

Patent Infringement by ANDA Filing

Mark Pohl †

Pharmaceutical Patent Attorneys LLC, Morristown, New Jersey USA

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Courts are in general designed to adjudicate past events (e.g., crimes and torts which have already occurred). Thus, for example, proving patent infringement merely requires showing the court the on-market product, and comparing it to the patent at issue. United States law, however, provides for a fundamentally-different kind of infringement: potential future infringement by a future generic pharmaceutical product which does not yet exist because it has not yet been approved for marketing. This type of infringement requires US courts to adjudicate future events, predicting the likely characteristics of the future generic pharmaceutical. In requiring a court to adjudicate a potential future event, this type of infringement can pose a unique evidentiary challenge to judges. This article discusses how US judges evaluate potential future infringement by generic pharmaceuticals in case of a 'Paragraph (iv)' challenge of the Orange Book listed patents or a potential challenge to the patents envisaged on the Paragraph (iv) declaration.

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To sell a new generic drug in a regulated market, the manufacturer must first file an application (an Abbreviated New Drug Application, ANDA) requesting permission to do so. United States law is somewhat unique in providing an economic incentive to file ANDAs before the innovator's patents have expired. To do so, the generic manufacturer files the ANDA pursuant to paragraph (iv) of the US' generic drug law (the Hatch-Waxman Act).

Filing an ANDA pursuant to paragraph (iv) of the US Hatch-Waxman Act announces the generic manufacturer's intent to begin selling that generic drug product in the future. Merely filing an ANDA, however, is not the same as offering a drug for sale. Thus, merely filing an ANDA does not actually infringe any patent. Rather, filing an ANDA is an artificial infringement, where courts in the United States must assess potential future infringement in the United States by a product not yet offered for sale in the United States.¹ To evaluate potential future infringement, courts in the United States generally look to the product specifications recited in the ANDA, as well as any other relevant extrinsic evidence.

The United States Court of Appeals for the Federal Circuit recently revisited this rule. This article discusses the current state of the rule.

Premise

To evaluate potential future infringement, courts in US consider the product specifications recited in the ANDA, as well as any other relevant extrinsic evidence. In so doing, a court in US may disregard extrinsic evidence which is non-credible.

Discussion

The Rule and Some Examples

To evaluate potential future infringement in the US, courts in US have generally looked to the product specifications recited in the ANDA, and also to relevant extrinsic evidence.

For example, *Glaxo Inc v Novopharm Ltd*² addressed a dispute over a generic version of Glaxo's Zantac® ranitidine. Glaxo manufactured Zantac® using a specific polymorphic form of ranitidine; polymorphic Form II. Glaxo obtained a patent on polymorphic Form II ranitidine and included that patent in its US medicines agency product dossier.²

Before that patent expired, Novopharm filed an ANDA seeking authorization to market ranitidine in the United States. Novopharm's ANDA and Glaxo's NDA, however, had a critical difference: while Glaxo said its product was made from polymorphic Form II, Novopharm said its product was made from Form I (ref. 2). Thus, Novopharm argued its product would not infringe Glaxo's patent on Form II. Novopharm

†Email: Mark.Pohl@licensinglaw.net

thus filed its ANDA pursuant to paragraph (iv) of the Hatch-Waxman Act, before Glaxo's US patent on ranitidine Form II expired.

This situation, while superficially simple, posed a deeper complication: once the US medicines agency approved Novopharm's 'non-infringing' ANDA, Novopharm would have been free to change its product specification to specify that its generic product contained Form II. Judge Lourie - the former head of patents & licensing for a multinational drug manufacturer - commented, 'The FDA's interest in fixing the exact nature of such a product to be sold, in discharging its own responsibility to ensure the purity, efficacy, and safety of the product, may cause the nature of the product originally applied for to differ somewhat from that ultimately approved.'² Thus, in reviewing the dispute, the US judges were concerned that they could not simply assume that the future generic drug would be identical to the non-infringing product described in the ANDA.

The Court of Appeals for the Federal Circuit thus held, the product specification set forth in the ANDA 'is not the sole factor' in an infringement analysis.² Rather, the court of appeals instructed that a US court must also review any pertinent 'extrinsic' evidence (that is, evidence outside the ANDA) illuminating what generic drug product would in fact likely be sold in the future.² In the ranitidine case, the lower court apparently in fact reviewed quite a bit of evidence outside the ANDA, including, for example, the Certificate of Analysis for the manufacturing batches used in the bio-equivalence studies to support the generic manufacturer's generic drug marketing application.³ That Certificate of Analysis showed that the manufacturing batches used in the bio-equivalence studies did not in fact contain the patented polymorph. Given this evidence, The Court of Appeals found no infringement.

