Skinny Labeling and the Inducement of Patent Infringement

by Terry G. Mahn

For several years, the Federal Circuit has steadily plied the doctrine of infringement by inducement. On November 1, it upheld a preliminary injunction against a generic drug launch in an inducement of infringement ruling that threatens the practice of "skinny labeling," as we know it. This would be a major blow to generics that carve patented indications out of their labels ostensibly to avoid litigation, yet market their drugs as being fully "substitutable" for the pioneer uses. If skinny labeling is curtailed, pioneers would be newly incentivized to explore and develop new uses for "old drugs" that will not be immediately "genericized," as they are currently. In the end, the public will benefit from these substantial new investments.

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Summary

In Astra Zeneca LP v. Apotex Inc. ("AstraZeneca"), the Federal Circuit ruled that a pioneer drug manufacturer would be irreparably harmed by the launch of a generic drug that would "necessarily" be used by "some consumers" in an infringing manner. The generic manufacturer claimed it did not possess the "specific intent" to induce infringement, because it had tried to remove all patented use information from its label, and in any event, its drug was approved by FDA for various non-infringing uses. Nonetheless, the court held that a manufacturer that intends to place a drug on the market knowing it will be used in an infringing manner by some consumers would be liable for inducing infringement, for which the appropriate remedy is an injunction. The court said it did not matter that the infringing use was mandated by FDA requirements, because the manufacturer had other options for avoiding inducement.

Although the patented use in AstraZeneca involved an on-label instruction for drug dosing, the broad holding in the case could just as easily apply to the widespread generic practice of "skinny labeling." By industry practice, a generic

drug is "skinny labeled" whenever the generic manufacturer omits a patented use from the approved pioneer label to avoid an infringement suit by the pioneer. Despite the omitted use, these drugs are approved by FDA as therapeutically equivalent to and fully "substitutable" for the pioneer and marketed as such by generic manufacturers. Because many state pharmacies are required by law to fill prescriptions with "substitutable" generics regardless of intended use, some consumers will necessarily receive and use "skinny labeled" generics in an infringing manner. Under the holding in AstraZeneca, this practice now appears to induce patent infringement.

Discussion

A. The Apotex ANDA

In 2000, FDA approved AstraZeneca's NDA for a budesonide (corticosteroid) inhalation suspension drug marketed under the name PULMICORT RESPULES. The Orange Book entry for the drug contained two patents, both of which include method claims directed to administering a budesonide composition once daily by nebulization. The approved label for the drug indicates that it can be administered either once or twice daily. The label also indicates that the drug can be administered in three strengths (0.25mg, 0.5mg and 1.0mg per 2mL vial) and directs the patient to "titrate down" to the lowest effective dosage to avoid possible adverse effects from excessive use of the medication. The "titrate down" language is required by FDA on all labels of inhaled corticosteroid products.

Apotex submitted an ANDA referencing the AstraZeneca drug but requested that it be approved only for administration on a twice-daily basis to avoid the Orange Book patents that claimed once-daily administration. FDA rules generally require a generic label to be identical to the pioneer label. However, one exception occurs when the pioneer drug is protected by a method-of-use patent and the generic applicant does not intend to seek approval for such use. To omit the patented use from its label, the generic applicant files a "section viii" statement with a proposed label that "carves out" all mention of the patent-protected language. For the AstraZeneca drug, Apotex filed a section viii statement omitting all references to the once-daily administration but left in place the downward titration language. Apotex also requested approval for only the two lowest strengths of the drug. FDA approved the Apotex ANDA on March 30, 2009.

B. The District Court Decision

One day after launch, AstraZeneca filed a Declaratory Judgment action and motion for preliminary injunction to stop the distribution of the Apotex drug on the grounds that, among other things, the downward titration language on the proposed label effectively instructed consumers to use the drug once daily, infringing the AstraZeneca patents. Apotex countered that the downward titration language did not instruct users to take the generic drug once daily and, in support, produced correspondence from FDA staff that confirmed that such language did not "teach" once-daily administration. Apotex also argued that because the generic drug had a substantial non-infringing use (twice-daily administration), the requisite intent to induce infringement could not be inferred from its proposed generic label.

