United States Court of Appeals for the Federal Circuit

FERRING B.V.,
Plaintiff-Appellant,

v.

WATSON LABORATORIES, INC. - FLORIDA,
Defendant,

AND

APOTEX, INC., AND APOTEX CORP.,
Defendants-Appellees.

2014-1377

Appeal from the United States District Court for the District of Nevada in Nos. 3:11-cv-0481-RCJ-VPC, 3:11-cv-0485-RCJ-VPC, 3:11-cv-00854-RCJ-VPC and 2:12-cv-01941-RCJ-VPC, Judge Robert Clive Jones.

Decided: August 22, 2014

JAMES B. MONROE, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Washington, DC, argued for plaintiff-appellant. With him on the brief were PAUL W. BROWNING, JUSTIN J. HASFORD and MARY E. CHLEBOWSKI.

DONALD R. MCPHAIL, Cozen O'Connor, of Washington, DC, argued for defendants-appellees. With him on the brief were BARRY P. GOLOB, KERRY B. MCTIGUE, W. BLAKE COBLENTZ, and AARON S. LUKAS.

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

DYK, *Circuit Judge.*

Ferring Corporation ("Ferring"), the owner of U.S. Patent Nos. 7,947,739 ("the '739 patent"), 8,022,106 ("the '106 patent"), and 8,273,795 ("the '795 patent") (collectively, the "patents-in-suit"), alleges that Apotex Corporation ("Apotex") infringed each and every claim of the patents-in-suit by filing an Abbreviated New Drug Application ("ANDA"). The United States District Court for the District of Nevada dismissed Ferring's claims as moot in light of Apotex's amendment to its ANDA which rendered the ANDA non-infringing. We affirm.

BACKGROUND

Tranexamic acid, the active ingredient in Ferring's patented product, is used to treat heavy menstrual bleeding, or menorrhagia, in women. Tranexamic acid has been widely used in an immediate release formulation for more than three decades to treat menorrhagia in other countries. The inventors of the patents-in-suit sought to develop a tranexamic acid formulation with fewer gastrointestinal side effects than the immediate release version used abroad, but with the same benefits. They attempted to do so by creating a formulation with a tranexamic acid release rate that matched the rate of absorption in the gastrointestinal tract. Ultimately, the inventors designed a modified-release formulation that would provide the same overall dosage of tranexamic acid, but reduce irritation of the gastrointestinal system with lower dosages released at a time.

Ferring's commercial product embodying the patented invention is known as Lysteda. In 2004, the Food and Drug Administration ("FDA") approved a fast-track designation for approval of Lysteda, and the Lysteda New Drug Application ("NDA") was approved in 2009. Lysteda is the first tranexamic acid drug approved by the FDA for treating menorrhagia in the United States.

Ferring[1] filed the applications that gave rise to the '795, '106, and '739 patents in 2008, 2009, and 2010, respectively. The '739 and '106 patents issued in 2011, and the '795 patent issued in 2012. Representative claim 1 of the '106 patent recites:

> 1. A tranexamic acid oral dosage form comprising:
>
> tranexamic acid or a pharmaceutically acceptable salt thereof; and
>
> a modified release material . . . ;
>
> wherein the modified release material is present in the formulation in an amount from about 10% to about 35% by weight [*i.e.*, "wt%"] of the formulation;
>
> wherein said dosage form provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5°C., of less than about 40% tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, less than about 70% by weight tranexamic acid or

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[1] The original patent applications were filed by Xanodyne Pharmaceuticals, Inc. Ferring purchased Lysteda and the rights to the patents-in-suit in 2010. We refer to Ferring and its predecessor as Ferring.

> pharmaceutically acceptable salt thereof released at about 45 minutes and not less than about 50% by weight of said tranexamic acid or pharmaceutically acceptable salt thereof released by about 90 minutes; and
>
> wherein each tranexamic acid oral dosage form provides a dose of about 650 mg tranexamic acid.

'106 Patent col. 68 l. 60 to col. 69 l. 21.

