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Skinny Labeling after *Hospira v. Burwell:* An End-Run around Pharmaceutical Method of Use Patents?

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The Drug Price Competition and Patent Term Restoration Act of 1984, better known as the Hatch-Waxman Act, codified two competing policy goals: first, encouraging research and development of new drugs by pioneering drug companies; and second, enabling competitors to bring lower-cost generic versions of those drugs to the market. Under the Hatch-Waxman Act, a company seeking to market a generic version of a previously approved drug (the reference listed drug, or "RLD") can file an Abbreviated New Drug Application ("ANDA") demonstrating that the proposed generic drug product is bioequivalent to the RLD. This demonstration of bioequivalency allows the generic applicant to rely on the safety and efficacy data previously submitted to FDA by the brand manufacturer and avoid performing its own costly laboratory and clinical testing.

In addition to FDA approval of its ANDA, however, the putative generic entrant must also contend with patents

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listed in FDA's Orange Book[1] as covering the RLD or its methods of use. An ANDA applicant seeking to market its drug prior to the expiration of patents covering the branded pharmaceutical has two options. The first, more commonly-used pathway requires the ANDA applicant to submit a so-called "Paragraph IV" certification to FDA, along with notice to the patentee, asserting that the patents listed in the Orange Book are either invalid or will not be infringed by the generic drug product described in the ANDA.[2] In response, the patentee can initiate an infringement action under 35 U.S.C. § 271(e)(2), seeking an injunction barring FDA approval of the ANDA. So long as the infringement suit is filed within 45 days of the Paragraph IV notice, final FDA approval of the generic's ANDA is automatically stayed for up to 30 months.

For RLDs protected only by method of use patents, a second pathway for ANDA approval exists: the filing of so-called "Section viii" certifications in conjunction with the use of "skinny labels." As branded pharmaceutical companies discover new uses for previously-identified drugs, method of use patents protecting these new use discoveries are becoming increasingly important. This article discusses the development of the Section viii pathway for ANDA approval and recent changes in the law that may pose additional challenges for branded drug companies seeking to rely on their method of use patents.

Section viii Certification

The statutory provision from which Section viii certifications derive their name, 21 U.S.C. § 355(j)(2)(A)(viii), reads in relevant part:

> [I]f with respect to the listed drug . . . information was filed [by the brand manufacturer] . . . for a method of use patent which does not claim a use for which the [ANDA] applicant is seeking approval under this subsection, [the applicant's ANDA shall contain] a statement that the method of use patent does not claim such a use.

An ANDA applicant may therefore seek approval under Section viii if it submits a statement to FDA that it will not market its generic drug for any use covered by the patents listed in the Orange Book for the RLD. The proposed "skinny" label for the generic product must also remove, or "carve out," all references to the patented method(s) of use.

FDA, however, has repeatedly disavowed sufficient knowledge of patent law to analyze the scope and content of patents listed in the Orange Book.[3] Instead, FDA requires each NDA holder to supply a "use code" that is intended to serve as a shorthand description of the scope of each method of use patent identified in the Orange Book.[4] FDA relies on these "use codes" to identify which indications are patent protected and must be excluded from the generic label for purposes of a Section viii certification. Until recently, it was established that "FDA [would] not approve such an ANDA [filed with a Section viii certification] if the generic's proposed carve-out label overlaps at all with the brand's use code."[5]

Unlike a Paragraph IV certification, a Section viii certification does not trigger a stay of final FDA approval of the ANDA, nor is notice of its filing to the NDA holder required. For this reason, Section viii is often described as a "secret" pathway for ANDA approval. But for branded drug companies, ANDA approval through the Section viii pathway presents a larger problem: having been deemed therapeutically equivalent to the RLD, the generic product approved by FDA through a Section viii certification is often prescribed for *all* uses for which the RLD is approved—including those patent protected indications that have been "carved out" from the generic label.[6] As a result, branded drug companies have consistently argued that the Section viii "carve out" of patented indications is, in reality, illusory.

