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What Form Is It? Lessons from 13 Polymorph Pharmaceutical Cases



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Introduction

Generic pharmaceutical companies are required to address all Orange Book-listed patents when filing an ANDA, either through acquiescence or challenge. Increasingly, these companies are being forced to consider patents covering polymorphic forms of the active ingredient. Under FDA regulations, different polymorphs of an active substance are considered the “same” drug under Hatch-Waxman. This provides generic manufacturers with the option of trying to design around polymorph patents, in addition to pursuing a traditional invalidity challenge. To assess the risks and rewards for generic and brand firms alike, this article introduces the current landscape of polymorph patent litigation and attempts to provide insight for future strategy.

Hatch-Waxman Background

Congress adopted the Hatch-Waxman Act, formally known as the Drug Price Competition and Patent Term

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Restoration Act of 1984, P.L. 98-417, to expedite and streamline both generic drug approvals and patent litigation involving generic drugs. To achieve the first goal, the Act allows drug companies (usually a generic company) to file an abbreviated application to the Food & Drug Administration (FDA) for a drug that has been previously approved by the FDA for another company (usually a brand company). This shortened application is called an Abbreviated New Drug Application (ANDA). Under Hatch-Waxman, a generic pharmaceutical company’s ANDA must have an active ingredient that is the “same as” the brand company’s Reference Listed Drug (RLD).¹ FDA regulations implementing this requirement provide that the term “same as” requires, *inter alia*, the ANDA and RLD products be “identical in active ingredient(s).”² In a 2007 guidance interpreting the “same as” requirement, the FDA stated that different polymorphic forms of the active ingredient in the RLD will be considered the same, and thus can be filed as an ANDA.³ As such, there is no regulatory bar to a generic company’s use of a different polymorph.

However, a brand company’s patent(s) may be a barrier to using some or all known polymorphs of a drug substance. The Hatch-Waxman Act allows brand companies to sue the generic company for patent infringement before the generic company begins to sell its product to consumers. To do so, a generic drug manufacturer submits a statement called a “Paragraph IV

¹ 21 U.S.C. § 355(j)(2).

² 21 C.F.R. § 314.92(a)(1).

³ FDA Guidance for Industry, ANDAs: Pharmaceutical Solid Polymorphism, Chemistry, Manufacturing, and Controls Information, July 2007 (“Polymorphism Guidance”), at 3 (“differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals within the meaning of the Act and FDA regulations”).

certification” with its ANDA stating that any patents that the brand company listed in the FDA’s Orange Book⁴ are invalid, unenforceable, or will not be infringed by the generic company’s proposed product. The Hatch-Waxman Act made submitting a Paragraph IV certification an act of patent infringement, allowing the brand company to sue the generic company for patent infringement based on the Paragraph IV certification and the ANDA before the generic company actually markets or sells its products.⁵

Scientific Background

A threshold for considering the patent landscape of “polymorphs” is to define that term.⁶ On a high level, polymorphism is the ability of a specific chemical composition (like a drug substance) to crystallize in more than one solid-state form. One common example related to polymorphism is how carbon atoms form both diamond and graphite. Crystallinity is central to understanding polymorphism. The structural differences in different polymorphs can affect various properties of the drug substance, including the melting point, dissolution rates, hardness, and stability. Crystal structures that have a slightly different molecular composition, such as solvates and hydrates, are often considered polymorphs in the ANDA context.⁷ In a solvate, the molecules of the solvent are “trapped” in the spaces between the drug molecules in the crystal structure. When the trapped solvent is water, the solvate is called a hydrate.

Polymorphs can be identified and characterized by a number of analytical methods. Two common methods used to define a polymorph in pharmaceutical patent claims are: 1) powder x-ray diffraction (PXRD or XRPD) and 2) infrared reflection absorption spectroscopy (IR).⁸ Each of these methods involves subjecting a sample to a particular form of electromagnetic radiation (e.g., x-ray or infrared). Each of these techniques generates data that can be used to identify and differentiate each discrete polymorphic form present in a sample. In essence, each distinct crystal structure yields distinct patterns in the PXRD or IR data (also called spectra). Spectra of pure samples of each polymorph

⁴ The Hatch-Waxman Act requires the FDA to publish Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. The Orange Book, *inter alia*, identifies drug products approved on the basis of safety and effectiveness by the FDA and lists patents that are purported to protect each drug. Patent listings and use codes are provided by the drug application owner, and the FDA is obliged to list them.

⁵ 35 U.S.C. § 271(e)(2).

⁶ Federal Circuit Judge Gajarsa’s concurring opinion in *SmithKline Beecham Corp. v. Apotex Corp.*, which we paraphrase here, is a helpful start. 403 F.3d 1331, 1348 (Fed. Cir. 2005).

⁷ Technically, these solvates and hydrates are called “pseudopolymorphs.” However, the broader use of the term “polymorphs” to include solvates and hydrates has been adopted by the Federal Circuit (*see* 403 F.3d at 1348) and the FDA, which defines polymorphic forms as “crystalline and amorphous forms as well as solvate and hydrate forms” Polymorphism Guidance at 3.

⁸ Other analytical techniques, such as single crystal x-ray diffraction (XRD), Raman spectroscopy, melting point, and differential scanning calorimetry (DSC), can also be used to identify and characterize polymorphs of drug substances.

provide a “fingerprint” for the polymorph. Under certain circumstances and using good experimental design, mixtures of polymorphic forms can be analyzed using PXRD or IR and other techniques as well.

Case Review

Bristol-Myers Co. v. U.S. Int’l Trade Comm’n, 1989 WL 147230 (Fed. Cir. 1989) (unpublished)

Notable holdings: A new crystalline form of a compound may not be obvious absent prior art suggesting the particular form and a suitable method of producing it.