The issue of infringement here relates entirely to dissolution rates, *i.e.*, the rate at which the salt dissolves into water. The following chart shows the dissolution rates specified in the asserted claims of the patents-in-suit:

Claimed Dissolution Rates of Patents-in-Suit			
	'739 patent, claim 1	**'106 patent, claim 1**	**'795 patent, claim 1**
15 minutes	No limitation	< 40 wt%	< 40 wt%
45 minutes	< 70 wt%	< 70 wt%	< 70 wt%
90 minutes	No limitation	≥ 50 wt%	≥ 50 wt%
120 minutes	100 wt%	No limitation	No limitation

Apotex sought to market a generic version of Lysteda. It attempted to design a generic product that would avoid infringement of Ferring's patent applications, but that would be bioequivalent to Lysteda. Apotex submitted its initial ANDA to the FDA on August 31, 2010 ("2010

ANDA"), seeking FDA approval for its generic version of Lysteda. The 2010 ANDA only had one dissolution specification: that at least 80 percent by weight of the active ingredient (tranexamic acid) would dissolve in 60 minutes.

After the '739 patent issued, Apotex filed a paragraph IV certification that the generic product specified in the 2010 ANDA did not infringe. Ferring then sued Apotex for infringement of the '739 patent. When the '106 and '795 patents issued, Apotex submitted paragraph IV certifications for those patents as well, and Ferring filed new complaints against Apotex asserting infringement of the newly issued patents. The three cases were consolidated with a suit that Ferring had filed against Watson Laboratories, Inc – Florida ("Watson") concerning the same patents.[2]

In 2012, the district court held a *Markman* hearing to construe the disputed terms. Although a number of terms were at issue, the only relevant construction for the purposes of this appeal is of the term "about" to mean "approximately." "About" is used in the patents-in-suit multiple times. However, only one use is relevant to this appeal: where it is used to describe the amount of tranexamic acid released at specified times (*e.g.*, "less than *about* 70% by weight . . . at about 45 minutes," '739 patent col. 69 ll. 61–63 (emphasis added)). Both parties suggested that "about" should be construed to demarcate particular numerical ranges, but disagreed as to what those

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[2] Watson also had filed an ANDA seeking to market a generic version of Lysteda, and certified that the ANDA was not infringing. Ferring then sued Watson. We today decide Watson's companion appeal, No. 14-1416, holding that Watson's product did not infringe Ferring's patents, which also were not shown to be invalid.

numerical ranges should be. Ferring proposed that "about 70% by weight" includes quantities within 10 percent of the 70 percent by weight specified value (*e.g.*, from 63 to 77 percent by weight at 45 minutes), and Apotex proposed that "about" means "plus or minus 5 percent by weight of the stated value" (*e.g.*, from 66.5 to 73.5 percent by weight at 45 minutes). J.A. 2505. The district court declined to adopt a numerical range and ruled that "'about' means 'approximately.'" J.A. 2506.

In January 2014, the district court held a trial on infringement. At trial, Ferring conceded, and the district court found, that Apotex's actual product, based on its dissolution sample data, did not infringe the patents-in-suit under 35 U.S.C. § 271(a). However, the district court, analyzing Apotex's 2010 ANDA under *Sunovion Pharmaceuticals, Inc. v. Teva Pharmaceuticals, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013), concluded that because the 2010 ANDA was silent with respect to the weight percent of tranexamic acid released at the times specified in the patent-in-suit, the ANDA permitted Apotex to sell an infringing product and "permitted [Apotex] to violate the patent." J.A. 8945. However, at trial, Apotex agreed to amend its ANDA specification to include a restriction that not less than 75 percent by weight of the tranexamic acid was released at 45 minutes. The district court made a finding at trial that a tablet with such a dissolution rate by weight at 45 minutes would be outside the scope of the patents-in-suit, and therefore, Apotex's proposed amendment would be outside the scope (because the amount was in excess of "the about 70% by weight" permitted by the patent claims), and would not be enjoined.