The district court disagreed. It concluded that the downward titration language would cause users to infringe AstraZeneca's method claims because titrating down from the starting dosage would necessarily lead to once-daily usage. Accordingly, the court held that the label was factual evidence of Apotex's intent to induce such infringement. Before issuing the preliminary injunction, however, the court gave Apotex an additional opportunity to provide evidence that it did not intend to induce infringement of the method claims. Apotex supplied further testimony as to its efforts to develop a non-infringing label. In the end, the court was not swayed and enjoined the launch of the Apotex drug.

C. The Federal Circuit Appeal

Apotex appealed the district court's decision on both direct and inducement of infringement. On the question of direct infringement, the Federal Circuit reviewed the generic label and agreed with the lower court that the downward titration instructions effectively directed a lowest-beginning-dose user (i.e., one taking the 0.25mg strength) to titrate down to once daily, since there was no other way for such user to titrate lower. It also reviewed a 2008 Citizen Petition dealing with the identical issue involving a proposed IVAX drug and concluded that FDA's decision in that case put Apotex on notice that downward titration may involve once-daily dosing. Notwithstanding FDA's belief to the contrary, direct infringement of the AstraZeneca patents would occur.

On the inducement question, Apotex recounted how it tried to include additional language on its label to ensure only twice-daily dosing but was rebuffed by FDA. It also asserted that it was improper for the lower court to infer intent, citing to the Federal Circuit's holding in Warner-Lambert Co. v. Apotex Corp. that "where a product has

substantial noninfringing uses intent to induce infringement cannot be inferred even when the [alleged inducer] has actual knowledge that some users of its product may be infringing the patent."

The Federal Circuit disagreed. While acknowledging the general rule set forth in Warner-Lambert, it noted that liability for inducing infringement may be found "where evidence goes beyond a product's characteristics or the knowledge that it may be put to infringing uses, and shows statements or actions directed to promoting infringement." Here, the court said Apotex had been found by the district court to possess the requisite specific intent to induce infringement, by including instructions on its proposed label that would cause some consumers to infringe the asserted method claims. Moreover, evidence that showed Apotex was aware of the infringement problem with the proposed label but proceeded with plans to distribute its generic product nonetheless. It was this conduct, the court said, and not merely the planned distribution of the generic drug, that formed the basis (circumstantial or otherwise) for the finding of specific intent.

The Federal Circuit also considered Apotex's contention that it could not possess specific intent because the proposed label contained only general recommendations and not specific recommendations for the infringing use. The court, however, said it was not a matter of specificity but whether the proposed label language would inevitably lead some users to practice the claimed method. It reiterated that the specific intent finding was not based solely on the proposed label but also on Apotex's decision to proceed with its plans to distribute the drug despite being aware that infringement would occur.

Skinny Labeling and Infringement by Inducement

A. Skinny Labeling

As a general rule, generic drugs must be labeled for the same conditions of use approved for the referenced pioneer drug. The Federal Food, Drug, and Cosmetic Act, however, allows a generic drug manufacturer to "carve out" of its label any use approved for the pioneer drug that is protected by exclusivity or patent, provided the generic is no less safe or effective than the pioneer for all the remaining non-protected conditions of use. Generic labels that omit such protected information are often referred to as "skinny labels." FDA rules allow these drugs to be marketed only for the non-protected conditions of use even though they might be prescribed or used by consumers for the carved-out use.

Using a patent-protected generic drug for a carved-out indication directly infringes the patent. Prescribing or dispensing the drug for such use indirectly infringes the patent. The problem, of course, is that no sensible pioneer drug company will pursue doctors, pharmacies or patients for patent infringement. Generic manufacturers, on the other hand, would make an ideal target, but historically they have managed to avoid litigation by making certain they do not actively promote their "skinny labeled" drugs for any patent-protected uses. Nevertheless, these drugs are placed on the market every day by generic manufacturers knowing they will inevitably be used by some consumers in an infringing manner. However, knowledge is not conduct, and without some manner of conduct, it has been difficult to charge generic drug manufacturers with the specific intent required to induce infringement. So "skinny labeled" generics have been getting a "pass" as long as manufacturers are careful to promote their drugs only for the labeled uses. In the wake of AstraZeneca this may no longer be enough.