In this case, the patent at issue concerned a crystal form of cefadroxil monohydrate, which is the active ingredient in Bristol-Myers Squibb’s (BMS’s) Duricef®. This case was brought before the Federal Circuit on appeal from a final determination of the U.S. International Trade Commission (ITC) denying BMS’s request for preliminary relief.⁹ In the ITC, after hearing arguments on anticipation and obviousness, the administrative law judge (ALJ) concluded the patent at issue would not likely be found anticipated, but would likely be found invalid as obvious.¹⁰ As a result, the ALJ denied BMS’s requested injunction.

On appeal, the Federal Circuit reversed the ALJ’s denial of temporary exclusion reasoning that the patent was not anticipated or obvious and the “[ITC] exceeded its discretionary authority, committed an error of law, and seriously misjudged the evidence.” The court reasoned that the ALJ applied an incorrect legal standard to determine the issue of obviousness. “The correct inquiry is not whether the [patented compound] *could have been* produced [based on the prior art] The question is whether it *would have been obvious* to make the [patented compound], based on the prior art.” The court further stated that “a new crystalline form of a compound would not have been obvious absent evidence that the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form.”

After the Federal Circuit reversed the denial of the injunction, the ITC took comments from the parties on the issue of temporary relief and, 12 days later, the ITC granted BMS a temporary exclusion order (preventing importation of allegedly infringing products) and issued cease and desist orders against the domestic respondents to the action.

While not a Hatch-Waxman case, or even a published decision, this case is notable in suggesting a significant evidentiary requirement—that the prior art suggest a particular structure.

⁹ Under 19 U.S.C. § 1337(e), the ITC can exclude articles from entering the country pending an investigation into whether the articles infringe a valid U.S. patent.

¹⁰ In an ITC proceeding, an ALJ hears arguments much like a district court would, and issues a determination similar to a district court’s opinion. Interested parties (e.g., future infringers) may appear as intervenors before the ITC. Akin to district court patent litigation, parties may appeal the ITC’s determination to the Federal Circuit, which gives deference to the ALJ’s findings and reviews the ALJ’s grant or denial of relief for abuse of discretion.

Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418 (Fed. Cir. 1994)

Notable holdings: Comparing an accused product to a patentee's commercial embodiment rather than the patent claims is reversible error. Selling a polymorph that converts to a patented polymorph *in vivo* may constitute inducement of infringement. When a patent claim describes an invention by reciting a PXRD pattern, the correct infringement analysis is whether an accused product exhibits the same pattern in PXRD analysis. When a patent claim recites a 37-peak PXRD pattern, proving an accused infringer's product exhibits 22 of those 37 peaks does not prove infringement.

In *Zenith*, the patented technology was for a "new" crystalline form of cefadroxil, which again is sold as Duricef® by BMS.¹¹ The patent at issue claimed the crystal form according to its x-ray diffraction properties. BMS conceded that, in its pre-ingested form, Zenith's product did not literally infringe the patent claim. Nonetheless, BMS argued that Zenith's product converted into the patented polymorphic form after it was ingested, thus the sale of Zenith's product induced infringement of BMS's patent.

Because its theory of infringement relied on the polymorphic form present in a patient's stomach after ingesting Zenith's product, BMS could not test for infringement directly. Instead, BMS had its expert perform a surrogate test, where he simulated the *in vivo* conditions of a patient's stomach. BMS's expert first compared the PXRD pattern of its Duricef® and determined that 22 peaks in the Duricef® pattern matched the claimed peaks. Based on this, the expert opined that Duricef® provided an appropriate reference pattern. The expert then compared Zenith's product after it was subjected to his surrogate conditions to simulate *in vivo* conversion with Duricef® using data from three tests: optical microscopy, birefringence comparison, and PXRD. Using these methodologies, BMS's expert concluded that Zenith's artificially-digested product contained the same polymorph as BMS's Duricef®.

While the district court found this sufficient to establish literal infringement, the Federal Circuit reversed, citing two principal reasons. *First*, the Federal Circuit found that the comparison of the accused product to the patentee's commercial embodiment, rather than the patent claims, was impermissible. *Second*, the patentee failed to prove the accused product embodied each and every one of the claim limitations. The court found the results of the optical microscopy and birefringence comparison only "inferentially relevant," as PXRD analysis is what the claims required. Also, the patent claims defined the polymorph with a 37-peak PXRD pattern, yet the patentee's proof demonstrated only 22 peaks, at best, which was insufficient to establish that, after *in vivo* conversion, Zenith's product met each and every element of the patent claim. The court reasoned:

Although the term "essentially" recited in the claim permits some leeway in the exactness of the comparison with the specified 37 lines of the claim, it does not permit ignoring a substantial number of lines altogether. It is the claim that sets the metes and bounds of the invention entitled to the protection of the patent system.

¹¹ This case was a declaratory judgment action brought by the generic company, Zenith.

Thus, in the absence of evidence comparing Zenith's product to the claims of the patent, the Federal Circuit held that BMS failed to prove infringement and reversed the district court's judgment.¹²

The key takeaway from this case is that all claimed peaks are part of the claim, and thus must be proven in the accused product to prove infringement.

Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043 (Fed. Cir. 1995) ("Novopharm I")

Notable holdings: A patent claiming a specific polymorph is not inherently anticipated by a prior art reference describing a process that does not always result in the polymorph.

The patent at issue in *Novopharm I* covered supposedly new forms of ranitidine hydrochloride (RHCl) (which is the active ingredient in Zantac®), characterized by IR spectra and PXRD diffraction patterns. Two claims were asserted:

1. Form 2 [RHCl] characterized by an [IR] spectrum as a mull in mineral oil showing the following main peaks: [list of 29 peaks].
2. Form 2 [RHCl] according to claim 1 further characterized by the following [PXRD] pattern expressed in terms of "d" spacings and relative intensities (l) (s = strong, m = medium, w = weak, v = very, d = diffuse) and obtained by the Debye Scherrer method in a 114.6 mm diameter camera by exposure for 12 hours to CoKa radiation and for 3 hours to CuKa radiation: [table of 32 peaks at certain relative intensities].

