 52-4). As of the priority date, the Bausch Study did not have any results. Accordingly, I do not think that a 12-month treatment period was within the common knowledge as of the priority date.

Furthermore, Salix has presented evidence that a POSA would have known that long-term administration of rifaximin, an antibiotic, was risky. Not only could long-term use of antibiotics lead to a superinfection, which could kill the patient, but, "A POSA would have been concerned that if an HE patient developed clinical resistance to rifaximin, [the POSA] would not be able to administer rifaximin the next time the patient experienced an HE episode." (D.I. 181 at 11; Tr. 388:3-9). The parties' experts disagreed about the level of risk associated with long-term administration of rifaximin and how a POSA would consider that risk. I credit Dr. DuPont's testimony that without further studies, a POSA would have been reluctant to administer rifaximin long-term. (Tr. 467:7-12). Thus, I think that the prior art does not provide enough of a reasoned basis for supplying the duration limitation.

Finally, Salix has presented evidence of secondary considerations of nonobviousness that weigh in favor of finding the HE patents nonobvious. The claimed HE methods met a long-felt need for maintaining remission and reducing the risk of breakthrough overt HE episodes. Salix argues, "As of October 2008, no drug had been approved for HE in over 30 years, and no drug had ever been approved to *prevent* HE recurrence." (D.I. 174 at 17). Norwich's expert responded that there was no need because physicians were already using a combination of rifaximin and lactulose to treat HE. (Tr. 222:7-20). As Salix points out, however, "Short-term, off-label use of rifaximin to *treat* HE did not meet a long-felt need for long-term *prevention* of HE recurrence." (D.I. 186 at 10).

There was also some skepticism in the industry. Salix points to comments from the FDA advisory committee expressing the concern "that indefinite use of rifaximin could change the gut flora and cause antibiotic resistance." (D.I. 174 at 17). Norwich argues that the FDA statements lack a nexus to the asserted claims. I disagree. "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330 (Fed. Cir. 2017) (citation omitted). But here, the potential antibiotic resistance would have resulted from the claimed method of treatment. Accordingly, I give some weight to the FDA comments as evidence of skepticism.

Ultimately, I find that Norwich has not shown by clear and convincing evidence that the asserted HE claims are invalid as obvious.

ii. Written Description

Norwich argues, "Claim 8 of the '573 patent, claim 6 of the '195 patent, and claim 11 of the '397 patent are invalid for lack of written description because the specifications of the patents fail to show that the administration of rifaximin alone (*i.e.*, in the absence of concomitant administration of lactulose) achieves the claimed effects." (D.I. 181 at 16). Norwich's argument seems to be that the specifications lack data supporting the efficacy of rifaximin alone. (*See id.*). This is not the standard for written description. The specifications all describe using rifaximin with or without lactulose. (JTX 19 at 16:62-17:3 ("This method includes: administering rifaximin to a subject daily that is being treated with lactulose, and tapering lactulose consumption.... In one embodiment, the baseline use of lactulose is no use."); JTX 11 at 16:62-17:3; JTX 22 at 10:49-57). I therefore find that Norwich has not shown a lack of adequate written description by clear and convincing evidence.

C. THE IBS-D PATENTS

Irritable bowel syndrome ("IBS") is characterized by symptoms including abdominal pain, bloating, frequency, urgency, gas, and changed bowel habits, such as diarrhea, constipation, or alternating diarrhea and constipation. (*E.g.*, Tr. 618:23-620:2). Subtypes of IBS include IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), or IBS with alternating diarrhea and constipation (IBS-A). (Tr. 622:9-623:1). The IBS-D subtype comprises about one-third of IBS patients. (Tr. 622:21-623:1). IBS may

be caused, for example, by abnormal motility, abnormal muscular coordination, changes in the microbiome in the colon or small intestine, intolerance to certain foods, or psychological factors. (Tr. 618:23-620:2).

Plaintiffs assert two claims in connection with the IBS-D patents.

Asserted Claim 3 of the '667 patent is a dependent claim that has three elements: (1) administering 550 mg of rifaximin three times a day (TID) for 14 days; (2) to treat one or more symptoms of IBS-D; (3) in a subject 65 years of age or older.

Asserted Claim 2 of the '569 patent is a dependent claim with two elements: (1) administering 550 mg of rifaximin TID for 14 days; and (2) after stopping rifaximin, achieving a durability of response that comprises about 12 weeks of adequate relief of symptoms.

1. Findings of Fact

1. Norwich is aware of the IBS-D patents.

2. Norwich's label will encourage administering rifaximin to adults aged 65 years or older with IBS-D.

3. Norwich's label will encourage administration of "one 550 mg tablet taken orally three times a day for 14 days" for the treatment of IBS-D, which inevitably will result in at least some patients

having a durability of response comprising about 12 weeks of adequate relief after stopping rifaximin.

4. Patients will take rifaximin according to the label and will directly infringe the asserted IBS-D claims.

5. Norwich's label will induce infringement of the asserted IBS-D claims.

6. The priority date for the IBS-D claims is February 26, 2008.

7. A person of skill in the art would have had a medical degree with training in gastroenterology or have been a practicing physician, such as an internist, with experience in treating IBS.

8. The prior art includes the '608 patent (JTX 132), the Pimentel Book (PTX 752), Yang (DTX 892), the RFIB 2001 Press Release (DTX 657), Pimentel 2006 (JTX 53), the RFIB 2001 Protocol (DTX 340), Cuoco (JTX 38), Barrett (JTX 71), Viscomi 2005 (JTX 64), Lin 2006 (JTX 69), Lauritano (DTX 384), and Scarpellini (JTX 60).

9. The RFIB 2001 Protocol and Pimentel 2006 disclose all limitations of the IBS-D claims.

10. A POSA would have been motivated to combine the RFIB 2001 Protocol and Pimentel 2006 with a reasonable expectation of success.

11. As of the priority date, the prior art disclosed positive results in using rifaximin to treat IBS-D for a range of doses. The asserted IBS-D claims describe a dosing regimen within the known range.

12. A POSA would have had motivation to treat IBS-D patients 65 years of age or older with rifaximin. A POSA would have had a reasonable expectation of success in treating this patient group with rifaximin.