B. Therapeutic Equivalence and Generic Substitution

When a generic drug is approved by FDA, it receives a therapeutic equivalence code that is entered in the Orange Book beside the drug name to indicate whether it is approved as therapeutically equivalent to the pioneer drug (an "A" code) or not therapeutically equivalent (a "B" code). FDA considers drugs to be therapeutic equivalents if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Significantly, FDA states that "products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product."

With very limited exception, generic drugs approved under an ANDA receive an A-rating when listed in the Orange Book. In this regard, FDA's therapeutic equivalence requirements are "use agnostic" – meaning that an ANDA approved under a section viii statement (carving out a patented use) receives the same A-rating in the Orange Book as a generic approved for all labeled uses. Thus, under the current system, "skinny labeled" generics are designated by FDA and listed in the Orange Book as being fully substitutable for pioneers irrespective of their labeled uses.

FDA states openly that it maintains the Orange Book therapeutic equivalence codes for the benefit of "state health agencies, prescribers and pharmacists." In 14 states, pharmacists are required

by law to substitute "equivalent" generic drugs for pioneer prescriptions unless the doctor specifies "brand only." In 36 other states, pharmacists have the discretion to substitute equivalent generics unless the prescription is designated "brand only." Forty-seven states allow generic drug substitution if requested by the patient, which, as a practical matter, means the decision to substitute is in the hands of the patient's health insurance carrier, which charges much lower co-payment fees for generic equivalent drugs. As for how pharmacists determine whether a generic is equivalent to (and substitutable for) a brand-name drug, 30 states (including the District of Columbia) require use of the Orange Book, with several other states accepting the Orange Book rating system as an option. Three states publish their own formularies, and 18 others define "generic equivalence" essentially to include any generic that is A-rated by FDA. In other words, a generic drug that is A-rated by FDA will be substituted by pharmacies throughout the country and used by consumers regardless of the approved uses on the generic label.

In almost all cases, neither the prescribing physician, nor the pharmacist or the insurance carrier, has any idea what uses are approved on an A-rated generic label, because there is no compendium that tracks such information. Doctors typically write prescriptions for brand-name drugs without reference to the indication or condition being treated, so there is no practical way for a pharmacist to determine (short of calling the doctor) what the drug is to be used for when the substitution decision is made. Unquestionably then, the current drug rating and distribution system ensures that "skinny labeled" generics will be routinely (and automatically) dispensed to patients and inevitably used in an infringing manner. FDA, state pharmacies and the generic manufacturing industry know that this is happening, but nonetheless have turned a "blind eye" due to the enormous political pressure for low-cost drugs. But, no government-run program that essentially institutionalizes patent infringement can forever endure.

C. Inducing Infringement in the Wake of AstraZeneca

There can be no disputing that direct infringement occurs whenever a generic drug is taken by or administered to consumers for a condition of use that is protected by patent. It does not matter what the prescribing physician intended, what the pharmacist is required to do or what the Orange Book therapeutic equivalence rating dictates. What matters is that "skinny labeled" drugs are being marketed by generic manufacturers with the knowledge that they will be used by some consumers in an infringing manner. The only question has been whether such infringement is being induced by the generic manufacturer's conduct. AstraZeneca suggests that it may well be.

The Federal Circuit makes clear in AstraZeneca that liability for inducing infringement may be found where the evidence goes beyond a product's characteristics, or the knowledge that it may be put to infringing uses, and shows "actions directed to promoting infringement." It is sufficient, the court said, for a patent holder to show evidence of a manufacturer's intent to induce infringement along with plans to market the drug knowing that such infringement will occur. In the case of a "skinny labeled" drug, the generic manufacturer appears to be in this same boat. Evidence of intent to induce infringement can be shown by the manufacturer's promotion of its drug as A-rated and fully substitutable for the patent-protected pioneer, knowing that it will be used by patients in an infringing manner. The decision to market the drug, knowing such infringement will occur, is what ultimately perfects the generic manufacturer's act of inducing the infringement.

