How amending ANDA specifications can win or lose pharmaceutical patent litigation

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Patent litigation has been an integral part of the pharmaceutical industry since enactment of the Hatch-Waxman Act in 1984. Congress adopted Hatch-Waxman, formally known as the Drug Price Competition and Patent Term Restoration Act of 1984, P.L. 98-417, to expedite and streamline both approval of generic drugs and patent litigation involving generic drugs.

To achieve the first goal, the act allows generic-drug companies to file an abbreviated application for Food and Drug Administration approval of a drug that has been previously approved by another company, usually a brand-name company. This shortened application is called an abbreviated new drug application.

To achieve the second goal, Hatch-Waxman allows brand-name companies to sue the generic company for patent infringement before the generic company begins to sell its product to consumers. To do so, the generic-drug manufacturer must first submit a statement called a paragraph IV certification with its ANDA stating that any patents that the brand-name company listed in the FDA's database of “Approved Drug Products with Therapeutic Equivalence Evaluations,” known as the “Orange Book,” are invalid, unenforceable or will not be infringed by the generic company’s proposed product.

The brand company can then sue the generic company for patent infringement on the basis of its paragraph IV certification and its ANDA.

Hatch-Waxman patent litigation can extend — or decimate — profits for branded drugs, and it can accelerate market entry for generic products. But the foundation for winning patent litigation does not just begin with a complaint or even a paragraph IV certification. Nor are attorneys the only personnel who can help a patent — and potentially a blockbuster drug — rise or fall in litigation.

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Two recent decisions from the U.S. Court of Appeals for the Federal Circuit highlight a potentially effective patent litigation strategy of which executives in a wide variety of pharmaceutical companies should be aware. Regulatory amendments to the specification in an ANDA for a generic drug product can be outcome-determinative in patent litigation. They can lead to non-infringement decisions that bring one generic competitor’s product to market without also accelerating the entry of other generic competition. These amendments concern not just in-house counsel, but also other pharmaceutical personnel — from forward-thinking formulators and product development executives who establish specifications prospectively to regulatory affairs staff who can execute an amendment strategy.

Below, we provide practice tips and potential pitfalls for companies that are considering amending ANDAs to avoid infringement in Hatch-Waxman litigation, and we synthesize the leading cases regarding this strategy.

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THE BASICS OF AN AMENDMENT/ NON-INFRINGEMENT STRATEGY

Unlike most patent infringement actions, which involve a product that is already on sale, pharmaceutical patents litigated under the Hatch-Waxman Act normally focus on what a generic company will probably sell in the future. Biobatches or other samples of generic products are sometimes manufactured and then produced to opposing counsel in litigation, but the infringement inquiry often focuses more narrowly on the ANDA specifications for the prospective generic drug product. The scope of these specifications may dictate the outcome of the litigation, which in turn can dictate the timing of market entry and the availability of lucrative regulatory exclusivities.

Recent decisions from the Federal Circuit reaffirm that amending ANDA specifications can be a useful tool in avoiding infringement in certain cases. Accordingly, a best practice from a litigation perspective is to amend, or initially craft, this specification with potential patent litigation in mind, or at least to consider amendments once litigation has arisen.
Of course, counsel will review the patents listed in the FDA’s “Orange Book” when evaluating whether to submit a paragraph IV certification in connection with an ANDA. But evaluating claims of patents listed in the Orange Book for a branded reference drug as soon as possible, ideally early in formulation development, may help in crafting a winning non-infringement defense.

**PRACTICE TIPS AND POTENTIAL PITFALLS**

The interaction between the patent infringement inquiry and the specification leads to interesting evidentiary questions for courts. For instance, is a court limited to the four corners of the generic-drug company’s submission to the FDA, meaning its ANDA? If not, what type of extrinsic evidence is useful or dispositive? Can the generic company amend its ANDA to avoid infringement? If so, when can it make the amendment?

In attempting or combating an amendment/non-infringement strategy, litigants should keep the following practice pointers and possible counterarguments in mind.