After trial, Apotex amended its ANDA on February 10, 2014 (the "February 2014 amendment"), to specify that "not less than 75%" by weight tranexamic acid would be dissolved at 45 minutes" (the "2014 ANDA"). J.A. 3634. The FDA approved the change on February 21,

2014. At a hearing on March 5, 2014, the district court concluded that the 2014 ANDA did not infringe the patents-in-suit. At this hearing, Apotex also agreed to stipulate and inform the FDA that both the district court and Ferring would be notified if Apotex ever attempted to change the dissolution specification in the future. Accordingly, on March 18, 2014, Apotex sent an additional letter to the FDA specifying that

> [t]he Honorable Judge Jones [*i.e.*, the district court judge] has therefore instructed Apotex to inform the FDA that Apotex will stipulate that its additional specification of [not less than] 75% in 45 minutes will not be removed from its ANDA *without first informing the Court, counsel for Ferring and the FDA*. Further, this stipulation will be referenced in a court-enforceable judg[]ment and order to be entered by the Court.

J.A. 5000 (emphasis added). The FDA acknowledged the second letter on March 19, 2014.

On March 24, 2014, the district court dismissed the case and "found that Apotex's [2010] ANDA No. 202286 infringed [the patents-in-suit]," but concluded that "Apotex having Stipulated to amend its ANDA No. 202286 [*i.e.*, the 2014 ANDA] . . . moots Plaintiff's Complaint with regard to Apotex's proposed ANDA amendment." J.A. 18.

Ferring appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).[3]

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[3] Ferring argues that we cannot consider whether the original 2010 ANDA is not infringing because Apotex has not filed a cross-appeal. However, this is simply an alternative ground for denial of relief to Ferring and would not enlarge the district court's judgment. Therefore, no cross-appeal was required.

DISCUSSION

We address whether either of Apotex's filed ANDAs—the original 2010 ANDA or the amended 2014 ANDA—infringed the patents-in-suit.

I. 2010 ANDA Infringement

Apotex's 2010 ANDA specified that "NLT [*i.e.*, not less than] 80% . . . of the labelled amount of tranexamic acid dissolved in 60 minutes." J.A. 5067. The district court concluded that under *Sunovion*, Apotex was infringing because Apotex *could* violate the patents-in-suit based on the 2010 ANDA, and Ferring makes the same argument on appeal. We disagree. *Sunovion* only applies when "an ANDA specification defines a compound such that it meets the limitations of an asserted claim." 731 F.3d at 1280. In *Sunovion*, that was the case. The ANDA specified an infringing product. *Id.* The *Sunovion* court concluded that a generic drug company could not then avoid infringement by certifying that it would not infringe, overriding the language of its own ANDA. *Id.* Here, however, the ANDA does not "clearly describe[] a product that meets the limitations of the asserted claims." *Id.* at 1280. Rather, the 2010 ANDA is silent with respect to the claim limitations of the patents-in-suit, which do not specify dissolved dissolution rate at 60 minutes.[4]

When an ANDA is silent with respect to infringement, as is the 2010 ANDA, the correct analysis is under *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570 (Fed. Cir. 1997), not *Sunovion*. *See also Sunovion*, 731 F.3d at 1279–80 ("In *Glaxo*, we likewise upheld a judgment of no

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[4] Ferring also contends that 80 percent by weight dissolution at 60 minutes is contained within one of its preferred embodiments. But claims are not measured by the preferred embodiments, but by the claim language.

literal infringement because the ANDA application specified only that the generic product would have one crystalline form with certain purity, but did not reveal whether a different crystalline form claimed by the asserted patents would be present at all." (citing *Glaxo*, 110 F.3d at 1569)). In *Glaxo*, the patent-holder argued, as Ferring does here, that "the alleged infringer must disprove infringement if the ANDA permits sale of a composition that may include an infringing product." 110 F.3d at 1567. We disagreed and concluded that "[t]he relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product. What is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists." *Id*. at 1570. For the patent-holder to prove that a *Glaxo*-type ANDA is infringing, it must rely on evidence that the ANDA applicant "would likely sell an infringing composition pursuant to an approved ANDA." *Id*.

