United States Court of Appeals for the Federal Circuit

BAYER SCHERING PHARMA AG AND BAYER HEALTHCARE PHARMACEUTICALS, INC.,
Plaintiffs-Appellants,

v.

LUPIN, LTD., AND LUPIN PHARMACEUTICALS, INC.,
Defendants-Appellees.

BAYER SCHERING PHARMA AG AND BAYER HEALTHCARE PHARMACEUTICALS, INC.,
Plaintiffs-Appellants,

v.

SANDOZ, INC.,
Defendant-Appellee,

AND

WATSON PHARMACEUTICALS, INC., AND WATSON LABORATORIES, INC.,
Defendants-Appellees.

2011-1143, -1228

Appeal from the United States District Court for the Southern District of New York in Case Nos. 10-CV-5423 and 08-CV-3710, Judge Paul G. Gardephe.

Decided: April 16, 2012

PETER B. BENSINGER, JR., Bartlit, Beck Herman Palenchar & Scott, LLP, of Chicago, Illinois, argued for plaintiffs-appellants. With him on the brief were ADAM K. MORTARA, PAUL J. SKIERMONT, SUNDEEP K. ADDY and MATTHEW R. FORD. Of counsel on the brief was LAWRENCE D. ROSENBERG, Jones Day, of Washington, DC.

MARK T. JANSEN, Kilpatrick Townsend and Stockton, LLP, of San Francisco, California, argued for all defendants-appellees. With him on the brief were GIA L. CINCONE; and CEDRIC C.Y. TAN and KRISTIN M. COOKLIN, of Washington, DC, for defendant-appellees Watson Pharmaceuticals, Inc., et al. Also on the brief were JOSEPH A. HYNDS and STEVEN LIEBERMAN, Rothwell, Figg, Ernst & Manbeck, P.C., of Washington, DC, for defendant-appellee Sandoz Inc.; and ROBERT F. GREEN and CHRISTOPHER T. GRIFFITH, Leydig, Voit & Mayer, LTD., of Chicago, Illinois, and JAMAICA P SZELIGA, of Washington, DC, for defendants-appellees Lupin Ltd, et al.

CHRISTOPHER N. SIPES, Covington & Burling LLP, of Washington, DC, for amicus curiae Pharmaceutical Research and Manufacturers of America. With him on the brief were ERIKA F. LIETZAN and ROGER A. FORD.

Before NEWMAN, PLAGER, and BRYSON, *Circuit Judges*.

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

Dissenting opinion filed by *Circuit Judge* NEWMAN.

BRYSON, *Circuit Judge*.

Bayer Schering Pharma AG and Bayer HealthCare Pharmaceuticals, Inc., (collectively, "Bayer") appeal from two judgments of the United States District Court for the Southern District of New York. In the first case, the court dismissed Bayer's patent infringement claims against Watson Pharmaceuticals, Inc., and Watson Laboratories, Inc., (collectively, "Watson") and Sandoz, Inc. In the second case, the court dismissed similar patent infringement claims against Lupin Ltd. and Lupin Pharmaceuticals, Inc., (collectively, "Lupin"). We affirm.

I

The Drug Price Competition and Patent Term Restoration Act of 1984 ("the Hatch-Waxman Act"), Pub. L. No. 98-417, 98 Stat. 1585, creates a procedure by which a drug manufacturer can obtain permission from the Food and Drug Administration ("FDA") to market a generic version of a previously approved drug. A manufacturer seeking to market a generic drug is entitled to submit an Abbreviated New Drug Application ("ANDA"), rather than submitting a full New Drug Application ("NDA"). *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 557 F.3d 1346, 1348 (Fed. Cir. 2009). The ANDA process streamlines FDA approval by allowing the generic manufacturer to rely on the safety and efficacy studies of a drug that has previously been approved upon a showing that the generic version and the relevant listed drug share the same active ingredients and are bioequivalent. *Caraco Pharm. Labs.,*

Ltd. v. Forest Labs., Inc., 527 F.3d 1278, 1282 (Fed. Cir. 2008).

In the case of drugs that enjoy patent protection, the Hatch-Waxman Act creates a mechanism that allows for prompt judicial determination of whether the ANDA applicant's drug or method of using the drug infringes a valid patent. The Act makes it an act of infringement to file an ANDA for a drug or for a use of the drug that is claimed in a patent. 35 U.S.C. § 271(e)(2)(A). That "artificial" act of infringement creates jurisdiction for a court to entertain an action by the patentee against the ANDA applicant in which issues of patent infringement and validity can be resolved. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).

The Hatch-Waxman Act requires an NDA applicant seeking FDA approval for a drug that enjoys patent protection to identify every patent that claims the drug or a use of the drug that could reasonably be asserted in an infringement action. 21 U.S.C. § 355(b)(1). The FDA lists the patents identified by the NDA applicant in a publication entitled Approved Drug Products With Therapeutic Equivalence Evaluations, which is universally referred to in the industry as the "Orange Book." In the case of patents claiming methods of use, FDA regulations provide that only patents claiming "indications or other conditions of use" that either have been approved by the FDA or are in a pending NDA are to be submitted for listing in the Orange Book. 21 C.F.R. § 314.53(b).