Laying the Groundwork for Use of Section viii Certifications

One of the first decisions to lay the groundwork for the use of Section viii certifications was *Warner-Lambert Co. v. Apotex Corp.*,[7] which established that a generic applicant could avoid infringement liability so long as the ANDA avoided marketing the drug for a patented use.

Apotex's ANDA sought approval for the use of a generic version of Warner-Lambert's Neurontin® (gabapentin) for the treatment of partial seizures in adults suffering from epilepsy. Neurontin, however, was also widely prescribed off-label for the treatment of neurodegenerative diseases. Warner-Lambert held a patent covering this off-label use, but not for the FDA-approved treatment of adult seizures.

In conjunction with its ANDA, Apotex filed a Paragraph IV certification asserting that its generic gabapentin would not infringe

Warner-Lambert's patent because Apotex's ANDA was directed exclusively to the treatment of adult seizures with no reference to the treatment of neurodegenerative diseases. Although "formally labeled" as a Paragraph IV certification, the Federal Circuit observed that Apotex's certification was "effectively a statement of non-applicable use pursuant to [Section viii]."[8] In response, Warner-Lambert filed an infringement suit alleging that Apotex's generic gabapentin would infringe Warner-Lambert's method of use patent by virtue of gabapentin's widespread off-label prescription for the treatment of neurodegenerative diseases.

The Federal Circuit sided with Apotex, holding that infringement under section 271(e)(2) of the Hatch-Waxman Act was limited to those uses approved by the FDA.[9] Because Apotex did not—and could not—seek approval for the off-label use of its generic gabapentin for the treatment of neurodegenerative diseases, the filing of Apotex's ANDA could not, as a matter of law, infringe Warner-Lambert's method of use claims.

The Federal Circuit also rejected Warner-Lambert's allegation that Apotex was liable for induced infringement under 35 U.S.C. § 271(b).[10] In the court's view, Apotex's "mere knowledge" that its generic product could be used for the patented treatment of neurodegenerative disease was insufficient to establish intent to induce infringement absent evidence that Apotex would "promote or encourage" doctors to infringe Warner-Lambert's neurodegenerative method patent.[11] Instead, the operative analysis was "whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed."[12] Since Apotex's ANDA did not seek approval for the patented treatment of neurodegenerative diseases, Apotex could not be found liable for induced infringement as a matter of law.[13]

Although arising out of a Paragraph IV certification, *Warner-Lambert* validated the use of a Section viii certification by establishing that a generic could avoid infringement liability by excluding or "carving out" the patented method of use from its ANDA, notwithstanding the possibility—or even likelihood—of infringing use by doctors once the ANDA was approved. The Federal Circuit subsequently held in *AstraZeneca Pharmaceuticals LP v. Apotex Corp.* that whether or not the "carved out" patented use was FDA-approved or off-label was irrelevant for purposes of the holding in *Warner-Lambert*.[14] Instead, the Federal Circuit affirmed that the infringement analysis focused exclusively on the approval sought in the ANDA without regard to whether the excluded use had also been approved by FDA.

Holding the Formal Line on Section 271(e)(2) Infringement

In *Warner-Lambert* and *Astrazeneca*, there was a clear divide between the patent-protected use and the indication set forth in the ANDA. That distinction was considerably less clear in *Bayer Schering Pharma AG v. Lupin, Ltd.*[15] There, several generics filed ANDAs, accompanied by Paragraph IV certifications, seeking approval to market a generic version of Bayer's Yasmin® oral contraceptive. Bayer filed suit, alleging infringement of one of its Orange Book patents under section 271(e)(2). The asserted patent, however, did not cover the use of Yasmin for the treatment of oral contraception alone; instead, Bayer's patent claimed the administration of drospirenone (one of the two active ingredients in Yasmin) to achieve a contraceptive effect, an anti-androgenic effect, and anti-mineralocorticoid effect simultaneously in a patient.[16]

Relying on *Warner-Lambert*, the Federal Circuit held that Bayer's infringement claim turned on whether or not FDA had approved the use of Yasmin for simultaneously achieving contraceptive, anti-androgenic, and anti-mineralocorticoid effects.[17] Although the "Indications" section of the label only identified the use of Yasmin for contraceptive purposes, Bayer argued that FDA had approved the combination indication because the "Clinical Pharmacology" section (which was reproduced in the generic labels) reported that drospirenone had been shown to have anti-mineralocorticoid and potentially anti-androgenic activity in animal studies.[18] According to Bayer, the reference to these pharmacokinetic effects, in conjunction with the contraceptive indication, established that the administration of Yasmin for achieving all three effects simultaneously had been approved by the FDA.

