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# IS IT TIME FOR FDA TO REVISE ITS ORANGE BOOK RULES TO DEAL WITH SKINNY LABELED GENERIC DRUGS?

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# Is It Time for FDA to Revise Its Orange Book Rules to Deal with Skinny Labeled Generic Drugs?

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## I. INTRODUCTION

Late last term in *Pliva v. Mensing,* the Supreme Court reviewed the Food and Drug Administration's (FDA's) generic drug labeling rules and concluded, in a 5-to-4 vote, that in terms of protecting the public health, those rules "make little sense."[1] This term, in *Caraco v. Novo Nordisk,*[2] the Court will review FDA's Orange Book[3] rules governing generic drug substitutions and will likely conclude that these rules "make even less sense."

The common thread in these cases is the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act),[4] a complex and schizophrenic piece of legislation designed to deliver low-cost generic medicines to the public quickly without undermining the enormous investments required for new drug discoveries.[5] Officially, *Caraco* is about the authority of courts to review the accuracy of patent information filed in the Orange Book by brand name (or "pioneer") manufacturers that are intent on slowing the pace of generic entry. Unofficially, the case is about the Orange Book itself—how it can inadvertently distort the scope of patent protection and potentially facilitate the unsafe use of generic drugs, the same issue that split the Court so deeply in *Pliva*. By granting *certiorari* in generic drug cases in back-to back terms, the Supreme Court may be signaling that after 27 years, the Hatch-Waxman "balance" is in need of re-calibration.

According to recent studies, generic drugs account for nearly 75 percent of all prescriptions written and 25 percent of all drug revenues.[6] Moreover, these percentages are certain to increase as an estimated $100 billion in pioneer drug revenues come off patent between now and 2015. The problem for both pioneer manufacturers and consumers is that new drug pipelines are not easy to fill. Various studies estimate the cost of researching, developing and obtaining approval for a new drug to be well over $1 billion. Even new uses for existing drugs can cost tens of millions of dollars to develop. What keeps these staggering investments coming in from pioneer manufacturers is the promise of new patent protection. As long as manufacturers can protect new discoveries long enough to recover their investment and return a reasonable profit, they will continue to feed the voracious drug development cycle. But if drug discoveries "go generic" too quickly the process breaks down, new drug investments dry up and, ultimately, the public health is made to suffer.[7]



### POLICY RECOMMENDATIONS

**FDA should:**

- Create and maintain a database providing information on generic label carve-outs so the public can determine if a generic drug has been approved as "use equivalent" to the pioneer drug.
- Consider labeling changes for skinny-labeled generics.
- Add "use equivalency codes" to the Orange Book.
- Create a second carve-out option for "skinny-labeled" generics to address patent concerns .

In a nutshell, this is what *Caraco* is about—the battle between a pioneer manufacturer trying to protect a large investment in a lucrative drug for as long as possible and a generic manufacturer trying to enter the market with a copy of that drug as quickly as possible. What is unique about this particular dispute is that it will focus Supreme Court attention, for the first time, on the Orange Book and the role it plays in the cost and delivery of national healthcare. What the Court will discover in *Caraco* is how FDA, in an effort to promote generic drug substitution on a national scale, has turned the Orange Book into a vehicle that can distort pioneer patent rights and put patient safety needlessly at risk. While *Caraco*, in theory, is a narrow statutory dispute over the type of patent information that can be listed in the Orange Book, in reality it is over federally driven drug substitution policies that are long overdue for reform.

## II. BACKGROUND

The Orange Book is a national compendium of FDA-approved drugs that actually pre-dates Hatch-Waxman.[8] It provides doctors, pharmacies and reimbursement agencies with important safety and effectiveness information about pioneer drugs and their generic equivalents. A generic found to be "therapeutically equivalent"[9] to a pioneer drug is given an "A" rating in the Orange Book and deemed fully substitutable for the pioneer. The Orange Book also contains information on pioneer drug exclusivity rights and patents that protect the drug product and its conditions of use.

Under the law, if a generic manufacturer seeks FDA approval to market a copy of a pioneer drug before all of the patents listed in the Orange Book have expired, it must either challenge the unexpired patents by filing a Paragraph IV certification[10] or, in the case of method of use patents, seek to omit a patented use from its label by filing a "section viii" statement.[11] A Paragraph IV certification requires the generic to provide notice of its FDA filing to both the pioneer drug holder and the patent owner. If either of these parties files a patent suit within 45 days, FDA approval of the generic application is automatically stayed for 30 months. In contrast, a section viii statement requires no notice to the pioneer or patent owner and no opportunity for stay of FDA approval. Use patents that can be carved out of a pioneer label, therefore, provide no regulatory impediment to generic entry.