Here, in accordance with *Glaxo*, Apotex has provided bio-batch data that shows what Apotex is likely to sell. Ferring's expert testified that none of the tablets produced by Apotex in discovery was infringing. At trial, Ferring conceded that "there's [no] basis for [the district court] to find Apotex has violated 271(a)," *i.e.*, that the product being sold by Apotex did not infringe the patents-in-suit. J.A. 8875:9–10. Therefore, the evidence shows that Apotex is *not* likely to sell an infringing product and that the district court erred in finding that the 2010 ANDA was infringing.

II. 2014 ANDA Infringement

We must also determine whether the ANDA now in effect infringes the patents-in-suit. Apotex amended that ANDA in 2014 in an effort to preclude infringement. Apotex's 2014 ANDA—the 2010 ANDA with the February

2014 amendment—specified that "each unit dissolved NLT [*i.e.*, not less than] 75% [by weight tranexamic acid] in 45 minutes." J.A. 3634. We first address whether the 2014 ANDA, stating that not less than 75 percent by weight tranexamic acid would be dissolved at 45 minutes, would likely infringe the patents-in-suit. The district court concluded that the 2014 ANDA would not infringe because the patents-in-suit required that *less than* about 70 percent by weight tranexamic acid be dissolved at 45 minutes, and therefore, the February 2014 amendment mooted Ferring's complaint. The district court construed the term "about" as "approximately," rejecting Ferring's proposed construction limiting the term to a particular numerical range.

Ferring argues that the 2014 ANDA infringes because Ferring's proposed construction of "about" to mean ± 10 percent should have been adopted by the district court, and, under that construction, the patented range of dissolution at 45 minutes would include from 63 to 77 percent by weight dissolution. Under this construction, the 2014 ANDA would infringe because 75 percent by weight dissolution would fall within the above patented range.

We disagree with Ferring's proposed construction. The reference in the specification that Ferring claims creates a tolerance does no such thing. The basis for Ferring's proposed construction is the claims' reference to the United States Pharmacopeia ("USP") 27 Type II Paddle Method. Ferring argues that under this method, test results may reflect plus or minus 10 percent of the stated value, *i.e.*, that "less than about 70% by weight" would mean less than 63 to 77 percent by weight. That is not what USP 27 states. USP 27 provides that

> In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within 10% of the specified

> weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.

J.A. 3820.

The USP cited by Ferring does not create a tolerance but, rather, provides that where a dissolution rate is measured using 900 mL volume as the patents-in-suit require, a chemist may use a volume of 810 mL or 990 mL sample for the assay. However, the chemist must still calculate the 70 percent by weight based on the exact volume of the sample actually used. The dissolution rate calculated based on that volume must be exact—"the calculated result is based upon the exact amount taken." J.A. 3820. Therefore, the USP does not suggest that "about 70% by weight" should be interpreted to include a 10 percent error tolerance.

"About" is not defined either explicitly or by implication by the specification. We think that the district court did not err in giving the term "about" its ordinary meaning and in refusing to give it a more specific construction. *See also Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1369–70 (Fed. Cir. 2005) (the term "about" should be given its ordinary and accepted meaning of "approximately" unless the patentee clearly redefines "about" in the specification). We affirm the district court's construction of "about" to mean "approximately," as well as its refusal to construe "about" to represent a particular numerical error rate. Under the circumstances it fell to Ferring, the party with the burden of proof on infringement, to produce evidence that the 2014 ANDA infringed by proposing a 75 percent by weight dissolution rate, under the district court's claim construction. Ferring produced no such evidence and made no claim that the

ANDA infringed under the district court's claim construction.[5]

We conclude that the 2014 ANDA specification speaks directly to the question of infringement and would not permit Apotex to market an infringing product.

