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PATENT USE CODES, THE ORANGE  
BOOK AND SECTION viii STATEMENTS: A  
RESPONSE TO TERRY MAHN'S *IS IT TIME FOR  
FDA TO REVISE ITS ORANGE BOOK RULES  
TO DEAL WITH "SKINNY-LABELED" GENERIC  
DRUGS?*

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# Patent Use Codes, the Orange Book and Section viii Statements: A Response to Terry Mahn's *Is it time for FDA to revise its Orange Book rules to deal with "skinny-labeled" generic drugs?*

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## I. INTRODUCTION

Since the Federal Circuit's decision in *Novo Nordisk v. Caraco*,<sup>1</sup> the issue of patent use codes has been at the forefront of the pharmaceutical community. Because the *Caraco* decision permits manipulation of the patent use codes listed in the Orange Book by brand companies to thwart generic competition legislation, corresponding Food and Drug Administration (FDA) regulations should be put in place to stop these practices. A simple solution is best—the use code descriptions should be the same as the claim language in the method of use patent.<sup>2</sup>

Terry Mahn's proposals in *Is it time for FDA to revise its Orange Book rules to deal with "skinny-labeled" generic drugs?*<sup>3</sup> would undermine the competitive framework designed by Congress when it amended Hatch-Waxman. The Hatch-Waxman Act was enacted to provide an abbreviated pathway for generic drug approval.<sup>4</sup> Rather than acknowledge that the issue in *Caraco* was that of a new drug application (NDA) filer abusing the system by purposefully drafting an overly broad use code in order to delay generic competition,<sup>5</sup> the article creates a non-existent "skinny-labeling problem" by questioning the safety and efficacy of generic drugs that have been approved for less than all of the indications of the brand pharmaceutical product. Regardless of the labeling, in order to obtain approval, the proposed product in an abbreviated new drug application (ANDA) must be shown to be bioequivalent to the reference listed drug (RLD).<sup>6</sup> Through the citizen petition process, brand pharmaceutical companies already have a method to address safety concerns relating to any generic product.<sup>7</sup> Thus, Mahn's article presents a straw man when it comes to the issue of safety and generic substitution.

The real issue is the brand pharmaceutical community's abuse of the use code regulations. Although the Hatch-Waxman Act was amended in 2003 to provide a private cause of action to correct or delete patent information improperly listed in the Orange Book, in *Caraco*,<sup>8</sup> the Federal Circuit construed that provision as inapplicable to use codes. The dissent accurately stated the net result of the majority's holding, namely that "a patent can be listed in the Orange Book as erroneously covering approved use A, despite the fact that the patent actually covers approved use B, and the counterclaim provision provides no mechanism for correction."<sup>9</sup> In order to prevent this abuse, FDA should require that use code information be identical to the claim language in the patent and, should that not be the case, generic companies should have a statutory remedy pursuant to the counterclaim provisions.

## POLICY RECOMMENDATIONS

- Require use code descriptions be identical to the claim language in the patent.
- Allow the declaratory judgment section of the statute to be used to correct improper use codes.
- Maintain adequate protections against any inappropriate use of the section viii immediate approval pathway that already exist within the current Hatch-Waxman framework.

## II. BACKGROUND

The Hatch-Waxman Act was originally enacted in 1984.<sup>10</sup> At that time, just under 20 percent of pharmaceuticals were generic.<sup>11</sup> One of the primary policy goals behind the Hatch-Waxman Act was to “make available more low cost generic drugs” to consumers.<sup>12</sup> To this end, Hatch-Waxman has been a great success. Presently, 75 percent of all prescriptions are filled with a generic drug. However, those prescriptions only account for 22 percent of the total dollars spent on prescription drugs.<sup>13</sup> During the past 10 years, generic drugs have saved the U.S. healthcare system nearly \$824 billion.<sup>14</sup> While this savings is ultimately a boon to American consumers and the U.S. healthcare system, it is not desirable to brand pharmaceutical companies. As a result, the statutory scheme has not been without its fair share of manipulation, most of which is the direct result of brand pharmaceutical companies’ attempts to delay or eliminate generic competition.