In this case, Novopharm filed an ANDA for a product made using Form 2 RHCl, the same polymorphic form as patented by Glaxo, and Glaxo brought an action for patent infringement. Novopharm argued that the patent was invalid because 1) Form 2 RHCl was inherently anticipated, 2) the patent was procured by inequitable conduct, and 3) Glaxo failed to disclose the best mode of making the form. The district court held in favor of Glaxo finding the patent valid and infringed and ordering that the FDA not approve Novopharm's ANDA until Glaxo's patent expired.

Novopharm appealed and argued that practicing a certain example in the prior art always yields Form 2 RHCl. To prove inherent anticipation, Novopharm's experts manufactured RHCl using the process disclosed in the prior art and identified the form produced using IR and PXRD analyses. Novopharm's experts performed the process 13 times, and each time the process resulted in the formation of Form 2 RHCl, not Form 1. However, prior to developing the process to make Form 2, Glaxo scientists had followed the example in the prior art and produced only Form 1. Further, when Glaxo's expert performed the process described in the prior art in connection with the litigation, he too produced only Form 1. The district court held that Glaxo's results from practicing the prior art were sufficient to demonstrate that

¹² The Federal Circuit did not address whether the inducement theory would have held up had BMS proven the product met the claims after *in vivo* conversion, and the Supreme Court denied BMS's petition for writ of certiorari. *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 513 U.S. 995 (1994).

following the prior art did not necessarily yield the claimed Form 2, thus the patent claim was not inherently anticipated. The Federal Circuit affirmed, upholding the district court's finding that the patent was valid and infringed.¹³ This case demonstrates the possibility of the Federal Circuit rigidly applying the "necessary" requirement of the inherent anticipation doctrine in polymorph cases.

Glaxo, Inc. v. Novopharm Ltd., 110 F.3d 1562 (Fed. Cir. 1997) ("Novopharm II")

Notable holdings: As in *Zenith*, a patentee must prove the accused compound exhibits each of the claimed peaks to establish infringement when the patent claims a polymorph using IR or PXRD peaks. The appropriate infringement analysis under § 271(e)(2) is the same as any other infringement analysis, and courts may properly look to evidence beyond the ANDA to determine whether the ANDA applicant's ultimate product, if brought to market, would infringe the patent.

In light of the results in *Novopharm I*, Novopharm filed a second ANDA, this time for a different polymorphic form of RHCl than the Form 2 used in Zantac®. In *Novopharm II*, Glaxo sued arguing that small amounts of Form 2 were nonetheless present in Novopharm's ANDA product. The district court interpreted the claims of the relevant patent as limited to "pure Form 2 RHCl," and therefore held that Novopharm did not infringe.

On appeal, the Federal Circuit reversed that construction holding that the claims were not so limited. But, ultimately, the claim construction issue was not determinative because the Federal Circuit found that Glaxo failed to put forward sufficient evidence of infringement. Instead, Glaxo relied on a single IR peak recited in Novopharm's ANDA to show that the ANDA product contained Form 2 RHCl. As described above, Glaxo's patent claimed Form 2 RHCl characterized by a 29-peak IR spectrum. Citing *Zenith*, the court held that Glaxo's "single-peak analysis" was "meaningless" and insufficient to meet the multi-peak claims because "it is elementary patent law that all limitations are material," and therefore all 29 claimed peaks must be identified.¹⁴

Glaxo also argued that the district court's "conventional infringement analysis" was flawed because the proper analysis should focus solely on the scope of approval sought in Novopharm's ANDA, which would theoretically cover Form 2 RHCl. Thus, Glaxo claimed the ANDA itself established infringement and shifted the burden to Novopharm. The Federal Circuit rejected this interpretation, holding that the infringement analysis under § 271(e)(2) is the same as in any other infringement suit, stating:

Thus, contrary to Glaxo's arguments, the patentee's burden of proving ultimate infringement is not met by the filing of the ANDA. The 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

¹³ The Supreme Court denied Novopharm's petition for writ of certiorari. *Glaxo, Inc. v. Novopharm Ltd.*, 516 U.S. 988 (1995).

¹⁴ The Federal Circuit explicitly declined to address whether small amounts of Form 2 in a mixture containing primarily Form 1 could infringe the claims as drafted.

determine whether infringement exists. The district court correctly chose to determine whether Novopharm would likely sell an infringing composition pursuant to an approved ANDA. In conducting this infringement analysis, the district court properly considered the ANDA itself, the materials submitted by Novopharm to the FDA, and other pertinent evidence provided by the parties.

Two months after the Federal Circuit affirmed the district court's finding of no infringement, Glaxo voluntarily dismissed all claims and waived its right to further review of the judgment.

Glaxo Group Ltd. v. TorPharm, Inc., 153 F.3d 1366 (Fed. Cir. 1998)

Notable holdings: Using a commercial embodiment to support an infringement analysis did not run afoul of *Zenith* when the ultimate comparison was between the patent claims and the accused product.

In *Glaxo Group*, the ranitidine saga continued. Generic company TorPharm filed an ANDA for a RHCl product that it contended would contain only non-infringing Form 1 RHCl. Glaxo brought suit alleging that TorPharm's product contained a small amount of Form 2 RHCl based on its expert's testing of the accused product. Using IR, Glaxo's expert generated spectra for 13 different mixtures of Form 1 and Form 2 RHCl ranging from 0% to 3.97% Form 2. The expert then analyzed the IR spectra using software that generated a calibration model using an algorithm. As part of the calibration process, Glaxo's expert confirmed that each of the 29 main peaks were present in analysis of the Form 2 reference sample. Using the calibration model, the expert determined TorPharm's ANDA product contained 0.5% Form 2 RHCl.