Alternatively, Ferring objects to the district court's decision to consider the 2014 ANDA, stating that 35 U.S.C. § 271(e)(4)(A) requires that once a section 271(e)(2) infringement is found based on the ANDA as first submitted, the district court *must* order a change in the effective date of the ANDA. Section 271(e)(2) provides that

> [i]t shall be an act of infringement to submit—an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act [*i.e.*, 21 U.S.C. § 355(j)] . . . for a drug claimed in a patent or the use of which is claimed in a patent . . . 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 . . . claimed in

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[5] While Ferring does not argue for infringement under the district court's construction of "about" to mean "approximately," it does argue that there is infringement under Apotex's proposed construction of "about" to mean ±5 percent. This involves a meaningless apples to oranges comparison. Under the ±5 percent construction, the "about 70% by weight" in the patent could mean as high as 73.5 percent. Because the ANDA allows a 5 percent variance in the weight of the tablet, comparing the total weight at the higher end (682.5 mg) with the amount dissolved using 75 percent by weight rate at 45 minutes using the sample size required by the patent (650 mg) yields a 71.4 percent dissolution rate, which is lower than 73.5 percent. There is no basis for making a calculation that utilizes tablets of different sample weights.

> a patent or the use of which is claimed in a patent before the expiration of such patent.

35 U.S.C. § 271(e)(2). Section 271(e)(4)(A) specifies that "[f]or an act of infringement described in [§ 271(e)(2)] 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." 35 U.S.C. § 271(e)(4)(A) (emphasis added). The district court is not precluded from considering an amended ANDA when deciding the issue of infringement.

Both section 355(j), referred to in section 271(e)(2), and the FDA's regulations contemplate that a pending application may be amended for various reasons.[6] For the purposes of section 271(e)(2), "an application" means the ANDA as filed and all amendments to that application that have been allowed by the FDA. There is no support for the proposition that the question of infringement must be addressed solely based on the initial ANDA filing, given that the statute contemplates that the ANDA will

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[6] For example, an applicant may amend and resubmit an application if the FDA refuses to file the initial application for various reasons, including where the reference drug is entitled to a 5-year exclusivity period. 21 C.F.R. § 314.101(a)(3); *see also* 21 U.S.C. § 355(j)(D)(ii) ("nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength"); 21 C.F.R. § 314.102(b) (permitting applicants to correct application deficiencies by amendment during the review process); *id.* § 314.100 (different review timelines when applicant submits a major amendment). Newly submitted data can also provide the basis for approval of a previously refused, suspended, or withdrawn drug application. *Id.* § 314.160.

be amended as a matter of course. Nor does it appear that Ferring contends otherwise.

Indeed, our own precedent conclusively establishes that sections 271(e)(2) and (4) require consideration of the amended ANDA. In *Bayer AG v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241 (Fed. Cir. 2000), the alleged infringer—a generic drug company—filed its ANDA and paragraph IV certification in 1997, whereupon it was sued for § 271(e)(2) infringement. *Id.* at 1246. In 1998, the generic drug company amended its ANDA to avoid infringement. *Id.* The district court in *Bayer* looked only to the language of the 1998 ANDA and concluded that the generic drug company did not infringe. *Id.* at 1246–47 We affirmed. *Id.* at 1249–50. We concluded there that an amended ANDA that addresses the issue of infringement and precludes such infringement is generally dispositive. *Id.*[7] Here, the conclusion is equally clear—the 2014 ANDA shows that Apotex is not permitted to sell an infringing product.

However, Ferring contends that this case is different from *Bayer* because the ANDA was amended after the finding of infringement. But the statute does not refer to the date of the infringement determination by the district court. Instead, it refers to the date that the ANDA was filed, and we have already determined that, in this respect, the statute refers not to the initial filing but to the filing as amended. A district court may reconsider its own finding of infringement in light of an amended ANDA or

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[7] We note that in other cases the challenged original ANDA was amended during the pendency of litigation. In those cases, this court and the district court considered the amended ANDA in determining the issue of infringement. *See Sunovion*, 731 F.3d at 1274–75, 1278.

other information. Only when the district court has entered a judgment finding that the operative ANDA infringes must it enter a § 271(e)(4) resetting order. We do not suggest that a district court must always consider any ANDA amendment. Allowing an amendment is within the discretion of the district court, guided by principles of fairness and prejudice to the patent-holder.