When an applicant files an ANDA seeking FDA permission to market a generic drug, it is required to address each patent in the Orange Book that relates to that drug. *Eli Lilly & Co.*, 557 F.3d at 1348. For method-of-use patents that will not expire prior to the proposed market-

ing of the generic drug, the ANDA applicant has two options.

First, the ANDA applicant can include a statement, known as a "section viii statement," that the applicant is not seeking approval for the method of use that is claimed in the patent. 21 U.S.C. § 355(j)(2)(A)(viii). When submitting a section viii statement, the ANDA applicant must include a proposed label that removes or "carves out" the claimed method of use. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1046 (Fed. Cir. 2010). The FDA will approve an ANDA with a section viii statement only if (1) there is no overlap between the proposed label submitted by the ANDA applicant and the use described in the Orange Book, and (2) removing the information about the claimed method of use from the label does not render the drug less safe or effective. *See* 21 C.F.R. § 314.127(a)(7); *see also* Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676, 36,682 (June 18, 2003) ("A section viii statement would not be appropriate [when] the ANDA applicant is seeking approval for exactly the same labeling as that in the NDA for which the patent was submitted.").

Second, the ANDA applicant can file a "paragraph IV certification," which states that the patent "is invalid or will not be infringed by the manufacture, use, or sale" of the generic drug. 21 U.S.C. § 355(j)(2)(A)(vii)(IV); *see Novo Nordisk*, 601 F.3d at 1361. If the ANDA applicant files a paragraph IV certification, it must also send a notice letter so advising the holder of the original NDA and the patent owner. 21 U.S.C. § 355(j)(2)(B).

For method-of-use patents, the "artificial" infringement claim provided by section 271(e)(2)(A) lies only against a patented use that has been approved by the

FDA. *Warner-Lambert*, 316 F.3d at 1356. As this court explained in the *Warner-Lambert* case, "because an ANDA may not seek approval for an unapproved or off-label use of a drug under 21 U.S.C. § 355(j)(2)(A)(i), it necessarily follows that 35 U.S.C. 271(e)(2)(A) does not apply to a use patent claiming only such a use." *Id.*; *see also AstraZeneca Pharm. LP v. Apotex Corp.*, 669 F.3d 1370, 1377-78 (Fed. Cir. 2012); *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1334 (Fed. Cir. 2003).

II

Bayer produces and markets Yasmin, an oral contraceptive. In 2001, the FDA approved the new drug application for Yasmin that was filed by Bayer's predecessor, Berlex Laboratories, Inc. That application sought FDA approval for the use of Yasmin "for oral contraception." The FDA approved the application, noting that it had "concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text."

The defendants in the two cases before us have all filed ANDAs with the FDA to market generic versions of Yasmin. The ANDAs, which track the original NDA as required, seek FDA approval for the use of the generic versions of Yasmin for oral contraception. In their respective ANDAs, the defendants have certified that the three patents that Bayer had listed in the Orange Book in connection with Yasmin are either invalid or would not be infringed by the manufacture, use, or sale of their generic version of Yasmin. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV). In March 2008, Watson and Sandoz sent notice letters to Bayer regarding their ANDA filings. In response, Bayer filed a complaint against Watson and Sandoz in April

2008, alleging infringement under section 271(e)(2)(A) of one of the three listed patents, U.S. Patent No. 5,569,652 ("the '652 patent"). Lupin sent Bayer a notice letter in June 2010 regarding its ANDA filing. Bayer filed a complaint against Lupin in July 2010 alleging infringement of the same patent.

The '652 patent is a method-of-use patent with two independent claims:

> 1. A method of simultaneously achieving, during premenopause or menopause a gestagenic effect, antiandrogenic effect, and an antialdosterone effect in a female patient in need thereof comprising administering an amount of dihydrospirorenone to said female patient, wherein said amount of dihydrospirorenone is effective to simultaneously achieve a gestagenic effect, antiandrogenic effect and antialdosterone effect in said patient.
>
> 11. A method of simultaneously achieving, during premenopause or menopause, a contraceptive effect, an anti-androgenic effect, and an anti-aldosterone effect in a female patient in need thereof comprising administering an effective amount of dihydrospirorenone and an effective amount of an estrogenic compound, wherein said effective amount of dihydrospirorenone is effective to simultaneously achieve a gestagenic effect, anti-androgenic effect, and an anti-aldosterone effect in said female patient.

Those claims recite that the claimed method achieves three effects simultaneously: a contraceptive (or gestagenic) effect, an anti-androgenic effect (which re-

duces the activity of male hormones and can be effective in treating conditions such as hirsutism or acne), and an anti-aldosterone effect (also known as an anti-mineralocorticoid effect, which can be effective in reducing excess water retention in the body).