Despite this evidence, the district court granted TorPharm's summary judgment motion for no infringement, reasoning that TorPharm was attempting to practice the prior art to produce Form 1 RHCl (the same prior art that Novopharm had offered to show anticipation in *Novopharm I*). Because that prior art reference was dedicated to the public upon expiration of its patent rights, according to the district court, TorPharm's product could not infringe the Form 2 patents without violating the rule against double patenting. The court also construed the asserted claims of the Form 2 patents in light of the prosecution history, again to avoid double patenting. The court's construction required that an accused product have improved drying and filtration characteristics in order to infringe.

On appeal, the Federal Circuit vacated and remanded, rejecting TorPharm's arguments in support of affirmance. *First*, the court dismissed TorPharm's argument that Glaxo's expert's analysis was deficient under *Zenith* because it compared TorPharm's product to Glaxo's commercial embodiment. The court reasoned that Glaxo's expert's use of the commercial embodiment was acceptable because, unlike in *Zenith*, the embodiment exhibited each of the peaks in the patent claims. Further, Glaxo's expert used the commercial embodiment as a means of calibrating a model, not as a substitute for the patent claims. The expert properly concluded that TorPharm's product contained Form 2 RHCl as claimed in the patent.

Second, TorPharm argued that the claims required Form 2 RHCl "showing" 29 "main" peaks in IR spectra,

and that “main” and “showing” should be construed by their dictionary definitions: “main” meaning “chief in size, extent, or importance,” and “showing” meaning “to cause or allow to be seen,” thus “visually identifiable.” According to TorPharm, any peaks exhibited by Form 2 crystals are overwhelmed by the predominant peaks exhibited by the Form 1 crystals in its product’s IR spectra. Thus, the 29 peaks of Form 2, even if present, are not “showing,” and could not be considered “main peaks.” The Federal Circuit rejected this argument, holding that TorPharm failed to recognize that “main” is a relative term. In order to be “chief in size,” the peaks must be measured relative to something. The Federal Circuit found it clear from the intrinsic record, including the prosecution history, that all the word “main” requires is that the peaks be “chief in size” relative to the baseline of the pure Form 2 compound. The Federal Circuit also rejected TorPharm’s argument that all 29 peaks must be “visually identifiable” in the IR spectrum to prove infringement. The court held that “show” requires only that Glaxo could “demonstrate with an acceptable degree of certainty, visually or by other appropriate means . . . that the accused product contains the 29 main peaks.” The court rejected TorPharm’s claim constructions as defining the words “relative to [TorPharm’s] overall compound, which is not the subject of the claim.” The Federal Circuit vacated the summary judgment of no infringement and remanded the case to the district court.

At some level, this decision seems to suggest that even trace amounts of a polymorph is sufficient to establish infringement. However, the Federal Circuit did not answer that question. Instead, citing to *Novopharm II*, the Federal Circuit again declined to approach the question of whether a “small” amount of Form 2 RHCl (here argued to be 0.5%) would infringe the patent. On remand to the district court, the parties settled and dismissed all claims, defenses, and counterclaims.

***Abbott Labs. v. Geneva Pharm., Inc.*, 182 F.3d 1315 (Fed. Cir. 1999)**

Notable holding: When a specific polymorphic form of a compound is manufactured and sold, it does not matter whether the polymorphic form was known at the time of sale for purposes of the “on-sale” bar of 35 U.S.C. § 102(b).

In *Abbott Labs*, the patent at issue claimed anhydrous Form IV crystalline terazosin hydrochloride (which is the active ingredient in Hytrin®), characterized by principal peaks in PXRD. Geneva Pharmaceuticals, Novopharm, and Invamed each filed ANDAs seeking approval to market a generic product containing the Form IV anhydrate. Abbott sued each company and the three actions were consolidated into one case in the Northern District of Illinois.¹⁵

The generic defendants moved for summary judgment arguing that the relevant claim of Abbott’s patent was invalid under the “on-sale” bar.¹⁶ The “critical date” for the on-sale bar was October 18, 1993, one year prior to the filing of the relevant patent. Geneva offered

¹⁵ *Abbott Labs. v. Geneva Pharm., Inc.*, No. 96 C 3331, 1998 WL 566884 (N.D. Ill. Sept. 1, 1998).

¹⁶ The “on-sale” bar requires that, before the critical date, the invention must be: 1) the subject of a commercial sale or offer for sale, and 2) ready for patenting (that is, reduced to practice). *Pfaff v. Wells Elecs., Inc.*, 52 U.S. 55 (1998).

evidence that, in December 1989, Geneva ordered a large quantity of anhydrous terazosin hydrochloride, which it received on July 10, 1990. Later, in August 1991, Geneva ordered another quantity of terazosin hydrochloride, which it received on December 12, 1991. In 1996, Geneva’s expert performed PXRD on the two lots from 1990 and 1991, respectively. After reviewing the PXRD diffraction patterns of the two lots, the expert concluded that both lots contained all of the “principal peaks” used to characterize Form IV crystalline terazosin and that the 1989 lot was pure Form IV crystalline terazosin hydrochloride, while the 1991 lot was a mixture of Form IV and Form II. In the litigation, Abbott admitted that the two lots contained Form IV terazosin hydrochloride and further confirmed that its own 1995 testing demonstrated that the two lots contained Form IV.

Despite not contesting that the two lots contained Form IV terazosin hydrochloride at the time they were tested, Abbott argued that the original product sold in the two lots may have consisted of a less stable crystal form of terazosin hydrochloride which converted, over time, to Form IV. In response, the generic defendants submitted the results of PXRD performed by the original manufacturer in 1990, which demonstrated that the lots contained Form IV. In light of the totality of evidence showing the lots contained Form IV, the court dismissed Abbott’s “speculation” that the lots might have undergone a transformation after the sale and held the claim invalid due to the on-sale bar.