13. The prior art did not teach away from using rifaximin to treat IBS-D according to the claimed methods.

14. There was some skepticism in the literature.

15. The asserted IBS-D claims are invalid as obvious.

16. The specification describes "durability of response" as including adequate relief from symptoms for 12 weeks.

17. A POSA would recognize that the inventor possessed the claimed durability of response.

18. A POSA would have reasonable certainty regarding the meaning of "adequate relief" and "durability of response."

2. Infringement

i. Age 65 and Over ('667 patent, Claim 3)

Claim 3 of the '667 patent requires administration of rifaximin to patients who are 65 years and older. I find that Norwich's label will induce administration to this patient population. Norwich's ANDA product is indicated for "adults." (JTX 73 § 1.3). "Adults" include people who are 65 years and older. The label's "Use in Special Populations" section describes "Geriatric Use." (JTX 73 § 8.5). The label states, "No overall differences in safety or effectiveness were observed between these subjects [aged 65 and over] and younger subjects for either indication." (*Id.*) Accordingly, Norwich knows and specifically intends that its ANDA product will be used to treat IBS-D in patients who are 65 and older.

ii. 12 Week Durability of Response ('569 patent, Claim 2)

Claim 2 of the '569 patent requires a "durability of response [that] comprises about 12 weeks of adequate relief." I find that Norwich's label will induce such a response in at least some patients. Salix argues, "By following [the dosing] instructions [on the label], some patients will inevitably have a durability of response comprising about 12 weeks of adequate relief." (D.I. 174 at 14). Salix's expert testified to this, and Norwich's expert admitted as much. (Tr. 537:12-540:4, 581:16-22 (agreeing that at least some patients "will experience adequate

relief of their IBS-D symptoms for 12 weeks after taking rifaximin 550 milligrams three times a day for 14 days")). "[A]n accused product that sometimes, but not always, embodies a claimed method nonetheless infringes." *Bell Communications Research v. Vitalink Communications Corp.*, 55 F.3d 615, 622-23 (Fed. Cir. 1995).

Norwich's label supports a finding of inducement. The product is indicated "for the treatment of irritable bowel syndrome with diarrhea." (JTX 73 § 1.3). The Clinical Studies section states, "The efficacy of rifaximin tablets for the treatment of IBS-D was established in 3 randomized, multi-center, double-blind, placebo-controlled trials in adult patients." (JTX 73 § 14.3). The third study, TARGET 3, tracked long-term response to treatment. In it, "382 [patients] experienced a period of symptom inactivity or decrease that did not require repeat treatment by the time they discontinued, including patients who completed the 22 weeks after initial treatment with rifaximin." (*Id.*). Norwich argues that TARGET 3 only measured two symptoms of IBS-D, rather than the claimed "adequate relief" of IBS-D symptoms, and that it reported "time to recurrence" rather than the claimed "durability of response." (D.I. 183 at 14). Even when a proposed label does not exactly track the claim language, a package insert containing directives that will "inevitably lead some consumers to practice the claimed method" provides sufficient evidence for a finding of specific intent. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). Accordingly, I find that Norwich's label will induce some patients to experience a 12-week durability of response as required by the patents and that Norwich will have the specific intent to induce infringement.

3. Obviousness

Salix asserts that the definition of a POSA is not outcome determinative. (D.I. 181 at 16). Noriwch has proposed that a POSA would have had a medical degree with training in gastroenterology or have been a practicing physician, such as an internist, with experience in treating IBS. (D.I. 181 at 17). I adopt Norwich's definition of a POSA.

Norwich argues that, as of the priority date, rifaximin was known to be safe and effective in treating IBS-D. Prior to February 2008, there was widespread off-label use of Xifaxan to treat IBS in the United States. As of January 2008, 74% of gastroenterologists polled by Salix had prescribed Xifaxan for IBS. (DTX 349-130). Prescription data showed that 27.7% of Xifaxan 200 mg tablet uses in November 2007 had been for IBS. (DTX 349-89; Tr. 832:2-833:23).

The prior art also discussed using rifaximin to treat IBS. In 1999, Dr. Pimentel applied for patents on the use of rifaximin to treat IBS. (JTX 132; JTX 133; Tr. 617:1-21). The '608 patent claims a method of "treating a subject suffering from [IBS], comprising administering rifaximin to the subject. . ." (JTX 132 at cl. 1; Tr. 620:3-621:9).[2] At a 2005 conference hosted by Salix, Dr. Pimentel disclosed that his practice group had used rifaximin to treat about 900 patients. (Tr. 627:7-628:5; DTX 582-4, 5). In 2006, Dr.

2. The '608 patent issued in 2010 but the parties agree that it was publicly accessible before the priority date. (D.I. 149, Ex. 1 ¶ 136).

Appendix B

Pimentel published a book titled *A New IBS Solution, Bacteria - the Missing Link in Treating Irritable Bowel Syndrome*, which recommended the use of rifaximin as a safe and effective way to treat IBS-D. (PTX 752; Tr. 623:25-624:21).

In 2006, three studies were published on the use of rifaximin to treat IBS. A randomized, double-blind, placebo-controlled study found rifaximin to be more effective than placebo in improving IBS. ("Pimentel 2006," JTX 53). A retrospective chart review of IBS patients who had tested positive for small intestine bacterial overgrowth ("SIBO") reported a significant reduction in the number of patients having IBS symptoms 4-5 months after treatment, and that 12 of 23 patients had "complete resolution of IBS symptoms." ("Cuoco," JTX 38 at 94). Another retrospective chart review of 8 patients disclosed, "rifaximin use resulted in complete resolution of clinical symptoms in 4 patients, with no IBS relapse (follow-up, 1 to 6 months)," and "partial symptom improvement was observed in 4 patients, 3 of whom were treated for an additional 2 months with rifaximin 400 mg three times daily cycle therapy (2 weeks on / 1 week off []) which resulted in a 50% to 70% improvement from baseline." ("Barrett," JTX 71; Tr. 639:9-640:5).

Norwich proposes three prior art combinations involving three pieces of prior art. Because I agree that Pimentel 2006 in light of the RFIB 2001 Protocol renders the asserted claims of the IBS-D patents obvious, I will not address the other two combinations.

Appendix B

Pimentel 2006 administered rifaximin, 400 mg TID for 10 days, to treat IBS patients aged 18-65. Pimentel 2006 taught, "rifaximin resulted in statistically greater global improvement in IBS than placebo," and "[i]mprovements were sustained through 10 weeks of follow-up" after 10 days of treatment. (JTX 53 at 562).

The "RFIB 2001 Protocol" (DTX 340) was a Phase II trial designed to administer rifaximin to patients aged 18 and over, 550-2,220 mg per day for 14 days for the treatment of IBS-D. The protocol included the outcome measures of providing adequate relief of symptoms and evaluating a durability of response over a 12-week post-treatment period. Salix announced the successful completion of this study on September 5, 2007 (the "RFIB 2001 Press Release") and disclosed, "Top-line results of this study demonstrate that... a 14-day course of rifaximin at 550 mg twice-a-day, provides a statistically significant improvement in both adequate relief of IBS symptoms and adequate relief of bloating, compared to placebo." (DTX 657-4; Tr. 656:12-657:10).

The RFIB 2001 Protocol and Pimentel 2006 disclose all limitations of the asserted IBS-D claims.