Watson and Sandoz moved for judgment of noninfringement on the pleadings under Federal Rule of Civil Procedure 12(c). They argued that their ANDAs related to the use of the generic form of Yasmin only for oral contraception and not for the combination of uses claimed in the '652 patent. Accordingly, they argued, they could not be held liable for inducing infringement of that patent. The district court granted their motions. The court held that because the FDA had not given approval for the use of the drug that was claimed in the '652 patent, Bayer could not state a claim for patent infringement. *Bayer Schering Pharma AG v. Sandoz, Inc.*, 741 F. Supp. 2d 541 (S.D.N.Y. 2010). The court explained that an action for infringement of a method-of-use patent could be brought under section 271(e)(2)(A) only if the FDA had approved the use claimed in the patent under the patent-holder's NDA. The court noted that the FDA had approved the use of Yasmin only for oral contraception, and not for the simultaneous treatment of three conditions, which was the use claimed in the '652 patent. Because the court concluded that there was nothing in the record to indicate that the defendants sought to promote their generic versions of Yasmin based on the anti-androgenic or anti-aldosterone properties claimed in the '652 patent, the court rejected Bayer's claim that the defendants were liable for inducement of infringement under 35 U.S.C. § 271(b). The court therefore granted the motion and entered judgment of noninfringement in favor of Watson and Sandoz. Based on that ruling, Bayer and Lupin stipulated to, and the court entered, final judgment in

Bayer's suit against Lupin as well. *Bayer Schering Pharma AG v. Lupin Ltd*, No. 1:10-cv-05423 (S.D.N.Y. Dec. 8, 2010). Bayer took appeals from both judgments, and we consolidated the two cases for appeal.

III

As the district court correctly noted, the issue in these cases is a very narrow one. The following propositions are not in dispute: First, Bayer does not enjoy patent protection for the drug Yasmin or for the use of the drug for contraception alone. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341 (Fed. Cir. 2009). Second, the '652 patent claims a method of use consisting of simultaneously achieving an anti-androgenic effect, an anti-aldosterone effect, and a contraceptive effect in a premenopausal or menopausal female patient in need of all three effects. Third, the only proposed "indication for use" in the NDA application filed by Bayer's predecessor was for oral contraception, and the only use set forth in the "Indications and Usage" section of the label attached to the FDA's approval letter was "for the prevention of pregnancy in women who elect to use an oral contraceptive." Fourth, the Indications and Usage section of the defendants' ANDAs used the same language and did not refer to the other effects claimed in the '652 patent. And finally, the parties agree that under 35 U.S.C. § 271(e)(2)(A), the '652 patent can be infringed only if the defendants' ANDAs seek FDA approval to market Yasmin for the three simultaneous effects covered by the '652 patent.

In light of those uncontested propositions, Bayer's quarrel with the district court is limited to contending that the FDA *did* approve the use of Yasmin to obtain all three effects simultaneously in menopausal and premeno-

pausal patients in need of all three effects, and that the defendants' ANDAs seek FDA approval for the same uses. Bayer contends that its label for Yasmin demonstrates that the FDA approved the use of the drug for all three effects, and that the similar label to be used by the defendants on their generic version of Yasmin likewise covers the use of the drug to obtain all three effects simultaneously in patients needing that combined treatment. Therefore, according to Bayer, the defendants are liable for inducing infringement by physicians and patients because the label instructs the use of the generic drug to obtain the three effects claimed in the '652 patent. The district court rejected Bayer's argument, and so do we.

A

This court's 2003 decision in *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003), sets the framework for analyzing this case. In *Warner-Lambert*, the patentee received approval from the FDA to market a particular drug for use in treating epilepsy. Warner-Lambert's patent for use of the drug in treating epilepsy had expired, but Warner-Lambert had an unexpired patent claiming the use of the drug for treating neurodegenerative disease. That latter use of the drug, however, had not been approved by the FDA. Apotex, a generic manufacturer, filed an ANDA seeking approval to market a generic form of the drug for the approved use of treating epilepsy. Warner-Lambert sued under its unexpired patent, but this court held that it is "not an act of infringement [under section 271(e)(2)(A)] to submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved" by the FDA. *Id*. at 1354-55.

A second case from this court, decided the same year, is even more closely on point. In that case, *Allergan, Inc. v. Alcon Laboratories, Inc.*, 324 F.3d 1322 (Fed. Cir. 2003), Alcon, a generic drug manufacturer, filed an ANDA seeking approval to market the unpatented drug brimonidine for the FDA-approved use of reducing intraocular pressure. Allergan had two patents that claimed other uses for which brimonidine was effective: protection of the optic nerve and neural protection. Those uses, however, were not approved by the FDA. This court held that because those additional uses were not approved by the FDA, the generic drug applicant could not be liable for infringement under section 271(e)(2)(A), even though brimonidine necessarily had those protective effects in patients who took the drug for the approved purpose. *Id.* at 1324.

Based on *Warner-Lambert* and *Allergan*, the defendants' conduct would constitute infringement under section 271(e)(2)(A) (or inducement of infringement under section 271(b)) only if the defendants' ANDAs sought approval for the use protected by the '652 patent, i.e., for the combination of a gestagenic effect, an anti-androgenic effect, and an anti-aldosterone effect in patients needing that combination of effects. Because the defendants' ANDAs are substantively identical to Bayer's NDA, the use or uses for which the ANDAs seek FDA approval are necessarily the same as the uses for which the FDA has given its approval by granting Bayer's NDA. The question to be answered, then, is whether the FDA has approved the use of Yasmin to achieve the combination of the three effects claimed in the '652 patent.