**Directly address one or more claim elements and clearly demonstrate non-infringement.**

A best practice is to draft specifications that directly address the infringement inquiry and are clearly inconsistent with at least one element of each patent claim. The Federal Circuit’s August 2014 opinions concerning two generic versions of Ferring B.V.’s Lysteda highlight the wisdom of this strategy for generic companies.

The two Ferring decisions reaffirmed that amendments to ANDA specifications, even those made to avoid infringement, can be considered in a Hatch-Waxman infringement inquiry. These decisions also addressed when a court should consider the ANDA specification alone versus when it should consider additional evidence to determine infringement.

Both generic firms, Apotex Inc. and Watson Laboratories were ultimately successful in the litigation. However, Apotex’s amended specification proved to be dispositive on its own, whereas the court looked to other evidence in Watson’s case. If the extrinsic evidence relating to Watson had been less favorable, this could have resulted in a split set of decisions, allowing Apotex to market its product while Watson could not.

In *Ferring I* the Federal Circuit found that the ANDA specification that Apotex amended during trial in 2014 did not infringe Ferring’s patents. The specific patent claims at issue required, among other things, specified dissolution release rates. Although Apotex’s original 2010 ANDA specification was silent on this point, its amended 2014 specification directly conflicted with the patent claims. Specifically, the claims required a dissolution rate such that “less than about 70 percent [of the drug was] released at about 45 minutes,” whereas Apotex’s amended specification required “not less than 75 percent [of the drug be] released” at that time.

In other words, it would be impossible to meet both the ANDA specifications and the asserted claim limitations. Because non-infringement in this case was clear from the face of the amended ANDA, the court did not need to consider other evidence.

In *Ferring II*, Watson had a tougher road to reversing the District Court’s finding of infringement. Unlike in Apotex’s case, Watson’s ANDA specification did not clearly conflict with the patent claims. Specifically, the Federal Circuit held that “Watson’s ANDA specification does not itself resolve the question of infringement” because “[t]here is no specification that calls for measuring the dissolution of [Watson’s] finished, coated commercial product in water.”

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The court looked to extrinsic evidence, the dissolution testing of product samples and biobatch data in the ANDA, and it ultimately found that Watson’s product would not infringe the patent.

Like Apotex, Watson had also amended its ANDA at the District Court’s suggestion. However, instead of directly addressing the claim elements relating to the dissolution rate, as Apotex did, Watson’s amendment narrowed its specification to require a certain hardness range for its tablets.

The Federal Circuit did not find that Watson’s amended specification spoke directly to the question of infringement. The panel did, however, consider the amended specification as further evidence of non-infringement because of the relationship between hardness and the dissolution rates in the patent claims.

Although Watson was ultimately successful because the extrinsic evidence showed non-infringement, the court afforded the Apotex amendment greater weight because it squarely addressed the claim element in question.

Earlier cases also counsel that ANDA specifications should clearly indicate that the proposed product cannot infringe the claimed patent. A specification permitting both a non-infringing and infringing product is not sufficient. In fact, such a broad range can sometimes lead to a finding of infringement, rather than non-infringement.

For example, in *Sunovion Pharmaceuticals Inc. v. Teva Pharmaceuticals USA Inc.*, 731 F.3d 1271 (Fed. Cir. 2013), the Federal Circuit reversed summary judgment of non-infringement, finding that a specification requiring less than 0.6 percent (that is, 0.0 percent to 0.6 percent) of a compound demonstrated infringement of a claim for products containing less than 0.25 percent of that compound.

Although this specification clearly permitted manufacture of both infringing and non-infringing products, the court reasoned that the specification “mandates a finding of infringement” because the “specification clearly describes a product that meets the limitations of the asserted claims.”

The court disregarded extrinsic evidence that the final product as manufactured would contain more than the 0.25 percent concentration of the compound allowed by the claims, and therefore would not infringe. The court reasoned “[a]llowing the defendant to avoid infringement based on its unconventional and unenforceable ‘guarantee’ when it is asking for and may receive FDA approval to market a product within the scope of the innovator’s patent, would be incompatible with the basic principles of patent law.”