I find that a POSA would have been motivated to combine Pimentel 2006 with the RFIB 2001 Protocol and would have had a reasonable expectation of success. Pimentel 2006 reported sustained improvement in IBS symptoms for patients aged 18-65 for at least 10 weeks on a 400 mg TID, 10-day regimen. The RFIB 2001 Protocol included no upper age limit, a 14-day dosing

regimen of 550 to 2200 mg per day, and the treatment of patients with IBS-D in particular. As of the priority date, a POSA would have known about the successful RFIB 2001 Protocol results. Widespread off-label use reflects a motivation to use rifaximin for the treatment of IBS-D with a reasonable expectation of success. As described above, several pieces of prior art reported success in treating IBS with rifaximin. The caselaw does not require "conclusive proof of efficacy." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). Rifaximin had been shown to be effective in treating IBS in Pimentel 2006 and IBS-D in the RFIB 2001 Protocol, which were randomized, placebo-controlled clinical trials. Together, I think this is strong evidence that a POSA would have a motivation to use rifaximin for the treatment of IBS-D.[3]

I also find that a POSA would have had the motivation to select an optimal dosing regimen from within the known range. The prior art describes positive results from a range of doses. Pimentel 2006 used 400 mg of rifaximin TID for 10 days and reported "global improvement in IBS." (JTX 53 at 558). Cuoco disclosed a total dose of 1200 mg for 14 days and reported significant reduction in the

3. The parties do not discuss whether there is any difference between the motivation to use rifaximin to treat IBS and to treat IBS-D. I think a POSA would have been motivated to treat IBS-D and would have had a reasonable expectation of success in doing so, even though much of the prior art describes the treatment of "IBS." About one third of IBS patients have IBS-D, and there is no evidence in the record that a POSA would expect an IBS-D patient to respond differently to treatment than a patient with another form of IBS. (Tr. 622:21-623:1).

number of patients having IBS symptoms. (JTX 38 at 91). Barrett disclosed 400 mg TID for 1-5 months. (JTX 71). In 2007, Quigley explained, "Antibiotic dose and duration of therapy have not been established. All studies to date have used different doses and antibiotic regimens; the optimal approach needs to be established in a prospective, placebo-controlled, dose-ranging study." (PTX 692 at 1142). The RFIB 2001 Protocol taught a range from 1100 mg to 2200 mg per day for 10-14 days. (Tr. 655:20-656:11). The RFIB 2001 Press Release reported that a "14-day course of rifaximin at 550 mg twice-a-day" dosage saw effective results. (DTX 657-4). The claimed dose is 550 mg of rifaximin TID for 14 days.

"Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or working ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289,1295 (Fed. Cir. 2012) (cleaned up). Here, a POSA would have been motivated to combine the prior art to achieve a dosage regimen within the known range. Salix's market research showed that 56% of physicians who prescribed Xifaxan for IBS used TID dosing and 62% had prescribed the drug to be taken for 10-14 days. (DTX 349-131). This market research is not prior art because it was not publicly available as of the priority date, but it reflects a POSA's state of mind. Pimentel 2006 taught, "Recent data suggest that the optimal dosage of rifaximin may, in fact, be higher than that used in our study." (JTX 53 at 562). A POSA would have been motivated to use TID dosing to maintain an effective concentration of rifaximin in the small intestine to control bacteria levels. (Tr. 672:4-23).

Finally, a POSA would have been motivated to improve the use of rifaximin to treat IBS by using a larger tablet to reduce patients' pill burden and improve compliance. (Tr. 674:1-16.).[4]

I further find that a POSA would have had the motivation to treat patients 65 years of age or older with a reasonable expectation of success. The prior art described rifaximin use to treat symptoms of IBS-D patients 65 years or older. (JTX 71 at 1-2; DTX 340-7; DTX 657-4). A POSA would have expected the effect observed in Pimentel 2006 to apply to older patients too. (Tr. 679:12-16).

Salix attacks Norwich's obviousness case on several fronts.

Salix argues that a POSA would recognize these prior art sources as flawed. Cuoco, for instance, is based on the unproven premise that SIBO contributed to IBS-D. Furthermore, its methodology was poor. (D.I. 181 at

4. Salix argues that Dr. Harary undermined his own testimony on the pill burden. Dr. Harary testified, "I don't think going from two pills to one pill would make a big difference, but if you have a larger number of pills, then going to one pill would be - would be convenient and the patients would be more comfortable taking them." (Tr. 674:12-16). As of the priority date, only 200 mg pills were available. I take Dr. Harary's testimony to be saying that three 200 mg pills would be needed to achieve a similar dose (600 mg, as opposed to the claimed 550 mg), and that three pills are more inconvenient than one pill. Accordingly, I do not see how Dr. Harary undermined his own testimony regarding pill burden.

19). Barrett was a retrospective chart review of only 8 patients and concluded that more research was needed. (*Id.*). Pimentel 2006 did not find an improvement in the symptoms of abdominal pain and diarrhea. (JTX 53 at 561). An editorial by Dr. Drossman noted that Pimentel 2006's limitations made its "findings inconclusive and raise[d] questions about the clinical significance of the results." (PTX 457 at 627; Tr. 767:11-18, 770:10-19). Finally, Salix argues that the RFIB 2001 Protocol did not disclose results, and "it was unrebutted that a POSA would not have reasonably expected RFIB2001 would be successful simply because the trial had begun." (D.I. 181 at 19-20).

I am unpersuaded by these arguments. It is fair to critique sources, and a POSA would take a source's shortcomings into consideration when evaluating the evidence. Obviousness does not require perfect evidence, however, and the available evidence persuaded a significant number of doctors who would have been qualified as POSAs to use rifaximin to treat IBS. Regarding Pimentel 2006's failure to find an improvement in abdominal pain and diarrhea, the patents are not directed to specific symptoms but to "adequate relief." There are many symptoms of IBS-D. The patents themselves do not claim relief from every symptom.

Finally, I find that Salix's press release disclosing success in the RFIB 2001 Protocol study is prior art, and thus a POSA would have known about the RFIB 2001 top-line results as of the priority date. Salix argues that the press release was derived from the inventor's work and thus cannot be prior art. (D.I. 181 at 20 (citing *Invitrogen*

Corp. v. Biocrest Mfg., L.P., 424 F.3d 1374, 1380-81 (Fed. Cir. 2005))). Norwich argues that Salix has waived this contention by failing to raise it in the Pretrial Order. (D.I. 185 at 8). Upon review of the Pretrial Order and its Exhibits (D.I. 147-149), I see Plaintiffs' acknowledgement that Norwich is asserting the press release as prior art (D.I. 149, Ex. 4, at 5 n.2), and I see a list of items the prior art status of which Plaintiffs contest, which does not include the press release (*id.* at 6 ¶28), and I do not see any discussion of derivation, so the argument is likely waived. But I do not need to decide waiver, however, because there is no evidence upon which to make a factual finding that the press release was derived from the inventor's work. "Since appellees have produced no evidence—unsurprising given their belated recourse to this argument—and provided no supported explanation demonstrating that the Brandt references were in fact printed publications authored by Dr. VanDenburgh for the purposes of § 102(a), we see no reason to remand to make further findings on this issue." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 969 (Fed. Cir. 2014). The *Allergan* Court thus concluded that the printed publications at issue were prior art. *Id.* at 969-70). The press release is therefore prior art. Its disclosure of positive results would give a POSA a reasonable expectation of success in using rifaximin to treat IBS-D.