The Federal Circuit disagreed, holding that "the label, taken in its entirety, fails to recommend or suggest to a physician that Yasmin is safe and effective for inducing the claimed combination of effects in patients in need thereof."[19] In particular, the court held that the passing mention of the multiple pharmacokinetic

effects of drospirenone in the "Clinical Pharmacology" section of the label was an insufficient basis for FDA approval of a combination indication.[20] The court concluded that absent an express recognition of safety and efficacy, the label could not have formed the basis for FDA approval of a combination indication, and a claim for infringement under section 271(e)(2) could not stand. The court reached this holding as a matter of law despite evidence suggesting that the administration of generic Yasmin could simultaneously induce all three pharmacological effects, as claimed in Bayer's patent. Put differently, evidence showing that the use of the generics' Yasmin products might inherently infringe Bayer's patent did not factor into the Federal Circuit's consideration of the generics' Section viii certifications.

In *Warner-Lambert*, the Federal Circuit announced a rule that focused exclusively on the indication identified in the ANDA and the use code's description of the patented method of use. In doing so, the Federal Circuit took pains to note that its infringement analysis under section 271(e)(2) continued to follow the "traditional infringement analysis."[21] In *Warner-Lambert*, however, the indication recited in the ANDA would not have practiced the patented method of use. In contrast, the evidence in *Bayer* at least established a likelihood that the indication on the generic label was co-extensive with the claimed method of use and would inherently infringe Bayer's patent. The Federal Circuit's affirmation of the district court's noninfringement finding as a matter of law therefore departed from the "traditional infringement analysis" in favor of the application of a bright-line rule from *Warner-Lambert*.

Use Code Amendments and *Caraco*

In response to decisions facilitating the use of Section viii certifications, a number of patentees began amending their use codes to cover all the approved indications for their marketed drug product. A generic entrant attempting to "carve out" the indications overlapping with these broadened use codes would then be left without an FDA-approved indication for which it could seek generic approval. Eventually, this strategy led to a number of instances where the amended use codes allegedly exceeded the scope of the underlying patent(s). Generic drug companies, in response, sought to force those NDA holders to narrow their use codes to conform to the scope of their patent claims. Whether the generic drug companies had the statutory right to do so was the issue addressed by the Supreme Court in *Caraco Pharmaceutical Laboratories v. Novo Nordisk A/S*.[22]

Novo marketed Prandin® (repaglinide), which had been approved for three different diabetes treatments: alone; in combination with metformin; and in combination with thiazolidinediones.[23] At the time Caraco sought FDA approval for its ANDA for a generic repaglinide, Novo listed a single patent in the Orange Book—the '358 Patent—covering the use of repaglinide in combination with metformin. The use code listed for the '358 Patent indicated that the patent covered the "use of repaglinide in combination with metformin to lower blood glucose."[24] Caraco filed a Paragraph IV certification against the '358 Patent, and Novo filed an infringement suit under section 271(e)(2).

Caraco subsequently attempted to convert its Paragraph IV certification to a Section viii certification carving out Novo's patented repaglinide/metformin combination treatment.[25] Soon thereafter, Novo amended its use code for the '358 Patent to read "[a] method for improving glycemic control in adults with type 2 diabetes."[26] Since this broader use code encompassed all three approved methods for treating diabetes with repaglinide, Caraco's proposed carved-out generic label could no longer avoid overlapping with the use code for the '358 Patent. Because, as the Court explained, "the FDA will not approve . . . an ANDA if the generic's proposed carve-out label overlaps at all with the brand's use code," FDA rejected Caraco's Section viii certification.[27]

In response, Caraco filed a counterclaim seeking an order requiring Novo to reinstate its original use code. Novo challenged Caraco's counterclaim, asserting there was no statutory basis for a counterclaim seeking to force the NDA holder to correct its patent use code.