The Federal Circuit affirmed the district court’s grant of summary judgment that the patent was invalid under § 102(b). The Federal Circuit found that both prongs of the two-part test for the on-sale bar were satisfied based on actual sales of the compound having the patented form. In response to Abbott’s argument that the parties to the sale did not know the specific polymorphic form(s) present in the compound, the court held that “[i]t is well settled in the law that there is no requirement that a sales offer specifically identify all the characteristics of an invention offered for sale or that the parties recognize the significance of all of these characteristics at the time of the offer.” The court further held that a sale still qualifies as a “sale” for purposes of § 102(b), even if the parties to the sale were not aware of the specific polymorphic form(s) of the material sold. Thus, the Federal Circuit affirmed that the sale of a particular polymorphic form more than one year before filing a patent application necessarily invalidates the patent pursuant to the on-sale bar under section § 102(b).¹⁷

***Glaxo Group Ltd. v. Ranbaxy Pharms., Inc.*, 262 F.3d 1333 (Fed. Cir. 2001)**

Notable holdings: A patentee may limit the scope of a patent’s claim to certain concentrations of specified forms of a compound. When a patent’s claims are limited as such, a product containing concentrations of forms of the compound outside the scope of the claims does not infringe. Precedent on the (in)validity and infringement of polymorph patent claims applies to amorphous form patent claims as well.

¹⁷ The Supreme Court denied Abbott’s petition for writ of certiorari. *Abbott Labs. v. Geneva Pharm., Inc.*, 528 U.S. 1078 (2000).

The patent at issue in *Glaxo v. Ranbaxy* claimed the amorphous form¹⁸ of cefuroxime axetil, which is the active ingredient in Ceftin®. Ranbaxy filed an ANDA seeking approval to market a generic cefuroxime axetil product containing 10 to 15% crystalline cefuroxime axetil, with the balance of the product being amorphous. The patent claimed the invention as “Cefuroxime axetil in amorphous form essentially free from crystalline material, and having a purity of at least 95% aside from residual solvents.”

On a motion for preliminary injunction, the district court interpreted the limitation “essentially free from crystalline material” as “excluding from the claimed invention any item having sufficient crystalline cefuroxime axetil that materially affects the basic characteristics of the invention.” Using that construction, the district court determined that Claim 1 encompassed cefuroxime axetil with a 10 to 15% crystalline content. Glaxo presented evidence that Ranbaxy’s proposed product contained no more than 15% crystalline material, thus establishing a likelihood of success on the merits. The district court entered a preliminary injunction, precluding Ranbaxy from marketing its ANDA product.

On appeal, the Federal Circuit vacated the preliminary injunction finding that Ranbaxy’s ANDA product will likely contain a larger amount of crystalline material than covered by Claim 1. The Federal Circuit looked to the prosecution history of the patent where Claim 1 had originally been dependent Claim 4. The court found that “essentially free from crystalline material,” as recited in original dependent Claim 4, would usually carry a narrower meaning than “substantially amorphous” recited in original Claim 1 because dependent claims are generally narrower in scope than the claims on which they depend. The court then considered the patent’s specification, focusing on Example 22, which stated “X-ray crystallography revealed the product was substantially amorphous with a small content of crystalline material.” Thus, the court reasoned cefuroxime axetil that is “essentially free from crystalline material” must have less than “a small content of crystalline material.”

The Federal Circuit also analyzed the prosecution history of related patents. During prosecution of other patents, Glaxo had stated “Example 22 of the specification has shown that the product contains approximately 10% crystalline material.” Based on the specification and the prosecution history, the Federal Circuit concluded that a maximum of 10% crystalline material was within the scope of Claim 1. Citing *Novopharm II*, the court vacated the preliminary injunction concluding that Ranbaxy’s ANDA product contained a higher content of crystalline cefuroxime axetil than permitted by Claim 1. Thus, the court held that Glaxo was unlikely to succeed in showing that Ranbaxy’s product literally infringed. After a later bench trial, the district court entered a judgment for the generic defendants finding no infringement but did not provide a publicly available opinion.

¹⁸ An amorphous form of a chemical compound is technically not a polymorph. Rather, an amorphous compound lacks long-range order of the positions of the atoms and is, thus, not crystalline. However, the issues of cases involving “amorphous form” patents are germane to the topics of this article.

SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331 (Fed. Cir. 2005)

Notable holdings: Even small amounts of the claimed compound may infringe a claim to a specific polymorph. If practicing the prior art today would necessarily result in infringement, the claim is invalid as anticipated (even if practicing the prior art at the time of filing would not have resulted in infringement).

In *SmithKline*, the patent at issue claimed a hemihydrate of crystalline paroxetine hydrochloride (PHC), which is the active ingredient in Paxil®. SmithKline’s U.S. patent claimed priority to a British patent relating to crystalline PHC that identified its invention as both the hemihydrate and the anhydrate forms, as well as mixtures that contain a major portion of either form. The U.S. patent, however, did not claim the anhydrate form or mixtures of the two forms. Rather, the claim of the U.S. patent in suit reads, in its entirety: “Crystalline paroxetine hydrochloride hemihydrate.” Apotex filed an ANDA seeking approval to market a drug containing PHC anhydrate. After construing the claim to require “commercially significant amounts” of PHC hemihydrate, the district court found that Apotex’s ANDA product did not infringe. The Federal Circuit dealt with a number of issues on SmithKline’s appeal.