Salix also points to skepticism in the literature regarding the connection between SIBO and IBS and whether to use antibiotics to treat IBS-D. Drossman criticized the Pimentel 2006 methodology, as discussed above. A 2007 Education Practice note by Eamonn M.M.

Quigley stated, "sound rationale for antibiotic therapy ha[d] not been established because the issue of SIBO in IBS ha[d] not been resolved." (PTX 692 at 1142; Tr. 777:20-21). Indeed, Salix argues, using antibiotics would have drawbacks: antibiotics could "exacerbate symptoms" or "lead to antibiotic resistance and opportunistic infections" like *c. difficile*. (PTX 664 at 1780; PTX 692 at 1142). A February 4, 2008 article by Vanner considered the evidence and concluded that there was insufficient evidence to recommend the use of antibiotics to treat IBS. (Tr. 779:3-8). Accordingly, Salix argues that the off-label use is best understood as physicians acting out of "desperation, not because they expected it to work." (D.I. 181 at 17).

Upon review of the evidence, it appears that IBS is a complex disease and the pathogenesis was unknown as of the priority date. The relationship between IBS and SIBO was actively being explored, provoking a debate within the field. Quigley, Vanner, and Drossman do not teach away from using rifaximin to treat IBS, and Salix does not argue that they do. Based on the evidence, I do not think a POSA would elevate these sources above the other prior art available. The RFIB 2001 Press Release—which was not cited by Quigley, Vanner, or Drossman—states, "The belief that bacteria in the small bowel may play a role in the symptoms of IBS gains additional evidence with this large, multicenter trial." (DTX 657-4). I do not think a POSA would have discounted prior art sources that were based upon the theory that SIBO contributed to IBS because studies such as the RFIB 2001 Protocol were testing that hypothesis at the time. More importantly, a

POSA would look to the top-line results from the RFIB 2001 Protocol as evidence that rifaximin could be effective in treating IBS-D, regardless of whether the results were based upon a link between IBS-D and SIBO.

Regarding the concerns of bacterial resistance, expert testimony shows that short-term administration did not raise resistance concerns. (Tr. 493:15-494:20). Furthermore, in 2007, a retrospective study of 84 IBS patients who were retreated with rifaximin noted that 69% of patients had a "clinical response" to rifaximin and that retreatment did not result in clinically relevant antibiotic resistance. (DTX 892-2, 5; Tr. 630:5-19, 631:9-18).

Accordingly, I do not think these concerns would dissuade a POSA from exploring the use of rifaximin in treating IBS-D. The 74% of gastroenterologists who had reported using rifaximin for IBS-D patients is real world evidence supporting the conclusion that there was a motivation to explore this treatment, despite the potential risks.

Regarding secondary considerations, Salix argues that there was skepticism that the claimed dosing regimen could safely and effectively treat IBS-D. (D.I. 174 at 17). Salix points to statements in Quigley, Drossman, and Vanner such as, "A sound rationale for antibiotic therapy has not been established . . . ," and, "There is insufficient evidence to recommend antibiotics for the treatment of [IBS] at present." (PTX 692 at 1142; PTX 693 at 1319). Furthermore, experts on the FDA advisory committee stated that using rifaximin 550 TID for 14 days was "a

completely different paradigm and a different treatment structure," and that Salix had proposed to "treat[] a disease which we know nothing or very little about with a drug that we know little or nothing about." (PTX 535 at 302, 307). The FDA advisory committee also expressed concern about antibiotic resistance. (*Id.* at 137).

Norwich responds that Salix's evidence of skepticism "fails" because rifaximin had already been used to safely and effectively treat IBS-D before 2008. (D.I. 183 at 18). I do not think this negates Salix's evidence of skepticism.

Regarding skepticism in the literature, Norwich argues that one of the articles was published before Yang and the RFIB 2001 Press Release, and the other two articles did not cite those references. (*Id.* at 20). I agree that evidence of skepticism is not as powerful when the skepticism is expressed by a source unfamiliar with the "prior art references that laid the groundwork for the inventors' experiments." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1365 (Fed. Cir. 2007). I still give some weight to these articles, especially Vanner, which was published less than a month before the priority date.

Regarding the FDA advisory committee, Norwich argues, "The cited passages from the 2011 FDA advisory committee meeting regarding the IBS-D indication did not criticize the safety or effectiveness of rifaximin to treat IBS-D in at least some patients." (*Id.* at 19). Norwich's expert did not address the FDA statements. I decline to adopt attorney argument in place of expert testimony.

Ultimately, I give some weight to Salix's evidence of skepticism from the literature and the FDA's statements. I do not think these experts "expressed disbelief," *United States v. Adams*, 383 U.S. 39, 52, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966), but there is a "range of third-party opinion that can constitute skepticism." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1378 (Fed. Cir. 2019). Ultimately, Salix has shown a small amount of skepticism but not enough to change the outcome of the obviousness analysis.

I find that the asserted IBS-D claims are invalid as obvious.

4. Written Description

Norwich argues that asserted claim 2 of the '569 patent lacks written description because it fails to show possession of the claimed "durability of response compris[ing] about 12 weeks of adequate relief of symptoms." (D.I. 176 at 30). The specification explains:

> As used herein, 'durability of response' includes for example, adequate relief of symptoms after removal of treatment, continuous adequate relief of symptoms after removal of treatment, or response that is greater than or superior to placebo response. . . . The duration of response, may be, for example, 2 days, 7 days, two weeks, 3 weeks, 4 weeks, 12 weeks, between about 1 week and about 24 weeks or longer.

'569 patent at 11:44-53. The specification also discloses a proposed study design in Figure 3 "to show durability of response." *Id.* at 6:10-12. Figure 3 shows a "4 Week Treatment Period" follow by a 12 week "Post-Treatment Phase." *Id.* at Fig. 3, 25:55-59. I think this is enough to show possession of the claimed 12-week durability of response.

Norwich argues that the disclosure is "effectively unlimited in time." (D.I. 176 at 31). "[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Here, the evidence shows that IBS-D is a complex disease and that not all patients achieve a 12-week durability of response. A POSA would recognize that the inventor adequately described a range of possibilities for the durability of response and was in possession of the claimed 12-week period.