This case serves as a reminder that, if possible, an ANDA amendment should not include a range that permits infringement.
In contrast to Sunovion, the Federal Circuit in Bayer AG v. Elan Pharmaceutical Research Corp., 212 F.3d 1241, 1249 (Fed. Cir. 2000) (“Bayer I”), found that Elan’s amended specification “mandates a finding of no literal infringement.” The Federal Circuit upheld the District Court’s summary judgment of non-infringement because the ANDA specification required a minimum specific surface area of 5 m²/g, which was too high to fall within the lower range of SSA claimed in the patent (1.0 to 4 m²/g).

Although the brand attempted to raise a question of fact by pointing to uncertainty about the SSA used to make the biobatch, the Federal Circuit rejected this argument, noting that the “biobatch does not control the issue of infringement” and “the ANDA directly addresses the question of infringement.”

Sunovion and Bayer I illustrate the importance of considering the claimed ranges when drafting or amending an ANDA amendment. To avoid infringement, specifications should ideally be drafted to have no overlap with the claims.

**Consider whether the specified property can change during manufacturing.**

As a corollary to the first point, a specification directed to a property that changes during manufacturing of the product may not “directly address” the infringement inquiry. For example, if the specified property is measured before the product is made into its final form (such as a tablet), and the manufacturing process can change that property, the specification may not require a finding of non-infringement without additional evidence.

At least one district court has looked beyond a non-infringing amended specification in a case in which the brand alleged that the tablet manufacturing process altered the drug in a way that made it infringing. In that case, Cephalon Inc.’s patent claimed compositions in which at least 95 percent of certain particles had a diameter smaller than 220 microns. During litigation, Apotex amended its ANDA so that no more than 80 percent of these particles in its drug were that small.

Despite this amendment, Cephalon argued that a step in Apotex’s tablet manufacturing process could still reduce the particle size in the final product to meet the size limitation in its claims.

The District Court found these allegations sufficient to merit looking beyond the facially non-infringing specification. However, the Federal Circuit ultimately found that Cephalon’s evidence was too unreliable to prove infringement.

In contrast, the Federal Circuit in the Bayer I case limited the infringement question to the specification, even though it was directed to a property that could theoretically change over time. Bayer argued that the surface area of Elan’s product could decrease between the time of the measurement required by the ANDA specification and the time the tablets were manufactured, thus leading to a final product that could possibly infringe the claims.

Companies should be aware that a finding of non-infringement under the ANDA specification may not preclude a later suit on the actual generic commercial product.

Pharmaceutical professionals and their counsel who are drafting or amending an ANDA specification to avoid infringement should be cognizant of whether properties can change during manufacture. As these cases demonstrate, certain specifications for ingredients that are subject to further

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The Federal Circuit rejected this argument because Elan’s ANDA required that the drug have a non-infringing specific surface area (i.e., an SSA ≥5 m²/g) to be used within five days after the measurement. Bayer failed to show that the SSA would decrease enough to infringe its patent within that timeframe.

This additional specification requirement regarding the time between measurement and manufacture ensured that the specification “directly addressed” the infringement analysis. Herefore, summary judgment of non-infringement based on the specification alone was proper, and consideration of the biobatch or other extrinsic evidence was unnecessary.

Although Bayer I resolved the infringement issue regarding Elan’s first ANDA and allowed it to market a 30-mg product, Bayer later sued for infringement of the same patent by Elan’s actual 30-mg commercial product under 35 U.S.C. § 271(a), as a traditional infringement, not Hatch-Waxman, case. In Bayer AG v. Biovail Corp., 279 F.3d 1340, 1342 (Fed. Cir. 2002) (“Bayer II”), the Federal Circuit reversed a district court’s summary judgment of non-infringement based on collateral estoppel of the ruling in Bayer I because:

- Bayer introduced new extrinsic evidence that required additional claim construction that was not done in Bayer I.

- “Infringement under [Hatch-Waxman] by submission of an ANDA is not synonymous with [traditional] infringement … by a commercial product.”