Under the Hatch-Waxman Act, FDA is required to maintain and publish a list of patents associated with approved drugs that may be infringed by generic entry.<sup>15</sup> This list is published in what is known as the Approved Drug Products with Therapeutic Equivalence Evaluations or, more commonly, the “Orange Book.”<sup>16</sup>

For an NDA applicant, the Orange Book may serve as a method to deter generic competition. Upon filing an NDA, the applicant must submit not only the necessary scientific information and clinical studies, but also a list of any patents that may reasonably be asserted against an allegedly infringing generic product.<sup>17</sup> FDA’s regulations provide that patents that may be listed include “drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method of use patents.”<sup>18</sup> For patents that claim a method of use, the only relevant patents are those that claim “indications or other conditions of use that are described in the pending or approved application.”<sup>19</sup> Once the NDA is approved, FDA then lists the relevant patents in the Orange Book, thus providing future ANDA applicants notice of the patents that the NDA applicant believes are applicable.

In 2003, FDA issued additional regulations relating to method of use patents. Specifically, the FDA regulations provided that the NDA holder must submit to the Orange Book, under penalty of perjury, information for each method of use patent claiming the approved drug.<sup>20</sup> This information, known as the “use code,” includes:

- (1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;
- (2) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and
- (3) The description of the patented method of use as required for publication.

21 C.F.R. § 314.53(C)(2)(i)(O).<sup>21</sup> Despite these detailed requirements, FDA does not verify any of the information listed in the Orange Book, viewing its role with respect to any patent issue as purely “ministerial.”<sup>22</sup>

When filing an ANDA, an ANDA applicant submits a certification as to each patent listed in the Orange Book.<sup>23</sup> In what is known as a “Paragraph IV certification,” the ANDA applicant certifies that the patent is invalid or will not be infringed by the proposed ANDA product.<sup>24</sup> A Paragraph IV certification carries with it both risk and reward. Upon filing a Paragraph IV certification, the ANDA applicant must provide notice to the NDA and patent holder(s).<sup>25</sup> The ANDA applicant may then be sued for infringement.<sup>26</sup> If the lawsuit is filed within 45 days of giving notice, a 30-month stay is initiated, during which FDA may not approve the ANDA.<sup>27</sup> As a reward for challenging weak patents, the statute provides an incentive to the first ANDA applicant to file a Paragraph IV certification: 180 days of generic market exclusivity.<sup>28</sup> This exclusivity is a driving force for the generic industry.

An ANDA applicant does have an alternative route for immediate approval in the case of a method of use patent.<sup>29</sup> In what is known as a “section viii statement,” the ANDA applicant can limit its application to unpatented uses.<sup>30</sup> In addition, a section

viii statement can be used when a drug is indicated for multiple uses, should the ANDA applicant choose to seek approval for only one or a portion of those indications.<sup>31</sup> Through the operation of a section viii statement, the ANDA labeling is revised to include only the indications for which the ANDA applicant seeks approval.<sup>32</sup>

In order to protect their market position, brand companies usually obtain multiple patents that relate to the approved drug. For example, an NDA applicant may list a patent for the active ingredient, additional patents for one or more formulations, and additional patents for multiple uses. This strategy—obtaining and listing as many patents as possible in the Orange Book—may delay generic competition because any patent listed on the Orange Book, whether properly listed or not, must be addressed by the ANDA applicant. This process was particularly problematic prior to the 2003 Amendments:

Orange Book listing elevates every patent as a potential source of delay to generic competition. As both innovator and generic drug manufacturers have learned, the Orange Book can be a strategic weapon, providing an advanced warning mechanism to the marketing department for possible tactical response, and giving the patentee/NDA holder almost automatic injunctive relief for even marginal infringement claims. Adding to a patentee/NDA holder's advantage is FDA's long-standing policy of avoiding patent disputes, as evidenced by its willingness to list in the Orange Book virtually any patent submitted by an NDA holder and its refusal to hear any challenge to the adequacy or completeness of a generic applicant's Paragraph IV certification. NDA holders, therefore, literally are encouraged by FDA rules to 'evergreen their drug patents.' By filing and refiling 'improvement' patents for the same basic drug product, they are able to create a minefield for generic applicants.<sup>33</sup>

Prior to the 2003 Amendments, each time the NDA holder listed an additional patent in the Orange Book, it created an opportunity for an additional 30-month stay.<sup>34</sup> For example, for Paxil® (paroxetine hydrochloride), additional stays were initiated beginning 17 months into the first 30-month stay.<sup>35</sup> This resulted in a total stay of 65 months, with the brand company generating more than \$1 billion in net sales during the year the second stay was issued.<sup>36</sup> The 2003 Amendments addressed this problem by providing a product-by-product certification scheme.<sup>37</sup> Under the current law, a patent listed on the Orange Book after the submission of an ANDA does not generate a new 30-month stay, even though a certification is required.<sup>38</sup> Now brand pharmaceutical companies are playing a new game: by inaccurately describing the scope of their method of use patents to FDA, they are limiting the immediate approval pathway provided by section viii.