In AstraZeneca, the Federal Circuit equated labeling with conduct and rejected the defense that nonspecific label recommendations could not demonstrate specific intent. The court said it did not matter if the labeling contains only general recommendation – what matters is whether the labeling language would inevitably lead some users to practice the claimed method. This same reasoning would appear to hold true for "skinny labeled" generics, only here it is not the physical label that inevitably leads to infringement, but rather, the A-rating bestowed by FDA, published in the Orange Book and promoted by the generic manufacturers. In the end, the result is the same. The generic manufacturer effectively relies on an "extrinsic label" for its drug that will inevitably lead some users to practice the pioneer's patent. It is this overall conduct that AstraZeneca seems to say is sufficient to show specific intent to induce infringement.

D. The Orange Book Is the Problem

It is clear from the foregoing discussion that FDA's long-standing Orange Book policies may be to blame; however, nothing prevents FDA from adopting therapeutic equivalence codes that can accommodate the legitimate practice of "skinny labeling" without sanctioning the unchecked infringement of pioneer patents. Rather than issuing A-ratings for a "skinny labeled" generic drug, FDA could, for example, employ an equivalence code that automatically alerts pharmacists (and doctors) to the possibil-

ity that the generic may not be approved for the intended uses and, thus, may not be fully substituted for the pioneer. Such codes already exist (B-ratings) and perhaps should be used here. Regardless, a better system needs to be implemented to ensure that generic labels are actually inspected to determine whether substitution is appropriate or would lead to an infringing use.

In the meantime, until a more accurate therapeutic rating system is put in place, manufacturers of "skinny labeled" generics that market their drugs as A-rated and fully substitutable for patent-protected uses will risk inducing infringement of pioneer patents under the holding in AstraZeneca.

1 *See e.g., Warner-Lambert Co. v. Apotex Corp.,* 316 F.3d 1348 (Fed. Cir. 2003); *Golden Blount, Inc. v. Robert Peterson Co.,* 438 F.3d 1354 (Fed. Cir. 2006); *DSU Med. Corp. v. JMS Co.,* 471 F.3d 1293 (Fed. Cir. 2006); *Ricoh Co. v. Quanta Computer Inc.,* 550 F.3d 1325 (Fed. Cir. 2008); *Vita-Mix Corp. v. Basic Holding, Inc.,* 581 F.3d 1317 (Fed. Cir. 2009); and *SEB S.A. v. Montgomery Ward & Co.,* 594 F.3d 1360 (Fed. Cir. 2010). *See also Aventis Pharma., Inc. v. Barr Labs, Inc.,* 411 F.Supp.2d 490, 518 (D.N.J. 2006), *aff'd,* 208 Fed.Appl. 843 (Fed. Cir. 2006); *Symantec Corp. v. Computer Assocs. Int'l, Inc.,* 522 F.3d 1279, 1292 (Fed. Cir. 2008); and *Broadcom Corp. v. Qualcomm Inc.,* 543 F.3d 683 (Fed. Cir. 2008).

2 *AstraZeneca LP v. Apotex, Inc.,* Nos. 2009-1381, 1424 (Fed. Cir. Nov. 1, 2010).

3 At least one district court has held that a manufacturer of a skinny labeled generic sold as substitutable for the pioneer induces infringement of the carved-out patent. *See Abraxis Biosciences, Inc. v. Navinta, LLC,* 640 F.Supp.2d 553 (D.N.J. 2009), *rev'd* on other grounds, No. 2009-1539 (Fed. Cir. Nov. 9, 2010).

4 Both the DOSAGE AND ADMINISTRATION and the PRECAUTIONS sections of the label direct the patient to "titrate down" to the lowest effective dosage.

5 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 14.94(a)(8)(iv).

6 Unlike a Paragraph IV certification, which challenges the Orange Book–listed patent, a section viii statement avoids the Orange Book patent altogether. Thus, no notice is given to the NDA holder or patentee that the ANDA has been filed and no opportunity exists for the NDA holder to bring an infringement suit and trigger a 30-month stay of FDA approval. See Applications for FDA Approval to Market a New Drug, Final Rule, 68 Fed. Reg. 36676, 36,682 (June 18, 2003).