5. Indefiniteness

Norwich argues that asserted claim 2 of the '569 patent is invalid as indefinite. (D.I. 176 at 28). As noted, Claim 2 includes the limitation, "durability of response compris[ing] about 12 weeks of adequate relief of symptoms." Norwich argues that "adequate relief of symptoms" is subjective opinion. (*Id.*). Salix responds that "adequate relief and "durability of response" have accepted meanings to a POSA. (D.I. 181 at 31). IBS-D is a collection of symptoms and there is no biomarker to

determine a successful overall treatment of IBS-D. (Tr. 507:24-508:7). I credit Dr. Schoenfeld's testimony that patient-reported "adequate relief is used to determine IBS-D treatment success in the field. (Tr. 519:15-22; 821:9-822:1). Thus, I reject Norwich's argument that claim 2 of the '569 patent is invalid as indefinite.

V. CONCLUSION

For the foregoing reasons, Norwich's ANDA will induce infringement of the HE, IBS-D, and Polymorph patent claims. The HE claims are nonobvious and Norwich has failed to show a lack of adequate written description. The asserted Polymorph and IBS-D claims are invalid as obvious.

I will enter a final judgment in accord with the conclusions of this opinion.

APPENDIX C — DENIAL OF REHEARING OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT, FILED JUNE 13, 2024

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2022-2153, 2023-1952

SALIX PHARMACEUTICALS, LTD., SALIX PHARMACEUTICALS, INC., BAUSCH HEALTH IRELAND LTD., ALFASIGMA S.P.A.,

Plaintiffs-Appellants,

v.

NORWICH PHARMACEUTICALS INC.,

Defendant-Cross-Appellant.

Appeals from the United States District Court for the District of Delaware in No. 1:20-cv-00430-RGA, Judge Richard G. Andrews.

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before Moore, *Chief Judge,* Lourie, Dyk, Prost, Reyna, Taranto, Chen, Hughes, Stoll, and Cunningham, *Circuit Judges*.[1]

1. Circuit Judge Newman and Circuit Judge Stark did not participate.

Appendix C

PER CURIAM.

ORDER

Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., Bausch Health Ireland Ltd., and Alfasigma S.p.A filed a combined petition for panel rehearing and rehearing en banc.

Norwich Pharmaceuticals Inc. also filed a combined petition for panel rehearing and rehearing en banc.

The petitions were referred as petitions to the panel that heard the appeal, and thereafter the petitions were referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petitions for panel rehearing are denied.

The petitions for rehearing en banc are denied.

The mandate of the court will issue June 20, 2024.

FOR THE COURT

June 13, 2024
Date

Jarrett B. Perlow
Clerk of Court

APPENDIX D — STATUTES AND PROVISIONS

21 U.S.C.S. § 355

§ 355. New drugs

Effective: December 29, 2022

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

(b) Filing application; contents

(1)(A) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as part of the application—

(i) full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use;

(ii) a full list of the articles used as components of such drug;

(iii) a full statement of the composition of such drug;

(iv) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(v) such samples of such drug and of the articles used as components thereof as the Secretary may require;

***

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible, it is contrary to the best interests of such human beings, or the proposed clinical testing poses no more than minimal risk to such human beings and includes appropriate safeguards as prescribed to protect the rights, safety, and welfare of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs. The Secretary shall update such regulations to require

inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 282 of Title 42.

(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

Appendix D

(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 (ii) through (vi) of subsection (b)(1)(A);

(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.

****

Appendix D

35 U.S.C.S. § 271

§ 271. Infringement of patent

Effective: March 23, 2010

(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.

Appendix D

21 C.F.R. § 314.94

§ 314.94 Content and format of an ANDA.

Effective: December 5, 2016

ANDAs are required to be submitted in the form and contain the information required under this section. Three copies of the ANDA are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of ANDAs to assist applicants in their preparation.

(a) ANDAs. Except as provided in paragraph (b) of this section, the applicant must submit a complete archival copy of the abbreviated new drug application that includes the following:

(1) Application form. The applicant must submit a completed and signed application form that contains the information described under § 314.50(a)(1), (a)(3), (a)(4), and (a)(5). The applicant must state whether the submission is an ANDA under this section or a supplement to an ANDA under § 314.97.

(2) Table of contents. The archival copy of the ANDA is required to contain a table of contents that shows the volume number and page number of the contents of the submission.

(3) Basis for ANDA submission. An ANDA must refer to a listed drug. Ordinarily, that listed drug will be the

drug product selected by the Agency as the reference standard for conducting bioequivalence testing. The ANDA must contain:

(i) The name of the reference listed drug, including its dosage form and strength. For an ANDA based on an approved petition under § 10.30 of this chapter and § 314.93, the reference listed drug must be the same as the listed drug referenced in the approved petition.

(ii) A statement as to whether, according to the information published in the list, the reference listed drug is entitled to a period of marketing exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

(iii) For an ANDA based on an approved petition under § 10.30 of this chapter and § 314.93, a reference to the FDA-assigned docket number for the petition and a copy of FDA's correspondence approving the petition.

(4) Conditions of use.

(i) A statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the reference listed drug.

(ii) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

Appendix D

(5) Active ingredients

(i) For a single-active-ingredient drug product, information to show that the active ingredient is the same as that of the reference single-active-ingredient listed drug, as follows:

> **(A)** A statement that the active ingredient of the proposed drug product is the same as that of the reference listed drug.
>
> **(B)** A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) For a combination drug product, information to show that the active ingredients are the same as those of the reference listed drug except for any different active ingredient that has been the subject of an approved petition, as follows:

> **(A)** A statement that the active ingredients of the proposed drug product are the same as those of the reference listed drug, or if one of the active ingredients differs from one of the active ingredients of the reference listed drug and the ANDA is submitted under the approval of a petition under § 314.93 to vary such active ingredient, information to show that the other active ingredients of the drug product are the same as the other active ingredients of the

reference listed drug, information to show that the different active ingredient is an active ingredient of another listed drug or of a drug that does not meet the definition of "new drug" in section 201(p) of the Federal Food, Drug, and Cosmetic Act, and such other information about the different active ingredient that FDA may require.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(6) Route of administration, dosage form, and strength

(i) Information to show that the route of administration, dosage form, and strength of the drug product are the same as those of the reference listed drug except for any differences that have been the subject of an approved petition, as follows:

(A) A statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) If the route of administration, dosage form, or strength of the drug product differs from the reference listed drug and the ANDA is submitted under an approved petition under § 314.93, such information about the different route of administration, dosage form, or strength that FDA may require.

(7) Bioequivalence.

(i) Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies. A complete study report must be submitted for the bioequivalence study upon which the applicant relies for approval. For all other bioequivalence studies conducted on the same drug product formulation as defined in § 314.3(b), the applicant must submit either a complete or summary report. If a summary report of a bioequivalence study is submitted and FDA determines that there may be bioequivalence issues or concerns with the product, FDA may require that the applicant submit a complete report of the bioequivalence study to FDA; or

(ii) If the ANDA is submitted pursuant to a petition approved under § 314.93, the results of any bioavailability or bioequivalence testing required by the Agency, or any other information required by the Agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. If

the proposed drug product contains a different active ingredient than the reference listed drug, FDA will consider the proposed drug product to have the same therapeutic effect as the reference listed drug if the applicant provides information demonstrating that:

(A) There is an adequate scientific basis for determining that substitution of the specific proposed dose of the different active ingredient for the dose of the member of the same pharmacological or therapeutic class in the reference listed drug will yield a resulting drug product whose safety and effectiveness have not been adversely affected.