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### III. ISSUES IN DISPUTE

#### A. NDA holders are drafting overly broad or inaccurate use codes in order keep generics off the market by rendering section viii null and void.

While Mahn's article argues that ANDA applicants are abusing the Hatch-Waxman regime, quite the opposite is true. The facts of the *Caraco* case neatly illustrate the problem. The ANDA applicant, Caraco, filed an ANDA for a generic version of Prandin® (repaglinide).<sup>39</sup> Prandin is approved for treatment of three uses: "(1) repaglinide by itself (i.e., monotherapy); (2) repaglinide in combination with metformin; and (3) repaglinide in combination with thiazolidinediones ('TZDs')."<sup>40</sup> Initially, Caraco filed a Paragraph IV certification with respect to U.S. Patent Number 6,677,358 ("the '358 patent").<sup>41</sup> Claim 4 of the '358 patent recited "[a] method of treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin."<sup>42</sup> The original use code description provided

to FDA by Ferring accurately described this claim, stating that the patent covered the “use of repaglinide in combination with metformin to lower blood glucose.”<sup>43</sup> Based on its understanding of the patent claim, as informed by the original use code, FDA recommended that Caraco file a split certification, amending its ANDA to include a Section viii statement as to the method claim.<sup>44</sup> FDA stated that it would approve Caraco’s revised label.<sup>45</sup>

Novo then took several steps to delay the approval of the ANDA and hamper the viability of Caraco’s section viii statement.<sup>46</sup> First, Novo moved for reconsideration, arguing that the revised label would present a safety and efficacy risk.<sup>47</sup> Second, Novo submitted a revised use code narrative for the ’358 patent.<sup>48</sup> The revised use code was broader, describing the patent’s single method claim as covering a “method for improving glycemic control in adults with type 2 diabetes mellitus.”<sup>49</sup> Due to the overlap between the revised, broadened use code and the carved-out label, Caraco’s section viii statement was not allowed.<sup>50</sup> And, consequently, Caraco’s label remained unrevised, with an indication that was stipulated to infringe the ’358 patent.<sup>51</sup> The ultimate end result: delay of approval of Caraco’s ANDA.

*Caraco* is not the first time the Federal Circuit has encountered manipulative practices relating to the Orange Book. As the dissent noted, “[s]ome NDA filers realized that they could block generic competition by making unwarranted claims to patent coverage, for example, by listing in the Orange Book a patent for a method of use when in fact the patent was clearly inapplicable.”<sup>52</sup> Moreover, as previously mentioned, prior to the 2003 Amendments, brand pharmaceutical companies used the Orange Book as a means to continually delay approval of ANDAs by obtaining multiple 30-month stays.<sup>53</sup> FDA’s policy of not policing the Orange Book has only encouraged new and innovative ways of abusing the system. In response, Congress enacted counterclaim provisions to allow ANDA applicants to file a counterclaim against the NDA holder to “seek[] an order requiring [the brand company] to correct or delete the patent information submitted by the holder under [21 U.S.C. § 355(b) or (c)] on the ground that the patent does not claim either—(a) the drug for which the application was approved; or (bb) an approved method of using the drug.”<sup>54</sup>

## **B. The Federal Circuit’s decision in *Caraco* has provided a safe harbor for manipulation of the use codes by brand pharmaceutical companies.**

The counterclaim provisions were enacted to “enforce the patent listing requirements at the FDA by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to have the brand company delist the patent or correct the patent information in FDA’s Orange Book.”<sup>55</sup> These provisions were enacted at the same time FDA promulgated its 2003 regulations. FDA stated in the preamble to the 2003 regulations that use codes are important to both the FDA’s and ANDA applicant’s ability to determine unpatented uses for the RLD, such that a section viii statement could be filed to obtain immediate approval.<sup>56</sup> Moreover, FDA sought to amend the previous practice, which required merely an unsworn certification from the NDA holder as to the appropriateness of its method of use patents for listing on the Orange Book.