Another best practice is to file the amendment to an ANDA as early as possible, possibly even before the lawsuit is filed. Although the Federal Circuit considered amendments that were made during litigation in Bayer I and the two Ferring cases, and it has even considered amendments after the original ANDA was found to infringe, the Federal Circuit has stated that it is not mandatory for a district court to consider an amendment. Rather, consideration of an amendment is within the court’s discretion, “guided by principles of fairness and prejudice to the patent-holder.” At least one district court has held that amending an ANDA after the Federal Circuit has affirmed a ruling of infringement and validity is too late. These decisions emphasize the importance of amending the ANDA as soon as possible. However, potential amendments should still be considered throughout the litigation process.
CONCLUSION
Filing amendments to ANDA specifications may be an effective strategy for avoiding patent infringement. However, practitioners who are considering these amendments should address and avoid the patented claims as directly as possible and amend as soon as practicable. W1
NOTES
1 Biobatches are batches of drug product that an ANDA manufacturer makes before they have FDA approval to market and sell their product. The biobatches are compared with the brand’s product to establish that they are bioequivalent with the brand.
3 Apotex proposed this amendment during trial on the 2010 ANDA, agreeing to include a “not less than 75 percent released at 45 minutes” limitation in its dissolution specification. Apotex submitted the amendment to the FDA about a month after trial, and the FDA approved the change within two weeks after Apotex’s submission; Apotex further agreed to notify the District Court and Ferring if Apotex ever attempted to change the dissolution specification in the future.
4 Reversing the District Court and finding non-infringement because the 2014 amended specification “speaks directly to the question of infringement and would not permit Apotex to market an infringing product.”
5 Only four of “the hundreds of coated commercial products tested” met some of the claim limitations, but these four “outliers were not representative of Watson's ANDA product”. The Federal Circuit came to a similar conclusion when it examined Apotex’s original 2010 ANDA specification, before its 2014 amendments. Apotex’s 2010 specification had a dissolution requirement at 60 minutes (i.e., a timeframe not addressed in the patent). Although the District Court found infringement because Apotex “could violate the patents-in-suit based on the 2010 ANDA,” the Federal Circuit reversed because the original specification was “silent with respect to the claim limitations of the patents-in-suit, which do not specify dissolved dissolution rate at 60 minutes.” As in Watson’s case, the Federal Circuit looked beyond Apotex’s 2010 specification to biobatch data and products that Apotex was actually selling to demonstrate non-infringement.
6 The District Court did not consider this amendment and issued final judgment barring sale of Watson’s generic products.
7 See also Abbott Labs. v. TorPharm Inc., 300 F.3d 1367, 1373-74 (Fed. Cir. 2002) (affirming that TorPharm’s product insert stating “a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship” meets the claim limitation of a composition with “a 1:1 molar ratio of sodium valproate and valproic acid”).
8 Reddy amended its original specification of “not less than 0.3 percent and not more than 1.0 percent” to overcome a deficiency identified by the FDA; neither the original nor the amended specification had been accepted by the FDA at the time of the opinion.
9 As the Federal Circuit stated in Sunovion, 731 F.3d at 1279, “we upheld a summary judgment of no literal infringement [in Bayer I] because the ... specification itself required that the proposed product have a specific surface area outside of the range claimed by the innovator’s asserted patent.”
11 Apotex’s original ANDA specification required that at least 20 percent of the modafinil particles be less than 250 microns. Thus, the specification could cover both infringing and non-infringing products.
12 Evidence showed a decrease in the SSA from 5.09 m2/g to 4.91 m2/g over a six-day period. On remand, the parties settled before further claim construction was conducted.
13 Ferring I, 764 F.3d at 1389-91; Ferring II, 764 F.3d at 1408; see also Biovail Corp. Int'l v. Andrx Pharmc., 239 F.3d 1297, 1304 (Fed. Cir. 2001) (reviewing 11 ANDA amendments disclosed shortly before appellate oral argument and affirming non-infringement, but noting that these amendments should have been disclosed earlier).
14 Ferring I, 764 F.3d at 1391 (“We do not suggest that a district court must always consider any ANDA amendment.”).
15 Id.