Similarly, in *Bayer AG v Elan Pharma Rsch Corp*,⁴ Bayer listed a patent claiming nifedipine crystals with a specific surface area (SSA) of 1.0 to 4 m²/g. Elan filed an ANDA with a product release specification requiring crystals with an SSA of greater than 5. In reviewing the dispute, the court of appeals reiterated the rule that infringement is not determined by the ANDA specification alone. Rather, the infringement analysis hinges on 'what the ANDA applicant will likely market.'⁴ The court of appeals thus held that one must consider not only the specification set forth in the ANDA itself, but also consider 'any other

relevant evidence submitted by the applicant or patent holder.'⁴ The court of appeals thus considered not only the product specification recited in the ANDA, but also (as in the Zantac® case) the Certificate of Analysis for the generic drug product used in the bio-equivalence studies (which Certificate of Analysis showed SSA of 6.15) and the testimony of the generic drug maker's active pharmaceutical ingredient (API) supplier, who testified that they only sell API with SSA of at least 4.7 or greater. The court of appeals found this evidence, while not contained in the ANDA itself, indicated that Elan's future generic drug product would likely not have the patented 'under 4' SSA, and thus would likely not infringe the patent in the future.⁴ The court of appeals thus confirmed that the ANDA did not infringe the patent.

Curiously, the court of appeals also editorialized that after their ANDA was approved, a generic drug manufacturer might conceivably return to the Food & Drug Administration (FDA) and ask to amend the product specification. The court thus conceded that an after-approval amendment could potentially specify SSA of less than 4. The court of appeals, however, commented that if that happened, the patent owner would be able to sue for infringement.⁵

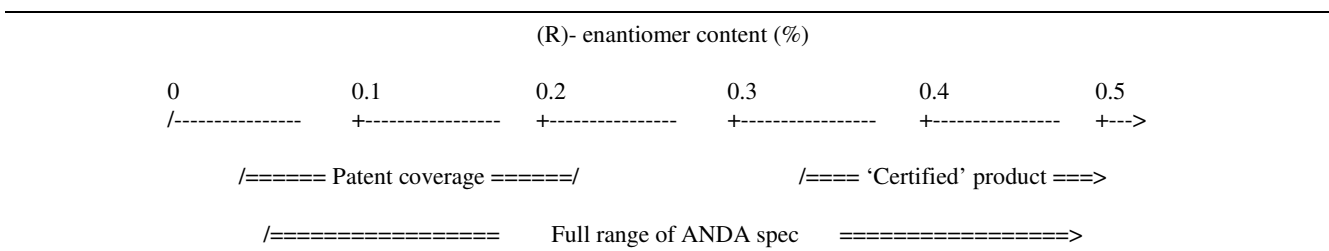
While the patent owner could indeed sue for infringement, however, as a practical matter this legal remedy is largely unavailable for the simple reason that there is no mechanism requiring a generic manufacturer to report such manufacturing changes to a patent-owning innovator manufacturer. Thus, to enforce this right, the innovator would need to continually purchase and test samples of the generic product.

Recent Events

The court of appeals recently revisited this issue in *Sunovion Pharma Inc v Teva Pharma USA Inc*.⁶ In *Sunovion*, the innovator drug manufacturer owned a patent claiming the active pharmaceutical ingredient [(S)-zopiclone] having as an impurity the (R)-enantiomer in an amount of less than 0.25% (ref. 6). A generic drug manufacturer (Dr Reddy's Laboratories) filed an ANDA with a product specification requiring the API have 'not more than 0.6%' of that impurity.⁶ Thus, the ANDA specification range of impurity (not more than 0.6%) literally overlaps the patented range (less than 0.25%). A generic drug product with the full impurity range allowed by the ANDA specification could thus have less than 0.25% impurity, and thus infringe the patent.

The generic drug maker thus submitted to the trial court a certification that its internal manufacturing release specifications require its final product to contain at least 0.30% of the impurity - thus avoiding literal infringement. That is, while the generic drug maker's ANDA specification literally allowed for a product with less than 0.25% impurity, the generic maker promised to not make a product having that low level of impurity, and indeed to maintain at least 0.30% of the impurity. In effect, the generic drug maker promised to, if needed, intentionally contaminate its product with a small amount of impurity, to stay away from the patented purity range.

