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Skinny labeling

A recent Supreme Court ruling highlighted a little-used but potentially significant method for generic drugs to gain marketing approval while at least some uses for the brand drug still enjoy exclusivity. In *Caraco v. Novo Nordisk*, the first ANDA case decided by the Supreme Court since the passage of the Hatch-Waxman Act in 1984, the Court unanimously upheld a generic manufacturer's statutory right to bring a counterclaim to compel brand manufacturers to correct or delete patent information submitted to the US Food and Drug Administration (FDA) and listed in the "Orange Book."[1] As a result, certain method-of-use claims for the branded product may be constrained, potentially enabling a generic manufacturer to carve out those still-exclusive uses and bring a generic product to market. This article considers the impact that so-called "skinny labeling" might have on generic entry and consumer welfare.

Background

The Hatch-Waxman Act of 1984 was designed to balance "two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market."[2] Under the Act, the Abbreviated New Drug Application ("ANDA") process reduces the costs and time required to commercialize generics while pioneer incentives are preserved by patent-protected revenues. Pioneers are required to list all patents claiming the drug as well as method-of-use patents (categorized by "use codes") in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the "Orange Book." Generics seeking FDA approval before all patents listed in the Orange Book have expired have two alternatives: (1) to assert that the patents are invalid or will not be infringed ('Paragraph IV' ("PIV") certification) or (2) to limit the application to unpatented uses or indications and to use a "skinny label" that 'carves out' protected uses ('Section viii' statement).

In the case of a typical PIV submission, the generic manufacturer must notify the patent holder after submitting their ANDA to the FDA. Subsequently, the brand manufacturer has 45 days to consider whether to file a patent infringement lawsuit. If the brand files suit, then the ANDA application is automatically postponed for 30 months (unless the patent expires or is deemed to be invalid or

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[1] *Caraco Pharmaceutical Laboratories v. Novo Nordisk*, Case No. 10-844 (Supr. Ct., 2012) (Kagan, J.) (Sotomayor, J., concurring).

[2] *Andrx Pharm., Inc. v. Biovail Corp*., 276 F.3d 1368, 1371 (Fed. Cir. 2002).

uninfringed). The first successful PIV ANDA applicant benefits from 180 days of exclusivity during which no other ANDA can receive final approval from the FDA.

By contrast, the Section viii statement application process may be a faster route to approval because Section viii ANDA filers are not obligated to notify brands and will not be forced into a 30-month stay. However, Section viii filings do not benefit from the 180-day marketing exclusivity and are limited to cases where the targeted brand drug has more than one approved indication or method-of-use patent.[3] Some of the differences between PIV and Section viii submissions are summarized in the table below.

Main differences between Paragraph IV and Section viii filings

	Paragraph IV	*Section viii*
Brand notification	Required after ANDA submission	Not required
ANDA Application Stay	30 months if the brand files suit	None
Market exclusivity	180 days for first successful applicant	None
Applicability	Invalid patent or patent that will not be infringed, even on products with single uses or indications	Products with unprotected uses or indications that can be "carved-out" from the label without sacrificing safety and effectiveness

The number of PIV certifications over the past decade has increased dramatically,[4] leading to a sharp decline in the length of exclusivity enjoyed by pioneers.[5] Since the FDA does not scrutinize Orange Book patent listings, viewing its role as merely "ministerial,"[6] pioneers have been accused of attempting to maintain exclusivity by listing follow-on patents on secondary drug features and overly broad use codes in the Orange Book. Under the 2003 amendments to the Act, however, Congress enacted provisions to allow ANDA applicants to file a counterclaim against the NDA holder to "seek…an order requiring [the pioneer] to correct or delete the patent information…on the grounds

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[3] "Patent use codes, the Orange Book and Section viii statements," Frederick R. Ball, Elese Hanson, The Food and Drug Law Institute, accessed December 3, 2012, (http://www.duanemorris.com/articles/static/ball_hanson_fooddrug_121411.pdf.

[4] For instance, the number of PIV suits filed increased from 35 to 165 between 2008–2011, according to Gregory Glass's "The Paragraph Four Report: Annual Trends," Parry Ashford Publications, accessed December 3, 2012, www.paragraphfour.com.

[5] The average time between launch and the first PIV challenge dropped from 18.7 to 8.2 years for drugs experiencing first generic entry in 1995 compared to those first experiencing generic entry in 2008. (H. Grabowski, M. Kyle, R. Mortimer, G. Long, and N. Kirson, "Evolving Brand-Name And Generic Drug Competition May Warrant A Revision Of The Hatch-Waxman Act," *Health Affairs*, 30 (11) (2011): 2157–2166.

[6] The FDA "has consistently held the position that its role in listing patents in the Orange Book is "ministerial" and that establishing an administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are beyond its expertise and authority. [Report and Order Accompanying the Patent Listing Rule, 68 Fed. Reg. at 36,683; *Caraco*, supra, Note 3 (Dyk, dissenting.)]

that the patent does not claim either—(aa) the drug for which the application was approved or (bb) an approved method of using the drug."[7]

In *Caraco*, the Supreme Court, reversing the Federal Circuit, upheld a generic manufacturer's statutory right to bring such a counterclaim to correct an overbroad use code in the Orange Book. The Court argued that because a PIV certification requires the generic label to be the same as the pioneer's, no carve-out label can be devised for overbroad use codes and infringement is unavoidable. As such, "the counterclaim offers the only route to bring the generic drug to market for non-infringing uses."