(B) The unchanged active ingredients in the proposed drug product are bioequivalent to those in the reference listed drug.

(C) The different active ingredient in the proposed drug product is bioequivalent to an approved dosage form containing that ingredient and approved for the same indication as the proposed drug product or is bioequivalent to a drug product offered for that indication which does not meet the definition of "new drug" under section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(iii) For each in vivo or in vitro bioequivalence study contained in the ANDA:

(A) A description of the analytical and statistical methods used in each study; and

(B) With respect to each study involving human subjects, a statement that the study either was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105 of this chapter, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter.

(8) Labeling —

(i) Listed drug labeling. A copy of the currently approved labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) for the listed drug referred to in the ANDA, if the ANDA relies on a reference listed drug.

(ii) Copies of proposed labeling. Copies of the label and all labeling for the drug product including, if applicable, any Medication Guide required under part 208 of this chapter (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) Statement on proposed labeling. A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) Comparison of approved and proposed labeling. A side-by-side comparison of the applicant's proposed

labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

(9) Chemistry, manufacturing, and controls.

(i) The information required under § 314.50(d)(1), except that the information required under § 314.50(d)(1)(ii)(c) must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product.

(ii) Inactive ingredients. Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant must identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.

(iii) Inactive ingredient changes permitted in drug products intended for parenteral use. Generally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

(iv) Inactive ingredient changes permitted in drug products intended for ophthalmic or otic use. Generally, a drug product intended for ophthalmic or otic use must contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies

and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.

(v) Inactive ingredient changes permitted in drug products intended for topical use. Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an ANDA may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

(10) Samples. The information required under § 314.50(e)(1) and (e)(2)(i). Samples need not be submitted until requested by FDA.

(11) Other. The information required under § 314.50(g).

(12) Patent certification —

(i) Patents claiming drug substance, drug product, or method of use.

(A) An appropriate patent certification or statement with respect to each patent issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For each such patent, the applicant must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(1) That the patent information has not been submitted to FDA. The applicant must entitle such a certification "Paragraph I Certification";

(2) That the patent has expired. The applicant must entitle such a certification "Paragraph II Certification";

(3) The date on which the patent will expire. The applicant must entitle such a certification "Paragraph III Certification"; or

(4)(i) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted. The applicant must entitle such a certification "Paragraph IV Certification". This certification must be submitted in the following form:

I, (name of applicant), certify that Patent No. (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this ANDA is submitted.

(ii) The certification must be accompanied by a statement that the applicant will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or its representative and to the NDA holder (or, if the NDA holder does not reside or maintain a place of business within the United States, its attorney, agent, or other authorized official) for the listed drug, with the requirements under § 314.95(b) with respect to sending the notice, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the ANDA refers to a listed drug that is itself a licensed generic product of a patented drug first approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, an appropriate patent certification or statement under paragraph (a)(12)

(i) and/or (iii) of this section with respect to each patent that claims the first-approved patented drug or that claims a use for such drug.

(ii) No relevant patents. If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (a)(12)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this ANDA or that claim a use of the listed drug.

(iii) Method-of-use patent.

(A) If patent information is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent, a statement explaining that the method-of-use patent does not claim a proposed indication or other condition of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act

and § 314.53 or in the opinion of the applicant, is claimed by a method-of-use patent, an applicable certification under paragraph (a)(12)(i) of this section.

(iv) [Reserved by 81 FR 69649]

(v) Licensing agreements. If the ANDA is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant must submit a paragraph IV certification as to that patent and a statement that the applicant has been granted a patent license. If the patent owner consents to approval of the ANDA (if otherwise eligible for approval) as of a specific date, the ANDA must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the ANDA as of a specific date.

(vi) Untimely filing of patent information.

(A) If a patent on the listed drug is issued and the holder of the approved NDA for the listed drug does not file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an ANDA for that drug that contained an appropriate patent certification or statement before the submission of the patent information is not required to submit a patent certification or statement to address the patent or patent information that is late-listed with

respect to the pending ANDA. Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information unless:

(1) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of patent issuance;

(2) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or

(3) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision.

(B) An applicant whose ANDA is submitted after the NDA holder's untimely filing of patent information, or whose pending ANDA was previously submitted but did not contain an appropriate patent certification or statement at the time of the patent submission, must submit

a certification under paragraph (a)(12)(i) of this section and/or a statement under paragraph (a)(12)(iii) of this section as to that patent.

(vii) Disputed patent information. If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn, the applicant must submit an appropriate certification or statement for each listed patent.

(viii) Amended certifications. A patent certification or statement submitted under paragraphs (a)(12)(i) through (iii) of this section may be amended at any time before the approval of the ANDA. If an applicant with a pending ANDA voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. An applicant must submit an amended certification as an amendment to a pending ANDA. Once an amendment is submitted to change a certification, the ANDA will no longer be considered to contain the prior certification.

(A) After finding of infringement. An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs and enters a

settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under paragraph (a)(12)(i)(A)(3) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (a)(12)(iii) of this section if the applicant amends its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the ANDA will no longer be considered to contain a paragraph IV certification to the patent. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.

(B) After request to remove a patent or patent information from the list. If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent or patent information will be removed and any applicant with a pending ANDA (including a tentatively approved ANDA) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. In the amendment, the applicant must state the reason for withdrawing the certification

or statement (that the patent has been removed from the list). If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished. After any applicable 180-day exclusivity has expired or has been extinguished, the patent or patent information will be removed and any applicant with a pending ANDA (including a tentatively approved ANDA) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. Once an amendment to withdraw the certification has been submitted, the ANDA will no longer be considered to contain a paragraph IV certification to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug identified in the ANDA, the applicant must submit an amended certification reflecting that there are no relevant patents.

(C) Other amendments.

(1) Except as provided in paragraphs (a)(12)(vi) and (a)(12)(viii)(C)(2) of this section:

(i) An applicant must amend a submitted certification or statement if, at any time before the date of approval of the ANDA, the applicant

learns that the submitted certification or statement is no longer accurate; and

(ii) An applicant must submit an appropriate patent certification or statement under paragraph (a)(12)(i) and/or (iii) of this section if, after submission of the ANDA, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims an approved use for such reference listed drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For a paragraph IV certification, the certification must not be submitted earlier than the first working day after the day the patent is published in the list.