Under the agency’s regulations, if a party disputes the accuracy of patent information listed in the Orange Book, that party must notify FDA and FDA will, in turn, request that the NDA holder confirm the correctness of the information.<sup>57</sup> However, FDA will not override the decisions made by the NDA holder.<sup>58</sup> In other words, consistent with FDA’s “ministerial role,” if the NDA holder chooses not to correct or amend the patent information, nothing will be done by the agency itself.<sup>59</sup> In view of this limited role, the only remedy for ANDA applicants lies with the courts.<sup>60</sup> With its decision in *Caraco*, the Federal Circuit has closed off that option for ANDA applicants who wish to have a use code description corrected.<sup>61</sup>



**C. FDA’s approval requirements for ANDAs are unaltered by the use of a section viii statement and ensure safety and efficacy of generic drugs, regardless of whether that drug is substituted for a carved-out indication.**

The Hatch-Waxman Act was designed to provide an abbreviated pathway for generic drug approval. Under the statutory and regulatory framework, an ANDA applicant may rely on the safety and efficacy data provided in the NDA for the same drug.<sup>62</sup> Two concepts are important to the abbreviated pathway: bioavailability and bioequivalence. Bioavailability is defined as “the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.”<sup>63</sup> The statute requires that the ANDA product be “bioequivalent” to the reference listed drug of the NDA.<sup>64</sup> Bioequivalence means that there is an “absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.”<sup>65</sup> Thus, bioequivalence is a comparison of the bioavailability of the ANDA product to the RLD.<sup>66</sup> FDA has promulgated regulations that outline how to demonstrate bioequivalence for a variety of products.<sup>67</sup> Since some products are taken orally, others applied topically, some are inhaled and others may be injected, the determination of bioavailability (and therefore bioequivalence) varies.<sup>68</sup> Nonetheless, *in vivo* studies are the most common method of proving bioequivalence.<sup>69</sup>

Aside from proving bioequivalence, the ANDA applicant must show that any changes made to the formulation do not pose safety or efficacy concerns. Specifically, section 355(j)(4)(H) provides that an ANDA must be approved unless, for example, there is information submitted or known to FDA which shows that:

- (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such (ii) conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.<sup>70</sup>

While FDA’s policies allow for liberal excipient changes with respect to solid oral dosage forms, the same cannot be said for various liquid formulations.<sup>71</sup> Moreover, in some circumstances there are financial disadvantages to changing an excipient.<sup>72</sup> In sum, contrary to Mahn’s assertions, both the statute and FDA regulations have more than adequate mechanisms in place to ensure the safety of generic drugs subject to a “skinny label.”

## IV. RESEARCH AND RESPONSE

**A. Require use code descriptions be identical to the claim language in the patent.**

In order to eliminate the possibility of an overly broad or inaccurate use code descriptions, FDA should revise its regulations to require that the use code description(s) is based on the exact language of the method claim(s) of the patent. The lesson learned from multiple Orange Book practices—listing patents in order to generate multiple 30-month stays prior to the 2003 Amendments,<sup>73</sup> listing patents that are irrelevant to the RLD<sup>74</sup> and now, revising the use code to cover more than the relevant method of use patent claims<sup>75</sup>—is simple: where there is any room for variability, there is room for abuse. Thus, from a policy perspective, legislation and corresponding FDA regulations should be put in place to stop these practices. A simple solution is best—the use code descriptions should be the same as the claim language in the method of use patent.