B

The FDA-approved label for an approved drug indicates whether the FDA has approved a particular method of use for that drug. An NDA that seeks FDA approval for a particular use for a drug must include "full reports of investigations" demonstrating that the drug is safe and effective for that use, 21 U.S.C. § 355(b)(1)(A), and it must include "the labeling proposed to be used for such drug . . . ," *id.* § 355(b)(1)(F). The FDA determines whether the information submitted with the application shows that the drug is safe and effective for the use described in the submitted label. *See id.* § 355(d) (FDA approval requires showing that "drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" and that there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof"); *see also* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (2006) ("The centerpiece of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively.").

The label for Yasmin that was approved by the FDA states in the Indications and Usage section that "Yasmin is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive." As noted, that characterization tracks the FDA's approval letter for Yasmin, which stated that the NDA "provides for the use of Yasmin . . . for oral contraception."

In claiming that the label recognizes FDA approval of all three effects claimed in the '652 patent, Bayer relies on the "Pharmacodynamics" subsection of the "Clinical Pharmacology" section of the label, which recites that drospirenone, one of the two active compounds in Yasmin,

> is a spironolactone analogue with antimineralocorticoid activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

While that passage states that Yasmin exhibits antimineralocorticoid activity and has the potential for antiandrogenic activity based on animal studies, neither that passage nor anything else on the label provides any safety or efficacy information associated with the possible use of Yasmin in treating patients who are in need of those effects. Thus, while the label mentions potential antimineralocorticoid and anti-androgenic activity, it does not do so in any way that recommends or suggests to physicians that the drug is safe and effective for administration to patients for the purposes of inducing these effects.

The FDA labeling regulation, 21 C.F.R. § 201.57, makes clear that the FDA has not approved the use of Yasmin to produce the pharmacological effects that are listed in the Clinical Pharmacology section of the label. The portion of the regulation that is addressed to the Indications and Usage section of the label requires the indications set forth in that section to be supported by "substantial evidence of effectiveness based on adequate and well-controlled studies." *Id.* § 201.57(c)(2)(iv). The regulation adds that indications or uses "must not be

implied or suggested in other sections of the labeling if not included in this section." *Id.* The reference in the Clinical Pharmacology section of the label to the anti-mineralocorticoid and anti-androgenic activity of drospirenone is certainly not a direct indication of an appropriate use for Yasmin, and even if it could be considered an "implied or suggested" indication of an appropriate use, the regulation expressly states that such implied or suggested uses do not constitute approved uses.

In addition, the FDA regulation requires the label to provide a summary of the essential scientific information needed for the safe and effective use of the drug. *See* 21 C.F.R. § 201.56(a)(1). The Yasmin label does not provide physicians with such a summary with respect to the drug's anti-androgenic and anti-mineralocorticoid effects, which is a further indication that the FDA did not approve the use of Yasmin to exploit those effects in treating patients.

Bayer points out that the sections of the regulation directed to the Indications and Usage portion of the label address only "the portion of the labeling that can detail the diseases or conditions the FDA has approved the drug to treat," and that other effects "that do not treat a disease or condition . . . will not be in the Indications section and will still be FDA approved." However, whether other effects may be described outside the Indications and Usage section of the FDA-approved label does not address the issue in this case. The regulation states that the Clinical Pharmacology section of the label must include "a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or toxicity." 21 C.F.R. § 201.57(c)(13)(i)(B).

That section of the label is also required to describe the clinically significant pharmacokinetics of a drug or its active metabolites; information related to in vitro and animal studies is permitted to be included in that section of the label only if the information is "essential to understand dosing or drug interaction information presented in other sections of the labeling." *Id.* § 201.57(c)(13)(i). Thus, the fact that certain of the effects of a drug are described in the Clinical Pharmacology section of the label does not mean that the FDA has approved the use of the drug to produce those effects; it only ensures that physicians are aware of the full range of the drug's pharmacological effects (especially those that might be considered adverse effects) when prescribing the drug for a purpose set forth in the Indications and Usage section and under the conditions described in other parts of the label.

Bayer notes that FDA-approved methods of use do not invariably appear in the Indications and Usage section of the label. For example, an FDA-approved method of use relating to the dosage or method of administration of a drug would appear not in the Indications and Usage section, but in the "Dosage and Administration" section of the label. But that does not help Bayer in this case. The '652 patent is narrowly focused on simultaneously achieving three effects in premenopausal or menopausal patients in need of all three effects; as the parties stipulated, the claim limitation referring to a "patient in need thereof" means a patient with a "perceived need for" all three effects. The patent does not claim a method of achieving a contraceptive effect in a patient in need of contraception in which the drug used to achieve the contraceptive effect has two generally beneficial additional effects. To practice the method claimed in the '652 patent, a physician must determine that all three effects are needed by a specific premenopausal or menopausal

patient. FDA approval of that method of use would require a showing that Yasmin was safe and effective for simultaneously obtaining those three effects in patients needing those effects. Acknowledgement of the safety and efficacy of that specific method of use would be evidenced by including it in the Indications and Usage section of the label. Therefore, the point is not simply that the method of use was not described in the Indications and Usage section that shows lack of FDA approval; the point is that the label, taken in its entirety, fails to recommend or suggest to a physician that Yasmin is safe and effective for inducing the claimed combination of effects in patients in need thereof.