Potential issues

The prospect of Section viii entry is daunting for pioneers. Compared to the traditional PIV situation, Section viii entrants are approved without prior notification to the innovator and with no 30-month stay recourse in which to address concerns regarding intellectual property protections and exclusivity. Following *Caraco*, active use codes will likely need to more closely conform to the scope of the method-of-use patents listed in the Orange Book.[8] Furthermore—since Justice Sotomayor noted in her concurring opinion in *Caraco,* that "FDA's guidance as to what is required of brand manufacturers in use codes [is] remarkably opaque" and the *Caraco* litigation arose "in some aspects because of FDA's opacity in describing what is required of brand manufacturers"[9]—should one expect some clarification to industry regarding guidance with respect to use codes? As a result, narrower use codes coupled with the FDA's tendency to generally approve "carve-out" applications,[10] likely implies that the *Caraco* ruling will provide additional impetus to generics regarding Section viii statements. Increased use of Section viii could yield important litigation, strategy, and policy issues concerning Hatch-Waxman litigation dynamics.

A major issue is a Section viii generic benefiting from automatic substitution for other indications that are subject to still-patented methods-of-use. Since the FDA's therapeutic equivalence requirements are "use agnostic," Section viii generics typically receive the same 'A' rating in the Orange Book as a generic approved for all labeled uses. Due to state laws and pharmacy regulations governing generic substitution (and which rely on the Orange Book), Section viii generics may be automatically substituted for the pioneer drug throughout the country, even for carved-out uses and indications.[11] As a consequence, in some respects, the value of any remaining patent life on carved-out methods-of-use could be greatly eroded. As a result, one would expect a reduction in the incentives for pioneers to engage in innovative activity related to new uses and indications for existing products. This is likely to become a progressively greater concern as pharmaceutical science advances and more complex molecules are developed with potentially disparate uses. Is such a change in the resulting tradeoff between static competition (lower prices for existing uses) and dynamic competition (incentives for

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[7] 21 U.S.C. § 355(j)(5)(C)(ii)(I).

[8] The FDA's 240-word limit for use codes may pose some limitations in this respect.

[9] *Caraco Pharmaceutical Laboratories v. Novo Nordisk* (S.. Ct., 2012) (Sotomayor, J., concurring, pp. 3–4).

[10] Since 2002, FDA has sided with generics in 19 out of 21 carve-out cases, with 6 cases still pending. "Decisions, Decisions, Decisions! Our Updated Labeling Carve-Out Citizen Petition Scorecard," FDA Law Blog, official blog of Hyman, Phelps & McNamara, P.C., accessed December 3, 2012, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/05/decisions-decisions-decisions-our-updated-labeling-carve-out-citizen-petition-scorecard.html.

[11] As per *Warner-Lambert v. Apotex* (Fed. Cir. 2003), if a product has substantial non-infringing uses, intent to induce cannot be inferred, even when the defendant has actual knowledge that some users of its products may be infringing the patent.

innovation for new uses) really what Congress intended or anticipated when it was assessing the balance of incentives that was at the crux of the Hatch-Waxman Act when it was introduced in 1984?[12] Alternatively, an initial increase in the use of Section viii statements may lead to further uncertainty with respect to induced or contributory infringement as "carve-outs" are seldom straightforward. For example, while the Federal Circuit has ruled that it is not an act of infringement to submit an ANDA for uses not subject to non-expired patents (*AstraZeneca v. Apotex,* Fed. Cir. February 2012), even in the presence of off-label prescriptions for the carved-out uses (*Warner-Lambert v. Apotex*, Fed. Cir. January 2003), and that references to preclinical studies and potential side effects will not induce doctors to prescribe the drug for the carved-out uses (*Bayer v. Lupin et al.,* Fed. Cir. April 2012), in *AstraZeneca v. Apotex, Fed. Cir. November 2010,* the generic was found to induce infringement, due to the inclusion of "downward titration" language mandated by the FDA in the skinny label. The risk of a contributory or induced infringement finding would depress the incentive to use Section viii statements as the generic companies would have no ability to restrict dispensing for non-infringing uses. Further, what might be an appropriate damages methodology in such circumstances? Would the *but-for* world be one in which the generic had not launched or one in which the generic had not been dispensed for infringing uses?

Finally, we note that there also could be potential antitrust implications of *Caraco*. For instance, although the Supreme Court did not address anti-competitive issues posed by the listing of overly broad use codes per se, the ruling may provide leverage to a generic[13] pursuing a patent misuse defense or antitrust counterclaim.[14]

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[12] Several studies have found that pioneers' incentives under the Act have been eroding, suggesting that R&D pipelines and new drug introductions insufficient to compensate for sales lost to generic competition. See, for instance, Congressional Budget Office (1998), "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry" accessed December 3, 2012, http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf and H. Grabowski and M. Kyle, "Generic competition and market exclusivity periods in pharmaceuticals," Managerial and Decision Economics 28 (2007): 491–502.

[13] In fact, anti-competiveness claims could be brought not only by generic manufacturers but also by purchasers, payers, or consumers who may allege overpayment due to the wrongful exclusion or delay of a generic's entry if it were due to an overly broad use code.

[14] The Supreme Court did solicit input from the DOJ in reaching its decision, and the DOJ's amicus brief illustrates potential anti-competitive issues associated with overly broad use codes (U.S. Supreme Court, Docket No. 10-844, *Brief of Amicus Curiae of United States*, pp. 29–33).

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