## B. Allow the declaratory judgment section of the statute to be used to correct improper use codes.

The Supreme Court should overrule the Federal Circuit's decision in *Caraco* and adopt the common sense rationale set forth in the dissenting opinion of Judge Dyk. As Judge Dyk explained, "[t]he very enactment of the counterclaim provision assumed that no alternative remedy was available to an ANDA applicant challenging an Orange Book listing. Today's decision strikingly limits the counterclaim provision with the consequence that, in all likelihood the ANDA applicant is left without any remedy to correct an erroneous Orange Book listing with respect to a method of use patent. This cannot be what Congress intended."<sup>76</sup> Due to FDA's policy of not monitoring patent information submitted to the Orange Book, ANDA applicants need a remedy in the courts. Thus, properly construed, the Hatch-Waxman Act allows a court to order a patent holder to correct patent information submitted to FDA. Specifically, the declaratory judgment provisions allow an ANDA applicant to file a "counterclaim seeking an order requiring the [patent] holder to correct or delete the patent information submitted by the holder ... on the ground that the patent does not claim ... an approved method of using the drug."<sup>77</sup> In other words, the statute allows an ANDA applicant a remedy in the courts to correct (or delete) patent information, including the use code, should it misstate the scope of the patent's method claims.

## C. Maintain adequate protections against any inappropriate use of the section viii immediate approval pathway that already exist within the current Hatch-Waxman framework.

Several factors mitigate against any abuse (or overuse) of the immediate approval pathway provided by section viii. First, while a section viii statement does not require notice to the NDA holder or patentee, section viii, in and of itself, does not provide for the 180 days of exclusivity:

Paragraph IV certifications and section viii statements have quite different consequences. Applicants submitting Section viii statements have no obligation to provide notice, nor must they wait thirty months for FDA approval. As the district court explained, "the FDA may [thus] approve a section viii application immediately, making it an attractive route for generic manufacturers, even though a section viii statement does not entitle a successful applicant to the 180-day period of exclusivity bestowed on Paragraph IV applicants."<sup>78</sup>

As a result, the statute still provides an enormous incentive to file a Paragraph IV certification. Second, the label must contain at least one approved indication.<sup>79</sup> Thus, the ANDA applicant cannot file multiple section viii statements, so as to eliminate every indication. Moreover, if there is only one approved indication for the RLD, a section viii statement is not a viable option.

A section viii statement is, however, a viable option for a RLD that is associated with several method of use patents. Under the veil of a concern for patient safety, Mahn argues that ANDA applications with labeling carve-outs should not be automatically substituted at the pharmacy level. In the preface to the Orange Book, FDA notes that "[t]herapeutic equivalence determinations are not made for unapproved, off-label indications." However, therapeutic equivalence is tied primarily to FDA's determination of bioequivalence. Products are therapeutically equivalent if:

(1) they are approved as safe and effective; (2) they 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) *they 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) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.<sup>80</sup>

Thus, the primary technical concern for determining therapeutic equivalence of an ANDA application is bioequivalence.

Given FDA's well-accepted regulations for determining bioequivalence, one thing is clear: it is not the actual safety of generic drugs that is a concern to the brand pharmaceutical industry, but rather the increasing acceptance of generic pharmaceuticals by consumers, pharmacists and doctors.<sup>81</sup> To the extent that safety is an issue for a particular drug, the citizen's petition process allows any party to raise those concerns with FDA.<sup>82</sup>

## V. IMPACT OF POLICY RECOMMENDATIONS

By requiring the use code descriptions to be the same as the claim language in the Orange Book-listed method of use patents, the proposed policy not only seeks to avoid overburdening FDA, but also seeks to eliminate manipulation of the use code regulations. While it may be impossible to anticipate the next loophole, the motivation of the brand pharmaceutical community is certainly clear. Any proposal to eliminate section viii or otherwise alter the substitution of generic drugs for brand drugs should be seen for what it is: a mechanism to preserve the profits of the brand pharmaceutical industry.

## VI. CONCLUSION

With rising healthcare costs, the proposed policy will help to improve affordability and access to healthcare for Americans. Generic drugs are an essential piece of healthcare reform and the proposed policy is in the true spirit of the Hatch-Waxman Act.