First, the Federal Circuit held that the claim was not indefinite reasoning that the language of the claim is not ambiguous; rather it describes a very specific compound. One of skill would have understood that the claim embraces PHC hemihydrate, without further limitation. The district court’s construction requiring “commercially significant amounts” of PHC hemihydrate was therefore incorrect. Even though the specification lauded the improved characteristics, it did not redefine an established structural definition. Without the district court’s limitation, the proper construction would include trace amounts, even if they are undetectable. The Federal Circuit then turned to the issue of infringement. Based on evidence of “seeding,” which is a process where once a small amount (i.e., a seed) of the hemihydrate was created, all later-produced batches of PHC would contain at least trace amounts of the hemihydrate unless “drastic conditions” were employed. Because Apotex did not follow these “drastic conditions,” the Federal Circuit held that SmithKline had proven infringement.

Second, the Federal Circuit also analyzed the question of validity. At the time of the invention, practicing the prior art did not result in practicing the invention. However, because of the seeding phenomenon, those who practiced the prior art after the invention would now automatically infringe. The Federal Circuit found this to be an untenable position as it would effectively result in a considerable extension of the patent covering PHC hemihydrate. The court reasoned that once the seeding phenomenon occurred, the prior art inherently anticipated the claimed invention. Thus, the court invalidated the claims as inherently anticipated.¹⁹

¹⁹ The Supreme Court denied SmithKline’s petition for writ of certiorari. *SmithKline Beecham Corp. v. Apotex Corp.*, 547 U.S. 1218 (2006).

Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282 (Fed. Cir. 2009)

Notable holdings: When a foreign patent discloses or claims multiple polymorphic forms of a compound and a later U.S. patent claims priority to the foreign patent, any forms in the foreign patent that are not claimed in the U.S. patent are “dedicated to the public” and may not be recaptured by the doctrine of equivalents (DOE). Bioequivalency for purposes of FDA approval is not the same as equivalency for purposes of DOE infringement of a patent.

In *Abbott*, one of the patent claims at issue covered crystalline cefdinir (which is the active ingredient in Omnicef®), characterized in Claim 1 by a 7-peak PXRD pattern. Claims 2-5 claimed crystalline cefdinir as a “product-by-process,” but did not recite any specific PXRD peaks. The patent defines “Crystal A” as “any crystal of [cefdinir] which shows substantially the same diffraction pattern as [the same 7 peaks as Claim 1].” The specification detailed the processes for making Crystal A, which matched the processes in the “product-by-process” Claims 2-5. However, these processes could not be used to produce any other forms of cefdinir. In contrast, the foreign parent application of this patent described both Crystals A and B of cefdinir. The disclosure regarding Crystal B was not included in the patent at issue. In construing the claims, the district court limited the term “crystalline” in all five claims to mean “Crystal A.”

Sandoz’s ANDA product was composed of mostly Crystal B cefdinir and was not produced by the processes claimed in Claims 2-5. Regardless, Abbott asserted that: 1) Sandoz’s product contained at least small amounts of Crystal A, 2) based on the language of Claim 1, Crystal A and Crystal B were equivalent for purposes of the doctrine of equivalents, and 3) Sandoz effectively admitted infringement by equivalents when it claimed to the FDA that its product and Abbott’s product were bioequivalent. The district court granted summary judgment of no infringement of Claims 2-5 literally or Claims 1-5 by equivalency.

Abbott appealed but the Federal Circuit affirmed the district court’s grant of summary judgment. The Federal Circuit reasoned that Abbott had disclosed Crystal B in the parent application but chose to limit the patent at issue to Crystal A, thus relinquishing any claim to Crystal B. The doctrine of equivalents could not be used to extend claims “to embrace known but unclaimed subject matter.” The court relied on the fact that Abbott disclosed Crystal B in the parent application but did not pursue a U.S. patent claiming it, holding Abbott “dedicated [Crystal B] to the public” and “foreclose[d] invocation of the doctrine of equivalents.” The Federal Circuit also stated that while Sandoz’s bioequivalency arguments to the FDA may be relevant to the function prong of the doctrine of equivalents, it is not dispositive:

[B]ioequivalency and equivalent infringement are different inquiries. Bioequivalency is a regulatory and medical concern aimed at establishing that two compounds are effectively the same for pharmaceutical purposes. In contrast, equivalency for patent infringement requires an element-by-element comparison of the patent claim and the accused product, requiring not only equivalent function but also equivalent way and result.

Bristol-Myers Squibb Co. v. Mylan Pharm. Inc., Case No. 09-cv-00651, 2012 BL 119969 (D. Del. May 16, 2012)²⁰

Notable holdings: The claims, the specifications, and the prosecution histories of three patents directed to certain polymorphic forms of a drug compound supported a broad construction of the patent claim terms. This construction did not require the compound to exhibit the same PXRD patterns and DSC data as recited in the claims, but rather only required that the compound be identifiable by PXRD or DSC analysis.

BMS and Merck each owned patents related to certain polymorphic forms of efavirenz which they jointly developed and marketed as the HIV treatment Sustiva®. The BMS patent claims Forms 1-5 of efavirenz, and the Merck patents claim Forms I, II, and III. The claims described different polymorphic forms based on peaks in their PXRD or DSC data. Several patent claim terms were in dispute, but the parties agreed that the court only needed to resolve one basic dispute: the construction of the different “Form” terms. The parties proposed the following claim constructions:

A. “Form 1,” “Form 2,” and “Form 4” (’372 patent)

1. *Plaintiffs’ Proposed Construction:* “a polymorphic crystal form of [efavirenz] that can be distinguished from other forms”
2. *Defendants’ Proposed Construction:* “a crystalline form of efavirenz characterized by the powder x-ray diffractogram and differential calorimetry [sic] thermogram depicted [for each Form in the Figures]”

B. “Form I,” “Form II,” and “Form III” (’071 and ’964 patents)

1. *Plaintiffs’ Proposed Construction:* “a polymorphic crystal form of [efavirenz] that can be distinguished from other forms by its x-ray powder diffraction pattern”
2. *Defendants’ Proposed Construction:* “a crystalline form of efavirenz characterized by at least the key diffraction peaks identified [for each Form in the specification and Figures]”

After a *Markman* hearing, the court noted that the dispute was essentially whether the various “Form” terms incorporate the entirety of the PXRD and DSC patterns in the Figures or are simply shorthand references whose characteristics are supplied by the PXRD and/or DSC values recited in the claims. The court adopted the plaintiffs’ proposed constructions for every “Form” term reasoning that they were better supported by the claims, the specifications, and the prosecution histories.²¹

²⁰ 2012 WL 1753670.