IV

Bayer relies on four pieces of evidence to support its argument that the references to anti-mineralocorticoid and anti-androgenic activity in the Clinical Pharmacology section of the Yasmin label indicate that the FDA has approved the use of Yasmin to induce those effects: (1) the FDA regulation that addresses the listing of patents in the Orange Book; (2) a declaration from Dr. Lee Shulman, a physician; (3) a declaration from Dr. Susan Allen, a former FDA official; and (4) marketing materials for Yasmin that were approved by the FDA. That evidence, however, demonstrates only that the FDA was aware that Yasmin could cause the effects discussed in the '652 patent. It does not go to the critical question of whether the FDA has found Yasmin to be safe and effective for the purpose of inducing those effects in a premenopausal or menopausal patient with a specific need for those effects. Absent that finding of safety and efficacy, and the recognition of such safety and efficacy on the Yasmin label, the Yasmin label cannot instruct (and the ANDA proposed

label cannot induce infringement of) the method of use claimed in the '652 patent.

A

Bayer first relies on the FDA regulation that addresses the requirement to submit patents for inclusion in the Orange Book, 21 C.F.R. § 314.53. Bayer argues that the regulation supports its contention that the FDA approved the pharmacological effects listed in the Clinical Pharmacology section of the Yasmin label because the regulation requires the submission not only of patents that claim "indications," but also patents that claim "other conditions of use." *Id.* § 314.53(b). In Bayer's view, that requirement shows that the FDA considered that infringement under section 271(e)(2)(A) could extend to the type of pharmacological effects detailed in the Clinical Pharmacology section of the Yasmin label. Bayer further contends that the regulation constitutes an interpretation of section 271(e)(2)(A), and that it is entitled to deference under *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).

Bayer's argument reflects a misinterpretation of section 314.53. The regulation implements the patent listing requirements of 21 U.S.C. § 355(b)(1), which requires a patent holder to submit those patents for listing in the Orange Book "with respect to which a claim of patent infringement could reasonably be asserted . . . ." The fact that Bayer submitted the '652 patent for inclusion in the Orange Book is not helpful to its case, for several reasons. First, the FDA does not make a determination as to whether particular patents should be listed in the Orange Book; it simply lists those patents that are submitted by patent holders. Second, the category of claims as to which infringement could reasonably be asserted is plainly

broader than the category of claims that are infringed. Section 355(b)(1) and its implementing regulations encourage broad disclosure and do not require NDA applicants to make an extrajudicial determination of actual infringement. Section 271(e)(2)(A) defines the filing of an ANDA as an act of infringement, but it does not alter the underlying patent infringement analysis, which requires in the case of a method-of-use patent that the accused infringer use the patented product for the use claimed in the patent. *See Warner-Lambert*, 316 F.3d at 1356. Nothing in the regulation provides any support for Bayer's position in this case.

B

Dr. Shulman, an obstetrician-gynecologist with experience in the clinical use of contraceptives, stated in his declaration that prescribing Yasmin as an oral contraceptive with the intent to produce an anti-mineralocorticoid pharmacological effect and an anti-androgenic pharmacological effect "is clearly stated and on-label." That opinion, however, is contrary to the contents of the FDA-approved label for Yasmin. The language of the Clinical Pharmacology section of the label does not indicate that the FDA has determined that the drug is safe or effective in inducing those effects in patients with a specific need for those effects, as claimed in the patent. *See Warner-Lambert*, 316 F.3d at 1356.

As to Yasmin's anti-mineralocorticoid effect, the label simply states that drospirenone is a spironolactone analogue "with antimineralocorticoid activity." It does not describe the extent of—or summarize the scientific evidence for—that activity in humans. The Dosage and Administration section of the label specifically describes the use of the Yasmin "[t]o achieve maximum contracep-

tive effectiveness"; it contains no discussion of the dosage required to achieve a therapeutic level of anti-mineralocorticoid effect. Even if knowing that drospirenone is a spironolactone analogue were all the information a physician would need to induce a desired therapeutic effect, the label contains no information regarding the safety of the drug in a patient needing such an effect.[1]

Similarly, as to Yasmin's anti-androgenic effect, the information in the Clinical Pharmacology section of the label indicates only that drospirenone has been shown to generate that activity in preclinical studies in animals. The FDA has not found the drug to be safe or effective in inducing an anti-androgenic effect in a human patient, and the label neither provides a statement to that effect nor summarizes any supporting research. Therefore, notwithstanding Dr. Shulman's understanding to the contrary, any prescription of Yasmin to produce either an anti-mineralocorticoid or anti-androgenic effect has not been approved by the FDA and is therefore "off label."

C

Dr. Allen, a former FDA official, stated that while she was at the FDA she oversaw the approval of the Yasmin NDA, including the preparation of final contents of the Yasmin label. Dr. Allen stated that the label indicates that the FDA approved Yasmin for a therapeutic effect

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[1] The dissent questions whether we are finding fault with the FDA procedures or the FDA-approved label. To the contrary, the lack of information on the label regarding dosage and administration to induce an anti-mineralocorticoid effect is completely appropriate for a drug that has not been found safe and effective for inducing that effect.