## SOURCES

- 1 Novo Nordisk A/S et al. v. Caraco Pharm. Labs., Ltd., 601 F.3d 1359 (Fed. Cir. 2010) (*cert. granted*) (hereinafter, "*Caraco*").
- 2 See SHASHANK UPADHYE, *GENERIC PHARMACEUTICAL PATENT AND FDA LAW*, at § 10.8, p. 549 (2011) (suggesting that to avoid the abuse of the use code regulations, "the FDA may require the Use Code to parallel the exact language of the patent claims and not allow brand companies to free-hand draft the Use Code language.").
- 3 Terry Mahn, *Is it time for FDA to revise its Orange Book rules to deal with "skinny-labeled" generic drugs?*, FDLI's Food and Drug Policy Forum, Vol. 1, Issue 19 (Oct. 12, 2011).
- 4 Drug Price Competition and Patent Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended 21 U.S.C. § 355) (commonly referred to as the Hatch-Waxman Act). The Hatch-Waxman Act was amended in 2003 by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) (hereinafter the "2003 Amendments"). The Federal Circuit has acknowledged that a "central purpose of the Hatch-Waxman Act ... is to enable competitors to bring cheaper, generic ... drugs to market as quickly as possible." See *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330,1344 (Fed. Cir. 2007).
- 5 Novo admitted that the decision to amend its use code was "a response to the section viii ruling ... in December '08 from the FDA." *Novo*, 601 F.3d at 1381 (dissenting opinion).
- 6 21 U.S.C. § 355(j)(2)(A)(iv); *Caraco*, 601 F.3d at 1366 ("Thus, the Act defined the term 'patent information' as 'the patent number and expiration date.' ... Therefore, to maintain consistency in the statutory terms, 'the patent

information' in the counterclaim provision must also mean the patent number and the expiration date." (internal citations omitted)).

- 7** See 21 U.S.C. § 505(q).
- 8** 21 U.S.C. § 355(j)(5)(C)(ii)(I).
- 9** *Caraco*, 601 F.3d at 1377 (dissenting opinion).
- 10** *Supra* note 4.
- 11** Susan Okie, *Multinational Medicines-Ensuring Drug Quality in an Era of Global Manufacturing*, 361 *NEW ENG. J. MED.* 737, 738 (2009).
- 12** H.R. Rep. No. 98-857, pt. 1 at 14 (1984), reprinted in 1984 *U.S.C.C.A.N.* 2647, 2647; see also *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991).
- 13** Lori Chordas, *Savings in a Bottle*, 111 *BESTS REV.* 38-40 (2011).
- 14** *Id.* at 38 (citing IMS Health).
- 15** See 21 U.S.C. § 355(b)(1), (c)(2).
- 16** See Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-month Stays on Approval of Abbreviated New Drug Applications Certifying that a Patent Claiming a Drug is Invalid or Will Not Be Infringed, 68 *Fed. Reg.* 36,676, 36,686 (June 18, 2003) (codified at 21 *C.F.R.* § 314).
- 17** Specifically, the statute requires the NDA applicant to submit "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and which respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1); see also § 355(c)(2).
- 18** 21 *C.F.R.* § 314.53(b)(1).
- 19** *Id.*
- 20** See 21 *C.F.R.* § 314.53(c)(2)(i)(O); (c)(2)(i)(Q).
- 21** The NDA applicant must amend its application to include the required patent information, including, in the case of a method patent, the use code description, should the patent issue after submission of the NDA. See 21 U.S.C. § 355(b)(1); 21 *C.F.R.* § 314.53(c)(2)(ii)(P).
- 22** See e.g., Report and Order Accompanying the Patent Listing Rule, 68 *Fed. Reg.* 36,683; see also 21 *C.F.R.* § 314.53(f); *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1347 (Fed. Cir. 2003).
- 23** 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).
- 24** 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Three other certifications exist, namely that I) there are not patents listed in the Orange book; II) the patent has expired; and III) the ANDA applicant is not seeking approval until after the patent expires. 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(III).
- 25** 21 U.S.C. § 355(j)(2)(B)(i).