Here, the district court concluded at trial that the 2010 ANDA permitted Apotex to infringe, but agreed not to enter an injunction or resetting order because Apotex agreed to amend its ANDA. We conclude that the district court did not abuse its discretion in reconsidering its judgment of infringement in light of Apotex's amendment.

Ferring also argues that its complaint was not mooted by Apotex's amendment. A case becomes moot when interim relief or events have eradicated the effects of a defendant's act or omission, and there is no reasonable expectation that the alleged violation will recur. *County of Los Angeles v. Davis*, 440 U.S. 625, 631 (1979). In cases where a defendant voluntarily ceases the challenged practice, it is necessary for the court to determine whether "there is no reasonable expectation that the wrong will be repeated." *United States v. W.T. Grant Co.*, 345 U.S. 629, 633 (1953). As a result, "'a defendant claiming that its voluntary compliance moots a case bears the formidable burden of showing that it is absolutely clear the allegedly wrongful behavior could not reasonably be expected to recur.'" *Already, LLC v. Nike, Inc.*, 133 S. Ct. 721, 727 (2013) (quoting *Friends of the Earth, Inc. v. Laidlaw Envtl. Servs. (TOC), Inc.*, 528 U.S. 167, 190 (2000)).

Ferring makes no argument that Apotex would file an infringing ANDA in the future. Apotex's 2014 amendment meets the governing standard. Apotex cannot sell an infringing product without modifying its ANDA. If

Apotex introduced a drug into interstate commerce without complying with the FDA approval process, it would be subject to additional penalties, including criminal sanctions or seizure of the unapproved drug. *Bayer*, 212 F.3d at 1250 (citing 21 U.S.C. §§ 331(d), 332(a), 333(a), 334(a)(1), 335a). Here, as in *Bayer*, "if [the generic drug company] attempts to change its ANDA specification, it must pursue approval of the change(s) [with the FDA]. Thus, [the patent-holder] would be able to sue under 35 U.S.C. § 271(e)(2)(A) if any proposed change puts the drug's [specification] into an infringing range." *Id*. Here too, Apotex has agreed to notify Ferring and the district court if an amendment to the ANDA is filed with the FDA. Therefore, even if the 2010 ANDA were infringing, the 2014 ANDA is properly considered for the purposes of § 271(e)(2) infringement, and any allegedly infringing conduct is unlikely to recur, given the restrictions that Apotex has placed on the amendment and the FDA's own governing statute.

Finally, Ferring argues that it was prejudiced by Apotex's late amendment of the ANDA, which precluded Ferring from presenting evidence at trial on the issue of infringement. But even at trial the district court made clear that it was inclined to allow an amendment by Apotex clarifying the dissolution rate of its product, and the district court judge discussed the language of the amendment on the record on January 30, 2014. Ferring did not request to reopen the record to submit additional evidence.[8] At the hearing on March 5, 2014, after Apotex's amendment had been approved, Ferring never requested that the district court reopen the record to

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[8] Ferring also argues here that it needed additional discovery to determine if Apotex's 2014 amendment was infringing, but Ferring never requested such discovery.

address infringement by the 2014 ANDA. In its appellate brief, Ferring even stated that it had "presented undisputed evidence," Appellant's Br. 45, relevant to the question of whether Apotex's ANDA infringed and relied on this evidence to argue that Apotex's 2014 ANDA was infringing. Ferring did not show what evidence it would have proffered if the record were reopened. Therefore, we conclude that Ferring has not shown that it was prejudiced by the timing of Apotex's amendment.

We affirm on the ground that Ferring has not established that either Apotex's 2010 or 2014 ANDA infringes the patents-in-suit.

AFFIRMED

COSTS

Costs to Apotex.