(2) An applicant is not required to submit a supplement to change a submitted certification when information on a patent on the listed drug is submitted after the approval of the ANDA.

(13) Financial certification or disclosure statement. An ANDA must contain a financial certification or disclosure statement as required by part 54 of this chapter.

(b) Drug products subject to the Drug Efficacy Study Implementation (DESI) review. If the ANDA is for a duplicate of a drug product that is subject to FDA's

DESI review (a review of drug products approved as safe between 1938 and 1962) or other DESI-like review and the drug product evaluated in the review is a listed drug, the applicant must comply with the provisions of paragraph (a) of this section.

(c) [Reserved]

(d) Format of an ANDA.

(1) The applicant must submit a complete archival copy of the ANDA as required under paragraphs (a) and (c) of this section. FDA will maintain the archival copy during the review of the ANDA to permit individual reviewers to refer to information that is not contained in their particular technical sections of the ANDA, to give other Agency personnel access to the ANDA for official business, and to maintain in one place a complete copy of the ANDA.

(i) Format of submission. An applicant may submit portions of the archival copy of the ANDA in any form that the applicant and FDA agree is acceptable, except as provided in paragraph (d)(1)(ii) of this section.

(ii) Labeling. The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (d)(1)(iii) of this section. This requirement applies to the content of labeling for the proposed drug product only

and is in addition to the requirements of paragraph (a)(8)(ii) of this section that copies of the formatted label and all proposed labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(iii) Electronic format submissions. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) For ANDAs, the applicant must submit a review copy of the ANDA that contains two separate sections. One section must contain the information described under paragraphs (a)(2) through (6) and (8) and (9) of this section and section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act and a copy of the analytical procedures and descriptive information needed by FDA's laboratories to perform tests on samples of the proposed drug product and to validate the applicant's analytical procedures. The other section must contain the information described under paragraphs (a)(3), (7), and (8) of this section. Each of the sections in the review copy is required to contain a copy of the application form described under paragraph (a) of this section.

(3) [Reserved]

(4) The applicant may obtain from FDA sufficient folders to bind the archival, the review, and the field copies of the ANDA.

(5) The applicant must submit a field copy of the ANDA that contains the technical section described in paragraph (a)(9) of this section, a copy of the application form required under paragraph (a)(1) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (a)(9) of this section contained in the archival and review copies of the ANDA.

Appendix D

21 C.F.R. § 314.107

§ 314.107 Date of approval of a 505(b)(2) application or ANDA.

Effective: December 5, 2016

(a) General. A drug product may be introduced or delivered for introduction into interstate commerce when the 505(b)(2) application or ANDA for the drug product is approved. A 505(b)(2) application or ANDA for a drug product is approved on the date FDA issues an approval letter under § 314.105 for the 505(b)(2) application or ANDA.

(b) Effect of patent(s) on the listed drug. As described in paragraphs (b)(1) and (2) of this section, the status of patents listed for the listed drug(s) relied upon or reference listed drug, as applicable, must be considered in determining the first possible date on which a 505(b)(2) application or ANDA can be approved. The criteria in paragraphs (b)(1) and (2) of this section will be used to determine, for each relevant patent, the date that patent will no longer prevent approval. The first possible date on which the 505(b)(2) application or ANDA can be approved will be calculated for each patent, and the 505(b)(2) application or ANDA may be approved on the last applicable date.

(1) Timing of approval based on patent certification or statement. If none of the reasons in § 314.125 or § 314.127, as applicable, for refusing to approve the 505(b)(2) application or ANDA applies, and none of the

reasons in paragraph (d) of this section for delaying approval applies, the 505(b)(2) application or ANDA may be approved as follows:

(i) Immediately, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that:

(A) The applicant is aware of a relevant patent but the patent information required under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act has not been submitted to FDA; or

(B) The relevant patent has expired; or

(C) The relevant patent is invalid, unenforceable, or will not be infringed, except as provided in paragraphs (b)(3) and (c) of this section, and the 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act has expired; or

(D) There are no relevant patents.

(ii) Immediately, if the applicant submits an appropriate statement under § 314.50(i) or § 314.94(a)(12) explaining that a method-of-use patent does not claim an indication or other condition of use for which the applicant is seeking approval, except that if the applicant also submits a paragraph IV certification to the patent, then the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(1)(i)(C) of this section.

(iii) On the date specified, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent will expire on a specified date.

(2) Patent information filed after submission of 505(b)(2) application or ANDA. If the holder of the approved NDA for the listed drug submits patent information required under § 314.53 after the date on which the 505(b)(2) application or ANDA was submitted to FDA, the 505(b)(2) applicant or ANDA applicant must comply with the requirements of § 314.50(i)(4) and (6) and § 314.94(a)(12)(vi) and (viii) regarding submission of an appropriate patent certification or statement. If the applicant submits an amendment certifying under § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4) that the relevant patent is invalid, unenforceable, or will not be infringed, and complies with the requirements of § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved immediately upon submission of documentation of receipt of notice of paragraph IV certification under § 314.52(e) or § 314.95(e). The 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act does not apply in these circumstances.

(3) Disposition of patent litigation —

(i) Approval upon expiration of 30-month period or 71/2 years from date of listed drug approval.

(A) Except as provided in paragraphs (b)(3)(ii) through (viii) of this section, if, with respect

to patents for which required information was submitted under § 314.53 before the date on which the 505(b)(2) application or ANDA was submitted to FDA (excluding an amendment or supplement to the 505(b)(2) application or ANDA), the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt of the notice of certification from the applicant under § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved 30 months after the later of the date of the receipt of the notice of certification by any owner of the listed patent or by the NDA holder (or its representative(s)) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action; or

(B) If the patented drug product qualifies for 5 years of exclusive marketing under § 314.108(b)(2) and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date of approval of the patented drug and within 45 days of receipt of the notice of certification from the applicant under § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved at the expiration of the 71/2 years from the date of approval of the NDA for the patented drug product.

(ii) Federal district court decision of invalidity, unenforceability, or non-infringement. If before the expiration of the 30-month period, or 71/2 years where applicable, the district court decides that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the 505(b)(2) application or ANDA may be approved on:

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

(B) 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, unenforceable, or not infringed.

(iii) Appeal of Federal district court judgment of infringement. If before the expiration of the 30-month period, or 71/2 years where applicable, the district court decides that the patent has been infringed, and if the judgment of the district court is appealed, the 505(b)(2) application or ANDA may be approved on:

(A) The date on which the mandate is issued by the court of appeals entering judgment that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(B) 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, unenforceable, or not infringed.

(iv) Affirmation or non-appeal of Federal district court judgment of infringement. If before the expiration of the 30-month period, or 71/2 years where applicable, the district court decides that the patent has been infringed, and if the judgment of the district court is not appealed or is affirmed, the 505(b)(2) application or ANDA may be approved no earlier than the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A).