The Supreme Court agreed with Caraco, finding that the Hatch-Waxman Act provided ANDA filers with the right to assert a counterclaim against the NDA holder to force it to amend its use code listed in the Orange Book.[28] *Caraco* therefore provided generic manufacturers with the ability to push back against brand manufacturers they assert have broadened their use codes beyond the scope of the listed patents in order to prevent the use of Section viii certifications. If an ANDA

filer succeeded in forcing a brand manufacturer to narrow its use code, the ANDA filer could then convert its Paragraph IV certification to a Section viii certification and seek approval through a carved-out ANDA.

Hospira v. Burwell: Further Erosion of Method of Use Patents?

While *Caraco* offered ANDA applicants the ability to curb the use of overly broad use codes by NDA holders, the decision also appeared to reaffirm the long-held understanding that FDA would not approve Section viii certifications where the carved-out generic label overlapped with the use code. But that understanding was called into question by FDA's recent approval of a generic version of Hospira's Precedex (dexmedetomidine hydrochloride) sedative, by way of a Section viii certification.

Precedex had been approved by FDA for two separate indications: (1) "sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting," ("Intensive Care Unit Sedation"); and (2) "sedation of non-intubated patients prior to and/or during surgical and other procedures" ("Procedural Sedation").[29] The Orange Book listing for Precedex identified, among others, an '867 Patent with the use code "Intensive Care Unit Sedation."[30]

Mylan and Par Sterile both filed ANDAs for generic versions of Precedex, accompanied by Section viii certifications and generic labels that excluded all references to "Intensive Care Unit Sedation." Shortly before FDA granted final approval of their ANDAs, however, Hospira sought to amend its use code to read "Intensive Care Unit Sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures."[31] Hospira explained that this amended use code was intended to clarify–without expanding–the original use code associated with the '867 Patent.[32] However, Hospira also asserted that some uses of Precedex for Procedural Sedation overlapped with the portion of the "Intensive Care Unit Sedation" use code–for example, if a patient was intubated for surgery while in the ICU. Citing the Supreme Court's statement from *Caraco* that FDA would not approve a Section viii certification "if the generic's proposed carve-out label overlaps at all with the brand's use code," Hospira argued that the only permissible "carve-out" would have to exclude both the Intensive Care Unit *and* Procedural Sedation indications, which would leave no FDA approved indications for which the generics' ANDA could be approved.[33] On this basis, Hospira petitioned FDA to deny approval of any ANDAs for generic Precedex that relied upon a Section viii certification.

FDA rejected Hospira's request, concluding that the generics' Section viii certifications and proposed labels properly "carved out" the use described by either version of Hospira's "Intensive Unit Sedation" use code.[34] In reaching its decision, FDA concluded that "it previously has determined that it can approve ANDAs for broad, general indications that may partially overlap with a protected method of use, so long as any express references to the protected use are omitted from the labeling."[35] Because the proposed "carved out" generic labels did not expressly reference the use of generic Precedex in an intensive care unit, FDA concluded that it could accept the generics' Section viii certifications.

FDA also dismissed the Supreme Court's statement in *Caraco* regarding the overlap between the generic label and the use code as "dicta" limited to the specific factual circumstances in *Caraco*. According to FDA, the passage from *Caraco* cited by Hospira pertained to situations where the approved indication and use code were "exact duplicates" of each other.[36] Under those circumstances, denial of a Section viii certification was appropriate. In contrast, FDA noted that the Supreme Court had observed in *Caraco* that "[o]nly if the use code provides sufficient space for the generic's proposed label will FDA approve an ANDA with a section viii statement."[37] Relying on this passage, FDA concluded that a generic label with a broad indication met the requirements for a Section viii certification even if that indication overlapped with a listed use code so long as they were not co-extensive and the generic label did not explicitly recite the use code.[38]

In the case of Precedex, Hospira had not asserted that either version of its "Intensive Care Unit Sedation" use code covered the entire Procedural Sedation indication, or that the generic label recited either version of the "Intensive Care Unit Sedation" use code.[39] Since there was "space" between the use code and the indication on the generic label, FDA determined that approval of Mylan's ANDA based on its Section viii certification was appropriate.