²¹ After a bench trial, the district court found the patents valid and infringed by Mylan’s proposed ANDA product, but did not issue a public opinion. Mylan appealed, but the parties settled and withdrew the appeal.

Schering Corp. v. Apotex Inc., Case No. 09-cv-06373, 2012 BL 152438 (D.N.J. June 15, 2012)²²

Notable holdings: If a supplier sells a drug product that converts from an unpatented polymorph to a patented polymorph before the expiration of its shelf life, the supplier may be liable for patent infringement. When certain peaks in a PXRD pattern are not relevant or illuminating in a specific analysis (e.g. when they are present in both polymorphic forms), an expert may rely on fewer than all of the claimed peaks, but accepted practice requires comparison of at least three peaks.

In *Schering*, the patent at issue claimed mometasone furoate monohydrate (MFM) and use of the same in a nasal spray formulation. Schering's commercial embodiment of the invention is Nasonex®. The relevant claims in Schering's patent are Claim 1: MFM itself; Claim 5: MFM exhibiting a specific PXRD diffraction pattern; Claim 6: a pharmaceutical composition of MFM in a carrier consisting essentially of water; and Claim 11: the composition of Claim 6 as a nasal spray. The patent also disclosed several analytical methods, including PXRD and IR, to determine whether a compound or formulation includes MFM. Apotex filed an ANDA seeking approval to market a product made with mometasone furoate anhydrate (MFA), not MFM.

While Schering admitted that Apotex was not directly manufacturing an infringing product, it sued Apotex alleging that Apotex's product converted to an infringing product during the product's two-year shelf life. Schering's expert analyzed Apotex's ANDA product and opined that the Apotex product converted to MFM after manufacture by removing the mometasone furoate (MF) from Apotex's tablets and conducting PXRD on the extracted material.

The district court held that Schering failed to prove infringement. For some of Schering's expert's testing, the court found the expert's process had fundamentally changed the substance of Apotex's ANDA product. Specifically, the court agreed with Apotex's expert who criticized Schering's expert's use of "shaking," "vortexing," and "washing" on the Apotex ANDA product prior to PXRD analysis, reasoning that these processes undermined the stability of Apotex's MFA. The court thus ignored the testimony regarding any samples that were shaken or vortexed. Analysis of samples not so treated were also deemed insufficient to prove infringement because Schering's expert did not compare at least three unique peaks in the PXRD patterns. The court found that it is "accepted practice to use at least three peaks, often more to identify material."²³

For invalidity, Apotex argued that MFM as claimed in the patent was both anticipated by a prior art patent (Shapiro) and obvious in light of Shapiro and other prior art references. The court found that Shapiro did not anticipate because: 1) an IR spectrum collected during prosecution of that patent application showed no water peaks in it and 2) Shapiro did not disclose a hydrate. As for obviousness, the court found that the patent would not have been obvious to a formulator in Sep-

tember 1990. The court reasoned that a formulator would not have been motivated to develop a nasal spray using MF because of potential toxic effects and found Apotex's expert testimony insufficient. The court did not reach the question of secondary considerations because it found that Apotex did not make out a prima facie case of obviousness.²⁴

Bristol-Myers Squibb Co. v. Apotex Corp., Case No. 10-cv-05810, 2013 BL 83014 (D.N.J. March 28, 2013)²⁵

Notable holdings: Patent claim language defining a polymorph by its PXRD pattern was broadly construed to account for measurement errors, different measurement conditions, and not requiring an identical order of intensity of the peaks as recited in the claim.

In this case, BMS sued Apotex based on an ANDA product that BMS claimed would infringe four of its patents covering various forms of dasatinib (Sprycel®) and methods of using it to treat cancer. The parties disputed the proper construction of certain claims in the patents including: 1) "Crystalline monohydrate of the compound of formula (IV)" and 2) dasatinib monohydrate "which is characterized by an x-ray powder diffraction pattern substantially in accordance with that shown in FIG. 1."

With regard to the first term, BMS argued that it should be construed by its plain meaning "the monohydrate of the compound of formula IV in a crystalline form" and argued that "monohydrate" means "a compound containing one molecule of water." Apotex countered that the term "crystalline monohydrate" is a general term encompassing multiple polymorphic versions of crystal lattice frameworks. Apotex argued that the term is only given meaning by the intrinsic evidence of the patentee's specified analytical testing. However, the court rejected Apotex's argument and did not limit the claim to the embodiments described in the specification, construing the term to mean "[t]he monohydrate of the compound of formula (IV) in a crystalline form."

As for the second term, BMS argued it should be construed as "which is characterized by an x-ray powder diffraction pattern that is substantially identical to those shown in FIG. 1 taking into account variations due to measurement errors and dependent upon the measurement conditions employed, but not taking into account the exact order of intensity of the peaks." Apotex argued that BMS's construction vitiates the definition of "substantially" and impermissibly broadens the scope of the claim. To counter BMS's suggestion that the exact order and intensity of the peaks should not be taken into account, Apotex's expert argued that "even slight differences in an XRPD pattern can result in an inability to uniquely identify the substance being considered." BMS, in turn, pointed out that "[Apotex's] expert recognizes that XRPD results can have measurement errors and can result in two x-ray diffraction patterns having different intensities but yet representing the same crystalline material." The court concluded in favor of BMS construing the XRPD-based claim as requir-

²² 2012 WL 2263292.