7 *See AstraZeneca LP v. Apotex, Inc.,* 623 F.Supp.2d 579 (D.N.J. 2009).

8 The court found that AstraZeneca was entitled to injunctive relief based on evidence that a generic launch would lead to unquantifiable damages due to worker layoffs and loss of consumer goodwill, and because a settlement agreement with Teva made any determination of economic harm speculative.

9 The appeal of the district court decision also dealt with validity and claim construction issues, which are not relevant to the infringement analysis herein.

10 AstraZeneca sought to prevent IVAX from "carving out" the once-daily dosing language from its label, but FDA ruled that the omission would be allowed because it would not make the generic less safe or effective than the pioneer drug. FDA also determined that downward titration did not "teach" once-daily administration, did not instruct that the dosing frequency "must" be once daily and, therefore, need not be "carved out" to avoid infringement. While this case shows the kinds of bad things that can happen when FDA ventures into the realm of patent law, FDA likely would not have allowed the "carve out" even if it understood the infringement issue, because a generic without the downward titration language would be less safe or effective than the pioneer for the remaining non-protected conditions of use (i.e., treating asthma). See 21 C.F.R. § 314.127(a)(7).

11 *AstraZeneca* at 32 *citing Warner-Lambert Co. v. Apotex Corp.,* 316 F.3d 1348, 1365 (Fed. Cir. 2003).

12 *Id. citing Ricoh Co. v. Quanta Computer Inc.,* 550 F.3d 1325, 1341 (Fed. Cir. 2008).

13 The Federal Circuit also noted that Apotex failed to provide evidence that any noninfringing use would be "substantial."

14 *AstraZeneca* at 34.

15 *See* 21 C.F.R. § 314.127(a)(7).

16 "A" codes are assigned to drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products. "A" products are those for which actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. "B" codes are assigned to drug products that FDA, at the time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products. "B" products, for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence, often have problems with specific dosage forms rather than with the active ingredients. *Approved Drug Products With Therapeutic Equivalence,* 30th Edition (2010) ("Orange Book") Preface at x and xiv.

17 Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration. They may differ in characteristics such as shape; scoring configuration; release mechanisms; packaging; excipients (including colors, flavors, preservatives); expiration time; and, within certain limits, labeling. Orange Book Preface at iv.

18 *Id.* FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) are approved as safe and effective; (2) are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity and identity; (3) are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) are adequately labeled; and (5) are manufactured in compliance with Current Good Manufacturing Practice regulations.

19 *Id.*

20 ANDAs approved under a Suitability Petition receive a "B" code rating in the Orange Book. *See* 21 C.F.R. § 314.93.

21 Orange Book Preface at i.

22 See , Steven C. Schachter, M.D.,(2007). *State Laws or Statutes Governing Generic Substitution by Pharmacists.* Epilepsy.com/Professionals. Retrieved from http://professionals.epilepsy.com.

23 *See* Wan-Chih Tom, Pharm.D., and Kayla Dotson, Pharm.D., *State Regulations on Generic Substitution,* Pharmacist's Letter, http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PL&pt=2&dd=220901&AspxAutoDetectCookieSupport=1#CHART1186 (last visited Nov. 9, 2010).

24 Only pioneer drug labels are listed in the Physicians' Desk Reference.

25 According to a 2007 study, physicians referred to medications by their brand names much more frequently than by their generic names (including drugs with generic formulations), a finding that was consistent with a 1999 study which found that physicians wrote most prescriptions (86%) using the brand name of the drug – consistent with the trend over the previous 20 years. *See Michael A. Steinman, et al. (2007). What's in a Name? Use of Brand versus Generic Drug Names in United States Outpatient Practice. J. GEN. INTERN. MED., 22-25.645-648 and Dong-Churl Suh. (1999). Trends of Generic Substitution in Community Pharmacies. PHARM. WORLD SCI., 21-26. 260-265.* Nevertheless, generics today account for about 70% of all prescriptions filled.

26 *AstraZeneca* at 32 *citing Ricoh Co. v. Quanta Computer Inc.,* 550 F.3d 1325 (Fed. Cir. 2008).