The impurity content of the patent, the proposed 'certified' generic product and the ANDA specification can be charted as shown:



The *Glaxo* and *Bayer* cases discussed above say that infringement is determined not merely by the product specification in the ANDA, but by any other extrinsic evidence such as actual Certificates of Analysis etc, showing what product the generic manufacturer will in fact sell in the future, when its marketing authorization is approved. Thus, the trial court, relying on the generic maker's written certification promising to avoid the patented purity range, found the proposed generic product would not infringe.

On appeal, the court of appeals disregarded the certification entirely and, looking solely at the four corners of the ANDA specification, found literal infringement. In so doing, the court noted, 'if an ANDA specification defines a compound such that it meets the limitations of an asserted claim, then there is almost never a genuine issue of material fact that the claim is infringed.'⁶ The court expressly dismissed reliance on extrinsic evidence, focusing only on the four corners of the ANDA specification:⁶

What Reddy has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur, and the fact that Reddy either tells the court that its manufacturing guidelines will keep it outside the

scope of the claims or has even filed a declaration in the court stating that it will stay outside the scope of the claims does not overcome the basic fact that it has asked the FDA to approve, and hopes to receive from the FDA, approval to market a product within the scope of the issued claims. In this case, Reddy's request for approval of levorotatory amounts from 0.0-0.6% is within the scope of the 'less than 0.25%' limitation of the '673 patent claims.

The court of appeals commented, 'Simply saying 'but I won't do it' is not enough to avoid infringement.'⁶

Curiously, in disregarding the generic drug maker's written certification of non-infringement, the court cited as its legal authority the *Glaxo* and *Bayer* cases

discussed above.⁶ Both of these cases, however, expressly require courts to consider extrinsic evidence. Further, the *Sunovion* opinion was written by Judge Lourie - the same judge who gave *Glaxo* judgment. Is this a sudden reversal in the law?

Two Interpretations

There are two ways to read this case. The simple read is that *Sunovion* provides a simple, if uneven, black letter rule. If the ANDA specification describes an infringing product, then the ANDA infringes as a matter of law. If the ANDA specification describes a non-infringing product, then the ANDA may infringe as a matter of fact. Heads I win, tails you might lose.

An alternative read is that *Sunovion* is not a new rule - it is merely the same old rule, albeit wrapped in a blanket of tact. When the FDA approved Lunesta® eszopiclone, FDA required it to have less than 0.3% of the (R)- enantiomer impurity.⁶ In filing its ANDA, however, the generic had initially asked FDA to approve a release specification which required at least 0.3% of the impurity. This greater amount of impurity might satisfy the patent lawyers, but left the FDA unimpressed: it rejected that request, demanding the generic 'tighten the [(R)- enantiomer] limit ... to NMT 0.30%.'⁶

The FDA having specifically rejected the generic maker's less-pure specification, one might ask whether the *Sunovion* court doubted whether the generic would (or indeed legally could) in fact sell the product it had certified it would. Underscoring this concern, the court noted that the generic maker had filed its certification with the trial court, but had not told the FDA about this.⁶ The court appears to have sensed that the generic was promising the court one thing, while promising the exact opposite to the FDA.

Its opinion tactfully avoids calling anyone a liar. The court nonetheless dismisses the certification as a 'so-called' certification and, calling it both 'unusual' and 'unenforceable,' disregarded it entirely.⁶

Thus, *Sunovion* is perhaps not a new, 'heads-I-win' rule; it is perhaps the old rule, albeit wrapped in a blanket of tact: in evaluating ANDA infringement, a court must consider extrinsic evidence on what product the generic maker will in fact sell in the future (*Glaxo*, *Bayer* cases), and if that extrinsic evidence is non-credible, the court may disregard it.

Summary

Sunovion can be read two ways: either a 'Heads-I-win' rule, or a tactful refusal to accept arguably incredible evidence. This presents a potential opportunity for a generic manufacturer: filing an ANDA which recites a specification of, e.g., 'NMT 0.6%' where the FDA accepts (in e.g., the ANDA, the API DMF, or a Citizen's Petition) a release spec of 'NLT 0.3%.'

Practice Insights

In addition to its substantive holding, *Sunovion* is a rich source of insights for the proper practice of patent appeals in the United States courts.

Appellate Practice

Sunovion exemplifies what generally does not work, and what does, in appellate practice. What generally does not work is re-litigating factual findings. In its appeal, *Sunovion* re-litigated the trial court's factual finding that the prosecution history limited a claim term. Indeed, *Sunovion* devoted over 90% of its briefing and oral argument to doing so. The Federal Circuit nonetheless left the trial court's factual finding here undisturbed.