- 26** 35 U.S.C. § 271(e)(2)(A). The Hatch-Waxman Act comprises a series of amendments to both the Federal Food, Drug, and Cosmetic Act (FDCA) and the Patent Act. See 21 U.S.C. § 355 (2006); 35 U.S.C. § 271 (2006). As the Federal Trade Commission has explained, the act “provided that certain conduct related to obtaining FDA approval that would otherwise constitute patent infringement would be exempt from infringement under the patent laws. In addition, generic applicants were permitted to rely on the brand-name company’s trade secret data demonstrating the safety and efficacy of the brand-name drug product.” Fed. Trade Comm’n., *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, at 4 (2002).
- 27** 21 U.S.C. § 355(j)(5)(B)(iii).
- 28** 21 U.S.C. § 355(j)(5)(B)(iii)(IV)iv); see also *Teva Pharms. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1318, (D.C. Cir. 2010).
- 29** See 21 U.S.C. § 355(j)(2)(A)(viii); 21 C.F.R. § 314.94(a)(12)(iii)(A).
- 30** *Id.*
- 31** *See id.*
- 32** It is often stated that select indications are “carved out” from the proposed labeling submitted with the ANDA.
- 33** Terry G. Mahn, *Patenting Drug Products: Anticipating Hatch-Waxman Issues During the Claims Drafting Process*, 54 *FOOD DRUG L.J.* 245, 250 (1999).
- 34** See Federal Trade Commission Study, *Generic Drug Entry Prior to Patent Expiration* (July 2002), at page 49, available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.
- 35** *Id.* at 49, Table 4-3.
- 36** *Id.*
- 37** See 21 U.S.C. § 355(j)(5)(B)(iii).
- 38** *See id.*
- 39** *Caraco*, 601 F.3d at 1363.
- 40** *Id.* at 1362.
- 41** *Id.* at 1363.
- 42** Claims 1 through 3 of the ‘358 patent are directed to a pharmaceutical composition comprising repaglinide and metformin, while Claim 5 is directed to a kit for use in the treatment of a patient having non-insulin dependent diabetes mellitus.
- 43** *Caraco*, 601 F.3d at 1362-63.
- 44** *Novo*, 601 F.3d at 1381 (dissenting opinion); see also *id.* at 1363.
- 45** *Id.* at 1363.
- 46** *See id.*
- 47** *Id.* After the use code was revised, Novo’s request for reconsideration was considered moot. *Id.*
- 48** *Id.*
- 49** *Id.*

- 50** *See id.*
- 51** *Id.*
- 52** *Caraco*, 601 F.3d at 1370 (dissenting opinion) (citing *Mylan Pharms., Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2002)).
- 53** *Supra* at nn. 32-36.
- 54** 21 U.S.C. § 355(j)(5)(C)(ii)(I) (emphasis added).
- 55** 149 Cong. Rec. 31,200 (2003) (statement of Sen. Schumer).
- 56** Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676, 36,685 (June 18, 2003) (“requir[ing] the NDA applicant or holder to identify specifically the approved uses claimed by the method of use patent ... would permit ANDA ... applicants, and us, to assess whether the ANDA ... applicant is seeking approval for a use the sponsor states is claimed in the listed patent, and thus determine whether the applicant must submit a patent certification or may submit a section viii statement...”).
- 57** 21 C.F.R. § 314.53(f).
- 58** *Id.*
- 59** *Id.*
- 60** “The Courts have the experience, expertise, and authority to address complex and important issues of patent law.” 68 Fed. Reg. at 36,683.
- 61** *See Caraco*, 601 F.3d 1359.
- 62** *See* 21 U.S.C. § 355(j).
- 63** 21 C.F.R. § 320.1(a).
- 64** 21 U.S.C. § 355(j)(2)(A)(iv).
- 65** 21 C.F.R. § 320.1(e)(emphasis added).
- 66** However, drugs may still be considered bioequivalent when there are intentional differences in rate, but such differences must be “reflected in the proposed labeling” and must “not [be] essential to the attainment of effective body drug concentrations on chronic use and [must be] considered medically insignificant for the drug.” *Id.*
- 67** 21 C.F.R. § 320.24.
- 68** *See* 21 C.F.R.320.1 *et seq.*
- 69** The FDA regulations do provide for waiver of *in vivo* bioavailability studies in limited circumstances. *See* 21 C.F.R. § 320.22(d); *see also* Guidance for Industry: Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (Aug. 2000).
- 70** *See also* 21 C.F.R. § 314.94.
- 71** *See* 21 C.F.R. § 314.94(a)(9)(iii)-(v).
- 72** *See* R. Dormer & K. Karst, *The Drug User Fee Catch-22*, 32 LEGAL BACKGROUNDER (May 22, 2009), published by Washington Legal Foundation, available at [http://www.wlf.org/upload/5-22-09DormerKarst\\_LegalBackgrounder.pdf](http://www.wlf.org/upload/5-22-09DormerKarst_LegalBackgrounder.pdf)