(contraception) and for the two additional pharmacological effects (the anti-mineralocorticoid and anti-androgenic effects). Regarding the pharmacological effects, Dr. Allen stated that listing those effects in the Clinical Pharmacology section of the label indicated that those effects were confirmed in Yasmin and are "'pertinent' to human use of the drug." However, just because those effects were confirmed and are "pertinent" to human use, and therefore important for a prescribing physician to be aware of, does not mean—as the dissent contends—that the drug is safe or effective for use in inducing those effects in a patient with a specific need for them. Moreover, Dr. Allen distinguished between the contraceptive effect of Yasmin and the other effects, stating that the FDA "approved" the "therapeutic effect (contraceptive)" and the "two additional pharmacological effects." Importantly, Dr. Allen did not say that Yasmin was approved for achieving those two additional effects in patients with a therapeutic need for those effects. Therefore, Dr. Allen's view of the effect of FDA approval does not draw into question the proposition that Yasmin was not approved for the purpose of inducing the three simultaneous effects recited in the '652 patent in premenopausal and menopausal patients.

D

Finally, Bayer argues that the FDA's approval of certain promotional materials highlighting the anti-mineralocorticoid and anti-androgenic properties of Yasmin indicates that the FDA approved those pharmacological effects. The problem with that argument is that the description of those effects is, in almost all cases, qualified. In the case of the anti-mineralocorticoid effect, the description is accompanied by a warning regarding the potential for hyperkalemia in high-risk patients. In the case of the anti-androgenic effect, the materials note

that this effect is "seen in preclinical studies." The FDA's regulations require such disclosure of "specific side effect[s] . . . in [approved] labeling." 21 C.F.R. § 202.1(e)(4). That treatment is in contrast to the "clinically proved benefits" of contraceptive efficacy and cycle control. The fact that Bayer was able to frame a required disclosure in a positive light without crossing the line into promoting such use does not mean that the FDA has approved a use not otherwise indicated in the approved label. *See* 21 C.F.R. § 202.1(e)(6)(i) (advertisement violates 21 U.S.C. § 352(n), among other reasons, if it "[c]ontains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is . . . useful in a broader range of conditions").

* * *

As applied to this case, *Warner-Lambert* and *Allergan* make clear that the defendants do not infringe Bayer's '652 patent under section 271(e)(2)(A) and that their sale of the generic form of Yasmin would not induce infringement of that patent. The defendants' ANDAs seek approval to market the generic form of Yasmin solely for contraceptive use, and there is no valid patent on the use of the drug for that purpose alone. The FDA-approved label for Yasmin does not indicate to physicians that the specific use claimed in the '652 patent, i.e., producing contraceptive, anti-mineralocorticoid, and anti-androgenic effects in premenopausal and menopausal women with a specific need of all three effects, is safe and effective. Therefore, we agree with the district court that the FDA has not approved such use and that the defendants cannot be held liable for infringement of the patent.

AFFIRMED

United States Court of Appeals for the Federal Circuit

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Plaintiffs-Appellants,

v.

SANDOZ, INC.,
Defendant-Appellee,

AND

WATSON PHARMACEUTICALS, INC., AND WATSON LABORATORIES, INC.,
Defendants-Appellees.

2011-1143, -1228

Appeal from the United States District Court for the Southern District of New York in Case Nos. 10-CV-5423 and 08-CV-3710, Judge Paul G. Gardephe.

NEWMAN, *Circuit Judge*, dissenting.

The district court dismissed this complaint on the pleadings under Fed. R. Civ. P. 12(c), thereby denying the patentee the opportunity to litigate infringement of its U.S. Patent No. 5,569,652 before the defendants market their generic counterpart of the Yasmin® product. My colleagues err in endorsing this dismissal, which is contrary not only to the Federal Rules and judicial precedent, but also to the premises of FDA generic drug practices and to the purposes of the Hatch-Waxman Act.

Motions for judgment on the pleadings pursuant to Rule 12(c) are considered under the same standards applicable to Rule 12(b)(6). *King v. Am. Airlines, Inc.*, 284 F.3d 352, 356 (2d Cir. 2002). Pleading standards are a matter of regional circuit law. *See CoreBrace LLC v. Star Seismic LLC*, 566 F.3d 1069, 1072 (Fed. Cir. 2009) ("The question . . . whether a Rule 12(b)(6) motion was properly granted is a purely procedural question not pertaining to patent law, to which this court applies the rule of the regional . . . circuit."). Review of the substantive patent law embodied in the pleadings is, however, in accordance with the law of this court.

The district court held, on the pleadings as a matter of law, that the generic counterpart of the Bayer product, brand name Yasmin®, does not infringe the '652 patent. My colleagues on this panel affirm, on the theory that some of the claimed properties of the Yasmin® product are not covered by the FDA-approved label, in part because these

properties are stated in a different part of the label. The FDA-approved label for Yasmin® recites use as an oral contraceptive in the section headed "Indications and Usage," and recites the properties of anti-androgenic activity (acne control) and anti-mineralocorticoid activity (diuretic effect) in the "Clinical Pharmacology" section. The '652 patent recites these three effects in the same claim.