What works - at least to garner the appellate court's attention - is a violation of procedural fairness below. In the trial court, the trial judge barred *Sunovion* any

opportunity to respond to the certification. The trial judge, in reviewing the generic's summary judgment motion of non-infringement, noted that the record was unclear on exactly what product the generic would in fact make. The trial court thus denied the generic's summary judgment motion without prejudice, and instructed the generic to submit a request for reconsideration along with a certification explaining exactly what product they would make. The trial judge then closed briefing without allowing *Sunovion* to respond. From the trial judge's standpoint, this perhaps seemed reasonable: the case was running very late on the 30-month calendar, the certification simply said what product the generic would make, and *Sunovion* ostensibly would have little basis to dispute what the generic says goes on in its own plant.

Nonetheless, this procedural shortcut deprived *Sunovion* of any opportunity to respond to certification. While the Federal Circuit's opinion does not dwell on this procedural unfairness, it was the most cogent argument raised in *Sunovion*'s appeal brief which helped attract the Federal Circuit's attention.

Another thing which works is litigating a new factual finding *de novo*. While the factual evidence pertaining to the prosecution history was fully litigated in the trial court, the factual record regarding the certification lacked any response from *Sunovion*, so the factual record below was one-sided and incomplete. Lacking a complete adversarial factual record from the trial court, the Federal Circuit visited this factual issue *de novo*, according no deference to the trial court.

Another thing which works is listening to the judge. During oral argument, *Sunovion*'s counsel argued claim construction. Judge Lourie interrupted, asking whether the court could rely on DRL's certification. *Sunovion*'s counsel gave a brief comment - then returned to arguing claim construction.⁷ In the excitement of presenting appellate argument, stopping to listen to a tactful invitation from a judge is perhaps easier said than done, but it can be critical to success.

Innovator-Side Trial Practice

The docket of the case and the trial below provide a model for innovator-side litigation practice. The innovator filed its infringement complaints on 20 March 2009. Its 30-month stay thus expired on 20 September 2011. The District Court did not produce a final (appealable) judgment, however, until 11 April 2013. The generic manufacturers unwilling

to accept 'at risk' launch liability, this delayed generics by seven months, gaining Sunovion about US\$ 700 million in incremental sales. The innovator law firm (Paul Hastings, NYC) accomplished this without having raised any serious allegation it intentionally delayed the trial - a stellar result, from an innovator's perspective.

Settlement Strategy

The settlement strategy is also informative. The small generics (near ten generic drug makers filed ANDAs) dropped out early. Shortly before the trial court's final judgment, the innovator settled with two of the three remaining generics (Mylan and Sun), allowing them to launch immediately (26 March and 3 April 2013, respectively).

Dr Reddy's, the third generic, was the only one to invest in an appeal to the court of appeals. Here, Dr Reddy's took what appears to be a calculated gamble that a win could provide it with 180 day exclusivity in the United States market. That gamble was not ill-considered: given the *Glaxo* and *Bayer* cases, the court of appeals might have concluded that based on all the evidence (including Dr Reddy's certification of non-infringement), the future generic product would likely not infringe.

The loss on appeal, however, delayed DRL's launch by 1½ years, providing a windfall of co-exclusivity to Sun and Mylan.

Conclusion

To evaluate potential future infringement, courts consider the product specifications recited in the ANDA, as well as any other relevant extrinsic evidence (*Glaxo*, *Bayer* cases). In so doing, a court may disregard extrinsic evidence which is non-credible (*Sunovion*).

References

- 1 *Eli Lilly & Co v Medtronic Inc* (1990) US Supreme Court Reports v 496 pp. 661, 675.
- 2 *Glaxo Inc v Novopharm Ltd* (1997) Federal Reporter (3rd edn) vol. 110, pp. 1562, 1564, 1566, 1567, 1569, 1570.
- 3 *Glaxo Inc v Novopharm Ltd* (1996), Federal Supplement vol. 931, p. 1280, 1288.
- 4 *Bayer AG v Elan Pharma Rsch Corp* (2000), Federal Reporter (3rd edn) vol. 212 pp. 1241, 1246, 1248-50.
- 5 *Bayer AG v Elan Pharma Rsch Corp* (2000), Federal Reporter (3rd edn) vol. 212 pp. 1250, citing United States Code Title 35, § 271(e)(2)(A).
- 6 *Sunovion Pharma Inc v Teva Pharma USA Inc* (2013) Federal Reporter (3d edn) vol. 731 pp. 1271, 1274-75, 1278-80.
- 7 Appeal oral argument transcript at 8:45 to 9:20.