(explaining that “FDA’s regulations preclude the submission of an ANDA for certain drug product category inactive ingredient changes—so-called ‘non-exception excipients’—unless the Agency waives such regulations under 21 C.F.R. § 314.99(b). Historically, FDA policy limits granting such waivers to cases in which an ANDA applicant seeks approval to market a drug product containing a non-exception excipient used in a discontinued, brand-name Reference Listed Drug (RLD) formulation that is not used in the currently- marketed RLD formulation. As a result, manufacturers unable to obtain a waiver for a non-exception excipient change are effectively forced to submit a 505(b)(2) application. While under the pre-FDAAA PDUFA law, such an application usually would *not* have qualified as a fee-paying application, the changes made to PDUFA under FDAAA require the payment of user fees by all FDC Act § 505(b) applicants. In short, such applicants become the victims of a “Catch-22.” That is, FDA’s unnecessarily narrow non-exception excipient policies preclude the submission and approval of an ANDA, which is not subject to PDUFA user fees, and effectively force the submission of a 505(b)(2) application. Meanwhile, Congress’ decision in passing FDAAA to make all 505(b)(2) applications fee-paying applications means that such applications are subject to user fees, which are quite substantial. For Fiscal Year 2009, the one-time full application fee is \$1,247,200, and annual product and establishment fees are \$71,520 and \$425,600 respectively. These fees will likely rise in the coming years.”).

- 73** *Supra* at n. 32-36.
- 74** *See Mylan*, 268 F.3d 1323.
- 75** *See Caraco*, 601 F.3d 1359.
- 76** *Caraco*, 601 F.3d at 1382.
- 77** 21 U.S.C. § 355(j)(5)(C)(ii)(I).
- 78** *Purepac Pharm. Co. v. TorPharm, Inc.*, 354 F.3d 877, 880 (D.C. Cir. 2004) (citing *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191, 195 (D.D.C. 2002)).
- 79** *See* 21 U.S.C. § 355(j)(2)(A)(i).
- 80** *Id.*
- 81** *Supra* n. 13.
- 82** *See* 21 U.S.C. § 355(q) (setting forth requirements for filing a request and providing for delay of the approval of a pending application if “necessary to protect public health.”).

## ABOUT THE AUTHORS

**Frederick (Rick) R. Ball** is vice-chair of the White-Collar Criminal Defense division of Duane Morris's Trial Practice Group and heads the firm's Pharmaceutical, Pharmacy, and Food Industry Group. Mr. Ball focuses his practice on assisting companies or individuals when they are adverse to state or federal governments, including administrative, civil and criminal matters, with the FDA, FTC, DEA, CMS, OIG and other federal and state regulatory agencies. Mr. Ball helps generic pharmaceutical companies, biologics manufacturers, food companies (including supplement manufacturers), pharmacies, long-term care providers and other healthcare providers navigate the complex challenges faced by state and federal regulation of their industries including complying with current good manufacturing practices, price reporting (AMP, AWP, ASP, etc.), the Foreign Corrupt Practices Act, False Claims Act and Anti-Kickback Statute, as well as meeting labeling and advertising requirements. Mr. Ball also assists generic manufacturers bring product to market through patent analysis and Hatch-Waxman litigation. Mr. Ball is experienced in conducting internal investigations and advising companies on actions following the investigation. Finally, Mr. Ball helps companies maintain their trade secrets and competitive advantage through trade secrets litigation and enforcement of restrictive covenants. Mr. Ball emphasizes a team approach to client problem solving and manages matters to achieve client goals both financial and legal. Mr. Ball is an Adjunct Professor of Law at DePaul University College of Law, where he helps train the next generation of lawyers.

**Else Hanson** practices in the area of intellectual property law with an emphasis on patent-related issues, including litigation, prosecution, licensing, due diligence and counseling for clients in the pharmaceutical, food science, biotechnology, chemical and healthcare industries with specific emphasis on the generic drug industry (ANDA). In particular, Ms. Hanson focuses on Hatch-Waxman litigation. Ms. Hanson has worked on opinions of counsel regarding patentability, invalidity, freedom-to-operate and priority of invention of U.S. patents and publications. In addition, Ms. Hanson helps generic pharmaceutical companies, biologics manufacturers, food companies and supplement manufacturers understand and become compliant with current FDA regulations, including good manufacturing practices, labeling and advertising requirements.

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