The court holds that the listing of some of the Yasmin® properties in the Clinical Pharmacology section of the FDA label, instead of the Indications and Usage section, removes the generic counterpart of the Yasmin® product from the scope of the '652 claims. That ruling is in error, for the portion of the FDA label in which a product's properties are described is irrelevant to whether the patent is infringed by sale or use of the product. The court also finds, albeit incorrectly, that "the label, taken in its entirety, fails to recommend or suggest to a physician that Yasmin is safe and effective for inducing the claimed combination of effects in patients in need thereof," maj. op. 16, and holds that this also requires non-infringement on the pleadings, as a matter of law. Neither the district court, nor this court, conducted a standard infringement analysis.

The infringement question is whether sale or use of the generic equivalent of the Yasmin® product, in accordance with the representations in the ANDA with respect to FDA approval for the generic equivalent of Yasmin®, infringes the '652 patent. FDA approval is embodied in the approved label for the Yasmin® product. The court concentrates on the inclusion of the anti-androgenic and anti-mineralocorticoid activity in the Pharmacodynamics section of the label instead of the Indications and Usage section. The purpose of the Pharmacodynamics section is to describe "[i]mportant pharmacologic effects other than the main desired effect" of the drug product. *See* FDA *Draft Guidance*

for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products—Content and Format, cited at Rep. Br. 10. The court now propounds the theory that the FDA label for Yasmin® is required to include specific dosages for the anti-androgenic and anti-mineralocorticoid effects in the same section of the label as "the main desired effect," in order for the patent to be infringed. Maj. op. at 18-19 ("The Dosage and Administration section of the label specifically describes the use of the Yasmin '[t]o achieve maximum contraceptive effectiveness'; it contains no discussion of the dosage required to achieve a therapeutic level of anti-mineralocorticoid effect. Even if knowing that drospirenone is a spironolactone analogue were all the information a physician would need to induce a desired therapeutic effect, the label contains no information regarding the safety of the drug in a patient needing such an effect."). I can't tell whether the court is holding that the FDA label is fatally flawed, but even if the FDA were somehow remiss (I discern no evidence thereof), this does not render ineffective the patent directed to the combination of these three effects, all of which are set forth in the FDA label for which the generic producers have filed their ANDAs. The placement of these effects in the FDA-approved label does not immunize the identical generic counterpart from infringement.

The FDA's mission is to "protect public health by ensuring that . . . drugs are safe and effective." 21 U.S.C. §393(b). In *FDA v. Brown and Williamson Tobacco Corp.*, 529 U.S. 120 (2000), the Court explained that:

> Viewing the FDCA [Food, Drug, and Cosmetic Act] as a whole, it is evident that one of the Act's core objectives is to ensure that any product regulated by the FDA is "safe" and "effective" for its intended use. . . . This essential purpose pervades the FDCA

> . . . . The FDCA requires premarket approval of any new drug, with some limited exceptions, and states that the FDA "shall issue an order refusing to approve the application" of a new drug if it is not safe and effective for its intended purpose.

529 U.S. at 133-34.

The panel majority is incorrect in its statement that the safety and efficacy of the anti-androgenic and anti-mineralocorticoid effects were never reviewed by the FDA. Maj. op. at 16 ("Absent that finding [by the FDA] of safety and efficacy, and the recognition of such safety and efficacy on the Yasmin label, the Yasmin label cannot instruct (and the ANDA proposed label cannot induce infringement of) the method of use claimed in the '652 patent."). The Clinical Pharmacology section of the Yasmin® label discusses these effects of the active ingredient drospirenone: "Drospirenone is a spironolactone analogue with antimineralocorticoid activity. . . . Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity."

The record contains, among other evidence, the expert declaration of Dr. Allen, FDA past Director of the Division of Reproductive and Urologic Drug Products, that these effects were demonstrated when Yasmin® was presented for FDA approval. Dr. Allen states:

> Each of the three effects identified in Claim 11 of the '652 Patent are listed in the professional labeling for Yasmin®. . . . The inclusion of statements describing these three effects in the FDA-approved labeling means that the FDA approved (a) the therapeutic effect (contraceptive) and (b) the two additional pharmacological effects (anti-androgenic and anti-mineralocorticoid) of Yasmin®.

When the FDA approved the Yasmin® NDA, it "concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling test." FDA Approval Letter (May 11, 2001). Dr. Shulman, a leading obstetrician-gynecologist with extensive experience in oral contraceptive research and clinical use, stated in his declaration that prescriptions of Yasmin® as an oral contraceptive with intent to produce the two further pharmacological effects are "on-label," and that he prescribes Yasmin® for these additional pharmacological effects. Dr. Shulman stated:

> The physician labeling for Yasmin® contains the data supporting the use of Yasmin® in the treatment method of claim 11 of the '652 patent. . . . Because drospireneone has anti-mineralocorticoid activity as disclosed in the Clinical Pharmacology section, the prescription of Yasmin® as an oral contraceptive with the intent to produce an anti-mineralocorticoid pharmacological effect is clearly stated and on-label . . . . Because drospireneone has anti-androgenic activity, the prescription of Yasmin® as an oral contraceptive with the intent to produce an anti-androgenic pharmacological effect is clearly stated and on label. . . . I have prescribed Yasmin® for premenopausal women in accordance with claim 11 of the '652 patent, continue to do so, and consider such prescriptions to be on-label.