Hospira immediately filed suit in district court seeking an injunction staying FDA's decision as a violation

of the Administrative Procedures Act ("APA").[40] According to Hospira, FDA's decision effected a change in settled law and adopted a new "rule" under the APA in violation of the required formal rulemaking procedures. Following a temporary stay of FDA's decision, the district court upheld FDA's decision as not arbitrary, capricious, or otherwise not in accordance with the law.[41]

Following the analysis laid out in *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), the district court first examined whether "Congress had spoken to the precise question at issue such that the intent of Congress is clear."[42] The district court concluded that the statute "does not speak to the 'precise question at issue'" because it failed to address, *inter alia*, what constitutes an "overlap" between the NDA holder's use code and the generic carved-out label or "the extent of 'overlap' that may (or may not) be permissible between an ANDA's label and the NDA holder's use code."[43]

The district court further held that under the second step of the *Chevron* analysis, FDA's statutory interpretation was entitled to deference because "it represents a reasonable accommodation of conflicting policies that were committed to the agency's care by the statute," and was consistent with the agency's prior interpretation of Section viii.[44] Like FDA, the district court dismissed as inapplicable "dicta" *Caraco*'s statement that FDA would not approve an ANDA with a Section viii certification if there was an overlap between the "carved-out" label and the Orange Book-listed use code.[45] Instead, the district court agreed with FDA that the circumstances of *Caraco* were distinguishable from the generic Precedex approval because of the "space" between the "Intensive Care Unit Sedation" use code and the "Procedural Sedation" indication on the generic label.[46] The district court rejected Hospira's focus on what doctors "may" do with generic Precedex, holding that "FDA is not obligated to consider how the product might be used by physicians beyond the approved labeling."[47] The possibility of infringing use, in the absence of an express reference to the use code was, in the court's view, "irrelevant."[48]

Discussion

For NDA holders whose products are protected by method of use patents, FDA's approach to the Section viii certification for generic Precedex and the district court's *Hospira* decision threaten to substantially erode the ability of branded drug companies to prevent the approval of ANDAs that include patented methods of treatment. Prior to *Hospira*, it was accepted that FDA approval of a Section viii certification centered on whether the use code and the remaining indications in the "carved out" generic label overlapped. Under this approach, a use code narrower than a broadly worded indication could not be "carved out" without excluding the entire indication, leaving nothing to be approved.

The approach adopted by the district court and FDA in *Hospira*, however, flips this analysis on its head: instead of searching for overlap between the generic label and the use code, it looks for any difference between the scope of the use code and the indication on the generic label. Under this new approach, as long as some discernible difference exists between the use code and the indication recited on the generic label, FDA will grant approval via a Section viii certification. The result is that method of use patents could be rendered largely ineffective to prevent approval of an ANDA under Section viii, as long as the indication for which approval is being sought is broader in scope than the use code associated with the listed patent. As the approval of Novo's generic Precedex demonstrates, the fact that the approved indication could–or likely would–infringe the NDA holder's method of use patent(s) does not factor into this analysis.

Further, FDA's and the district court's attempt to distinguish *Caraco*–which requires the opposite result–is open to attack. The Supreme Court's discussion of Section viii certifications in *Caraco* was independent of the factual circumstances presented by the use codes, or by Novo's ANDA. Moreover, the passage cited by FDA and the *Hospira* court concerning the existence of "space" between the use code and the generic label was part of the Supreme Court's discussion of FDA's rejection of a Section viii certification where the use codes and the generic label overlap. Contrary to FDA's and the *Hospira* court's description of this passage, the Supreme Court simply reiterated the need for the absence of any overlap (or the existence of "space," as the Court described it) between the use code and the generic label in order for approval via Section viii.[49] The conclusions of FDA and the district court regarding the use of a Section viii certification for generic Precedex approval therefore appear to rely upon a misreading of *Caraco*.