²³ While Schering's expert opined that three peaks were in fact present, the court disagreed because other testimony established that two of the expert's three peaks were not actually unique peaks under the well-accepted Brack formula.

²⁴ The parties cross-appealed, and the Federal Circuit affirmed rendering judgment *per curiam* without an opinion. *Merck Sharp & Dohme Corp. v. Apotex Inc.*, 517 Fed. App'x 939 (Fed. Cir. 2013).

²⁵ 2013 WL 1314733.

ing a substantially identical diffraction pattern “taking into account variations due to measurement errors and dependent upon the measurement conditions employed, but not taking into account the exact order of intensity of the peaks.”

After the claim construction order, the parties moved for summary judgment.²⁶ After extensive briefing on the motions (under seal), the parties settled in September 2013 and the case was dismissed without resolution of infringement or invalidity of this patent.

In re Armodafinil Patent Litigation Inc., 939 F. Supp. 2d 456 (D. Del. 2013)

Notable holdings: Adopting the standard from *Novopharm I*, a patent claiming a specific polymorph is not inherently anticipated by a prior art reference that describes a process that sometimes results mixtures of polymorphs that include other polymorphs. A specific polymorphic form of a compound would not have been obvious to one skilled in the art, when the state of the art at the time of development required a high number of crystallization trials and trial-and-error experimentation to identify the specific polymorphic form(s) of a sample.

The patent at issue in this case claimed a specific form (Form I) of armodafinil, methods for producing Form I armodafinil, and pharmaceutical compositions consisting of Form I armodafinil, which is the active ingredient in Nuvigil®. The four generic defendants in the consolidated action, Watson, Sandoz, Lupin, and Apotex,²⁷ each submitted an ANDA for generic armodafinil products, and plaintiff Cephalon sued each for patent infringement. The claims asserted against the generic defendants covered Form I armodafinil described by PXRD peaks and intensities and/or more generally as “Form I” armodafinil. After a *Markman* hearing, the court construed “a laevorotatory enantiomer of modafinil in a polymorphic form that produces a powder X-ray diffraction spectrum comprising . . .” to mean “a crystal form of Armodafinil having the claimed powder X-ray diffraction features.” After this ruling and before the bench trial, the generic defendants stipulated to infringement of the asserted claims as construed.

However, the generic defendants argued that Cephalon’s patent was invalid as anticipated and obvious. Regarding anticipation, the defendants argued that the prior art disclosed a method of making armodafinil crystals that inherently produced Form I. In support of this contention, generic defendants offered expert testimony and testing where “[the experts] performed Preparation I of the [prior patent] as persons of ordinary skill in the art in [the relevant period of time] and obtained Form I armodafinil thus proving anticipation.” One of defendants’ experts testified that the armodafinil produced in those experiments was confirmed by PXRD analysis to be Form I armodafinil as claimed in Cephalon’s patent. In contrast, Cephalon’s experts’ test-

²⁶ Apotex moved for summary judgment that BMS lacks a recoverable remedy for its infringement claims, and, separately, for invalidity under 35 U.S.C. § 112 (lack of enablement, lack of written description, or failure to distinctly claim the invention).

²⁷ One of the authors (MSM) represented Apotex in this litigation.

ing yielded only amorphous, non-crystalline forms of armodafinil after following some of the steps in Preparation I. The court found that the defendants did not carry their burden to show inherent anticipation because the experts performed the method in the prior art patent “using different, but reasonable experimental conditions,” and did not consistently produce only Form I armodafinil in all tests. Thus, the prior art patent did not teach a method necessarily and inevitably producing the plaintiff’s claimed Form I armodafinil. Citing to *Novopharm I*, the court concluded that Cephalon’s patent was not anticipated by the prior art where testing demonstrated that the prior art could yield “crystals of the claimed polymorph or a different polymorph.”

For obviousness, the defendants argued that, in light of the same prior art patent and other references in the prior art, a skilled artisan would have: 1) identified the most stable polymorph of armodafinil — Form I — for use in pharmaceutical composition, 2) expected to obtain the most stable polymorph using well-known and routine techniques, 3) known that the PXRD patterns recited in the claims are intrinsic to Form I when measured with routine techniques, and 4) been motivated to make a pharmaceutical composition consisting essentially of Form I. The generic defendants focused on the importance of identifying the most stable polymorph citing the “significant adverse consequences associated with a change in the polymorphic form during [development,] manufacture[,] or storage.” Cephalon countered that a skilled artisan would not have sufficient information to predict whether armodafinil would crystallize in polymorphic forms or what the structure of those polymorphic forms would be.

The court agreed with Cephalon. Focusing on the relevant time frame of invention, the court cited publications discussing the relatively high number of “crystallization trials” required in studies of polymorphic forms of compounds, the difficulty in predicting crystal structures, and the need to identify polymorphic forms of compounds by “trial and error experimentation.” The court concluded that Form I armodafinil would not have been obvious because the prior art did not suggest the particular structure of Form I or any structure or method of making Form I. Having rejected both defenses, the court enjoined defendants from manufacturing, using, offering for sale, or selling their ANDA products and further enjoined the FDA from approving defendants’ ANDAs prior to the expiration of the patent.²⁸

Conclusion

Given FDA regulations and guidance, patent strategy and litigation relating to polymorphs are sure to be critical in future Hatch-Waxman litigation. The case law surrounding polymorphs is complex, fact-specific, and full of potential landmines for generic and branded companies alike. Determination of the risks of infringement and validity require a detailed scientific analysis as well as consideration of numerous, and at times conflicting, legal precedent. We hope this article provides a starting point for that analysis.

²⁸ The defendants appealed to the Federal Circuit, where the case was settled after briefing and oral argument was completed.