(v) Grant of preliminary injunction by Federal district court. If before the expiration of the 30-month period, or 71/2 years where applicable, the district court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that:

(A) The patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(ii) of this section; or

(B) The patent is infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(iii) or (iv) of this section, whichever is applicable.

(vi) Written consent to approval by patent owner or exclusive patent licensee. If before the expiration of the 30-month period, or 71/2 years where applicable, the patent owner or the exclusive patent licensee (or their representatives) agrees in writing that the 505(b)(2) application or ANDA may be approved any time on or after the date of the consent, approval may be granted on or after that date.

(vii) Court order terminating 30-month or 71/2-year period. If before the expiration of the 30-month period, or 71/2 years where applicable, the court enters an order requiring the 30-month or 71/2-year period to be terminated, the 505(b)(2) application or ANDA may be approved in accordance with the court's order.

(viii) Court order of dismissal without a finding of infringement. If before the expiration of the 30-month period, or 71/2 years where applicable, the court(s) enter(s) an order of dismissal, with or without prejudice, without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification sent by the 505(b)(2) or ANDA applicant, the 505(b)(2) application or ANDA may be approved on or after the date of the order.

(4) Tentative approval. FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with this section. In order for a 505(b)(2) application or ANDA to be approved under paragraph (b)(3) of this section, the applicant must receive an

approval letter from the Agency. Tentative approval of an NDA or ANDA does not constitute "approval" of an NDA or ANDA and cannot, absent an approval letter from the Agency, result in an approval under paragraph (b)(3) of this section.

(c) Timing of approval of subsequent ANDA.

(1) If an ANDA contains a paragraph IV certification for a relevant patent and the ANDA is not that of a first applicant, the ANDA is regarded as the ANDA of a subsequent applicant. The ANDA of a subsequent applicant will not be approved during the period when any first applicant is eligible for 180-day exclusivity or during the 180-day exclusivity period of a first applicant. Any applicable 180-day exclusivity period cannot extend beyond the expiration of the patent upon which the 180-day exclusivity period was based.

(2) A first applicant must submit correspondence to its ANDA notifying FDA within 30 days of the date of its first commercial marketing of its drug product or the reference listed drug. If an applicant does not notify FDA, as required in this paragraph (c)(2), of this date, the date of first commercial marketing will be deemed to be the date of the drug product's approval.

(3) If FDA concludes that a first applicant is not actively pursuing approval of its ANDA, FDA may immediately approve an ANDA(s) of a subsequent applicant(s) if the ANDA(s) is otherwise eligible for approval.

(d) Delay due to exclusivity. The Agency will also delay the approval of a 505(b)(2) application or ANDA if delay is required by the exclusivity provisions in § 314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act. When the approval of a 505(b)(2) application or ANDA is delayed under this section and § 314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act, the 505(b)(2) application or ANDA will be approved on the latest of the days specified under this section and § 314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act, as applicable.

(e) Notification of court actions or written consent to approval.

(1) The applicant must submit the following information to FDA, as applicable:

(i) A copy of any judgment by the court (district court or mandate of the court of appeals) or settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a patent described in paragraph (b)(3) of this section invalid, unenforceable, or not infringed, or finding the patent valid and infringed;

(ii) Written notification of whether or not any action by the court described in paragraph (e)(1)(i) of this section has been appealed within the time permitted for an appeal;

(iii) A copy of any order entered by the court terminating the 30-month or 71/2-year period as described in paragraph (b)(3)(i), (ii), (vii), or (viii) of this section;

(iv) A copy of any written consent to approval by the patent owner or exclusive patent licensee described in paragraph (b)(3)(vi) of this section;

(v) A copy of any preliminary injunction described in paragraph (b)(3)(v) of this section, and a copy of any subsequent court order lifting the injunction; and

(vi) A copy of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in paragraph (b)(3) of this section).

(2) All information required by paragraph (e)(1) of this section must be sent to the applicant's NDA or ANDA, as appropriate, within 14 days of the date of entry by the court, the date of appeal or expiration of the time for appeal, or the date of written consent to approval, as applicable.

(f) Forty-five day period after receipt of notice of paragraph IV certification —

(1) Computation of 45-day time clock. The 45-day clock described in paragraph (b)(3) of this section as to each recipient required to receive notice of paragraph IV certification under § 314.52 or § 314.95 begins on the day after the date of receipt of the applicant's notice of paragraph IV certification by the recipient. When the 45th day falls on Saturday, Sunday, or a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(2) Notification of filing of legal action.

(i) The 505(b)(2) or ANDA applicant must notify FDA in writing within 14 days of the filing of any legal action filed within 45 days of receipt of the notice of paragraph IV certification by any recipient. A 505(b)(2) applicant must send the notification to its NDA. An ANDA applicant must send the notification to its ANDA. The notification to FDA of the legal action must include:

(A) The 505(b)(2) application or ANDA number.

(B) The name of the 505(b)(2) or ANDA applicant.

(C) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.

(D) A statement that an action for patent infringement, identified by court, case number, and the patent number(s) of the patent(s) at issue in the action, has been filed in an appropriate court on a specified date.

(ii) A patent owner or NDA holder (or its representative(s)) may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in paragraph (f)(2)(i) of this section.

(iii) If the 505(b)(2) or ANDA applicant, the patent owner(s), the NDA holder, or its representative(s) does not notify FDA in writing before the expiration of the 45-day time period or the completion of the Agency's review of the 505(b)(2) application or ANDA, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of paragraph IV certification, the 505(b)(2) application or ANDA may be approved upon expiration of the 45-day period (if the 505(b)(2) or ANDA applicant confirms that a legal action for patent infringement has not been filed) or upon completion of the Agency's review of the 505(b)(2) application or ANDA, whichever is later.

(3) Waiver. If the patent owner or NDA holder who is an exclusive patent licensee (or its representative(s)) waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or NDA holder who

is an exclusive patent licensee (or its representative(s)) submits to FDA a valid waiver before the 45 days elapse, the 505(b)(2) application or ANDA may be approved upon completion of the Agency's review of the NDA or ANDA. FDA will only accept a waiver in the following form:

(Name of patent owner or NDA holder who is an exclusive patent licensee or its representative(s)) has received notice from (name of applicant) under (section 505(b)(3) or 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act) and does not intend to file an action for patent infringement against (name of applicant) concerning the drug (name of drug) before (date on which 45 days elapse). (Name of patent owner or NDA holder who is an exclusive patent licensee) waives the opportunity provided by (section 505(c)(3)(C) or 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act) and does not object to FDA's approval of (name of applicant)'s (505(b)(2) application or ANDA) for (name of drug) with an approval date on or after the date of this submission.

(g) Conversion of approval to tentative approval. If FDA issues an approval letter in error or a court enters an order requiring, in the case of an already approved 505(b)(2) application or ANDA, that the date of approval be delayed, FDA will convert the approval to a tentative approval if appropriate.