The Hatch-Waxman Act was designed as a compromise to balance

the competing interests of branded and generic manufacturers. Following *Hospira*, the Section viii approval pathway threatens to unbalance this compromise by providing a route for generic drug manufacturers to obtain immediate FDA approval of uses for their generic drug products that are covered by the branded pharmaceutical's method of use patent(s). In the case of generic Precedex, the parties settled their dispute before the Federal Circuit had an opportunity to address Hospira's appeal. It remains to be seen whether other district courts–and FDA–will follow the *Hospira* court's reasoning or if they will instead restore the balance between branded and generic manufacturers envisioned by the drafters of the Hatch-Waxman Act.

1. Formally published under the more prosaic title "Approved Drug Products with Therapeutic Equivalence Evaluations."
2. 21 U.S.C. § 355(j)(2)(A)(vii)(IV)
3. *See, e.g.*, *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1676 (2012).
4. Instructions for the submission of use codes are provided with Form FDA 3542a, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048352.pdf.
5. *Id.* at 1677 (citing 68 Fed. Reg. 36682-36683 (2003)).
6. The therapeutic equivalency ("TE") rating granted to the generic product by FDA does not specify the indication for which it was approved. So long as a generic drug receives a TE rating of "AB," pharmacies can substitute the generic drug for the branded drug for all indications.
7. 316 F.3d 1348 (Fed. Cir. 2003).
8. *Id.* at 1360.
9. *Id.* at 1355-56.
10. *Id.* at 1364.
11. *Id.*
12. *Id.*
13. The Federal Circuit further noted that its decision was supported by evidence demonstrating the existence of substantial noninfringing uses for gabapentin. *See id.* at 1365.
14. 669 F.3d 1370, 1379-80 (Fed. Cir. 2012).
15. 676 F.3d 1316 (Fed. Cir. 2012).
16. *Id.* at 1320.
17. *Id.* at 1321.
18. *Id.* at 1322.
19. *Id.* at 1324.
20. *Id.* at 1323.
21. *Warner-Lambert*, 316 F.3d at 1356.
22. 132 S.Ct. 1670 (2012).
23. *Id.* at 1678.
24. *Id.* at 1679.
25. *Id.*
26. *Id.*
27. *Id.* at 1677 (citing 68 Fed. Reg. 36682-36683 (2003)).
28. *Id.* at 1682.
29. Docket No. FDA-2014-N-0087, FDA Letter (Aug. 18, 2014), at 1.
30. *Id.* at 9.
31. *Id.*
32. *See Hospira, Inc. v. Burwell*, No. GJH-14-02662, 2014 WL 4406901, at *7 (D. Md. Sept. 5, 2014).
33. FDA Letter at 9 (citing *Caraco*, 132 S. Ct. at 1677).
34. *Id.* at 10.
35. *Id.* (emphasis added). FDA noted that it had previously approved generic tramadol and generic oxandrolone where the respective generic labels contained broadly-worded limitations, despite the fact that those limitations could arguably include the patented methods of use.
36. *Id.* at 11-12.
37. *Id.* at 12 (citing *Caraco*, 132 S. Ct. at 1677).
38. *Id.*
39. *Id.*
40. *See Hospira*, 2014 WL 4406901, at *1.
41. *Id.*
42. *Id.* at *10 (internal citations and quotes omitted).
43. *Id.* at *11.
44. *Id.* at *12 (quoting *Phillip Morris USA, Inc. v. Vilsack*, 736 F.3d 284, 290 (4th Cir. 2013)).
45. *Id.* at *13.
46. *Id.* at *16-*17.
47. *Id.* at *17 (emphasis in original).
48. *Id.*
49. *Caraco*, 132 S. Ct. at 1677.