In *Bell Atlantic Corp. v. Twombly*, 550 U.S. 544 (2007), the Court cautioned that "Rule 12(b)(6) does not countenance . . . dismissals based on a judge's disbelief of a complaint's factual allegations." 550 U.S. at 556 (quoting *Neitzke v. Williams*, 490 U.S. 319, 327 (1989)). Bayer has sufficiently alleged that an "intended use" for Yasmin®, as approved by

the FDA, is the simultaneous treatment of all three effects. The majority's statement at n.1 that Yasmin® "has not been found safe and effective" is contrary to the record.

All of the defendants state in their ANDAs that their product is identical to the Yasmin® product and that the biological effects are identical, with no carve-outs from the methods and uses set forth on the FDA label. Contrary to representations made on this appeal, defendant Sandoz described Yasmin® to the district court as "the only drug that combines the properties of oral contraception, antimineralocorticoid (antialdosterone), and anti-androgenic properties, which cause exceptional control of acne and greatly reduced fluid retention." J.A. 1212. Sandoz stated that "[n]o other product offers this combination of therapeutic properties and contraception." J.A. 1216.

The evidence before the district court, presented in response to this motion, supported the statement in Bayer's complaint that a "significant proportion of drospirenone and ethinylestradiol prescriptions are written with the intent of producing three pharmacological effects – gestagenic, antialdosterone, and anti-androgenic." Even were these threshold facts disputed – and they were not – it is improper for a court to make contrary findings under Rule 12(c). In considering a motion to dismiss, "the court is to accept as true all facts alleged in the complaint." *Kassner v. 2nd Ave. Delicatessen Inc.*, 496 F.3d 229, 237 (2d Cir. 2007).

My colleagues hold that the '652 patent cannot be infringed, as a matter of law, unless the label specifically authorizes physicians to prescribe Yasmin® to treat acne or as a diuretic. Maj. op. at 19. This criterion of infringement is as irrelevant as it is factually incorrect. Bayer states, and the record adduced on this motion supports, that "Bayer promoted the '652 patented method because Yasmin®'s

unique pharmacological profile differentiated it from other oral contraceptives. The FDA pre-cleared advertising containing this promotion because it is consistent with Yasmin®'s FDA-approved labeling," Rep. Br. 27. No contrary evidence is in the record. The adverse inferences drawn by the district court and the adverse findings made by this court are inappropriate as well as incorrect, for it is not disputed that all of the defendants seek approval of their Yasmin® counterpart on representations of chemical and biological identity to the approved Yasmin® product.

The infringement inquiry is whether the generic counterpart, when used in accordance with its proposed ANDA authorization, would infringe the patent. The Hatch-Waxman Act does not alter the inquiry into infringement. As summarized in Harman, *Patents and the Federal Circuit* 494 n.161 (9th ed. 2009): "The inquiry under § 271(e)(2) is a standard infringement test. The only difference is that the allegedly infringing drug has not yet been marketed and therefore the question of infringement must focus on what the ANDA applicant will likely market if its application is approved." *See also Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1366 (Fed. Cir. 2003) ("The proper inquiry under § 271(e)(2)(A) is whether, if a particular drug were put on the market, it would infringe the relevant patent.").

Whether a patent is infringed is a question of fact, and cannot be resolved on pleadings by adverse inference or assumption. Contrary to the theory of the panel majority, *Warner-Lambert* does not support this dismissal. In *Warner-Lambert* the patented neurodegenerative use was not the label-approved use, and was not the use for which the ANDA was submitted. 316 F.3d at 1364 ("In the absence of any evidence that Apotex has or will promote or encourage doctors to infringe the neurodegenerative method patent [for the "off-label" use], there has been raised no genuine

issue of material fact."). In contrast, for Yasmin® it is not disputed that the three properties recited in the patent claim are coextensive with the FDA-approved label. Bayer's complaint, and the several declarations provided in response to this motion, show that the FDA so recognized, and also show that physicians prescribe Yasmin® for this combination of effects. The court errs in ruling as a matter of law that the FDA-approved label for Yasmin® does not encompass the three effects stated in the label and claimed in the '652 patent. Bayer's complaint contains well pleaded and well-supported factual allegations, and states a plausible claim of infringement. The complaint "state[s] a claim for relief that is plausible on its face." *Twombly*, 550 U.S. at 570.

This appeal is from dismissal and judgment on the pleadings. However, a plaintiff's nonconclusory factual allegations must be taken as true at this stage. *See Swerkiewicz v. Sorema N. A.*, 534 U.S. 506, 508 n.1 (2002) (on a motion to dismiss, the court "must accept as true all of the factual allegations contained in the complaint."). These firm premises are reinforced in *Ashcroft v. Iqbal*, 556 U.S. 662 (2009). Yet the court discounts Bayer's factual allegations, creating adverse inferences unrelated to either FDA approval or the criteria of infringement. *See Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1331 (Fed. Cir. 2003) ("a court must employ a traditional infringement analysis, focusing on all elements of infringement"). The court in *Allergan* explained once again that the "only difference in the analysis of a traditional infringement claim and a claim of infringement under section 271(e)(2) is the timeframe under which the elements of infringement are considered." *Id.*

Bayer is entitled to the opportunity to resolve patent infringement at the Hatch-Waxman stage. Dismissal of the

complaint was contrary to the premises of the Federal Rules, and contrary to the purposes of the Hatch-Waxman Act. I respectfully dissent.