Critical to any discussion about Orange Book patents is the fact that FDA does not read or construe patent claims. Instead, it relies exclusively on the information submitted by the pioneer. When a method of use patent is submitted for Orange Book listing, the pioneer is required to select a "use code" that describes the scope of the patent in terms of the uses approved on the label. For example, a patent use code might describe a specific disease or condition the drug is approved to treat, a method for dosing the drug, or instructions on how to deal with an adverse side effect. FDA rules allow pioneers to draft their own use codes (arbitrarily limited to 240 characters), which are entered in the Orange Book without review. In theory, pioneers are kept "honest" in their submissions by the requirement that they sign the Orange Book listing form under "penalty of perjury."[12]

If a generic applicant seeks to carve out a method of use patent with a section viii statement (rather than challenge the patent with a Paragraph IV certification), it provides FDA with a proposed label that omits the information described in the patent use code. FDA must then decide whether the generic drug, with the use code information omitted from its label, is as safe and effective as the pioneer drug for all *remaining non-protected* conditions of use. If the generic is found to be as safe and effective as the pioneer, it is approved with an "A" rating entered in the Orange Book even though it will have different uses on its label than the pioneer. If the generic is found not to be as safe and effective as the pioneer with the use code information omitted, the application cannot be approved under a section viii statement.[13] The generic manufacturer must then file either a Paragraph III certification, indicating that it will wait for the patent to expire, or a Paragraph IV certification to challenge the patent.

Very often, patent claims do not literally correspond with the use code listed in the Orange Book or with the approved uses on the label. This may be due to differences in drug/patent terminology or because a patent may be construed as "reading on" an approved use based on what is disclosed in the file history rather than the claim language itself. For example, a patent

that claims a method for treating acid reflux might be listed in the Orange Book for a drug approved to treat heartburn if the file history indicates that heartburn was within the scope of the patent claims. The patent use code, in such case, might properly read "method of treating heartburn" even though that condition is not explicitly stated in any patent claim.

Language differences can be problematic, however, when a use code is drafted so broadly that it goes beyond the patent claims and covers non-patented uses on the label. In the example above, suppose that the acid reflux drug contains several indications on the label, heartburn being only one of them, and the listed patent claims *only* the heartburn indication. A use code that reads "method for treating acid reflux" might be technically accurate because heartburn is a type of acid reflux, even though it potentially overstates the scope of the patent claim. Thus, a generic manufacturer that seeks to carve out the patented use would be forced to carve out all indications that fall within the language of the broad use code. Arguably, this type of use code would distort the scope of patent protection and eliminate the opportunity for a section viii carve-out of the patented heartburn indication. Inasmuch as FDA will not even attempt to construe patent claims, it is forced to adhere to the use code listed in the Orange Book even when the language is overbroad on its face.[14] The issue in *Caraco* is whether a generic can challenge an overbroad use code that is listed in the Orange Book.

## III. ISSUES IN DISPUTE

### A. The Orange Book Counterclaim Statute

For many years following the passage of Hatch-Waxman, generic manufacturers complained that pioneers were "gaming" the Orange Book by listing patents that did not claim the drug or approved uses, solely to impede generic competition. In 2003, Congress adopted a counterclaim provision for generics that were sued by pioneers for infringement, to seek the removal of improperly listed patent information. That statute provides in relevant part:



> [If the NDA holder] … for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the [generic] applicant, the [generic] applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder … on the ground 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.[15]

Clearly, Congress was intending to prevent pioneer manufacturers from listing inapplicable patents to improperly trigger a 30-month stay of generic approval. Caraco is asking the Supreme Court to construe this statute to include the listing of use codes that could have the same effect. More specifically, Caraco contends that the statute allows a generic manufacturer to challenge an overbroad use code, which blocks the filing of a section viii statement and prevents the generic from selling a non-patent-protected use of a drug.[16] The district court interpreted the statute as operating in this manner but the Federal Circuit, in a split decision, overturned that ruling and held instead that Congress intended the statute to allow courts only to order a correction of the patent number and expiration date listed in the Orange Book but not use code language.[17]

By granting *certiorari*, the Supreme Court appears ready to weigh in on the dispute. Either outcome, though, has its downside. If the Court determines that the statute allows use code challenges it will, in effect, countenance the current practice whereby generics carve patented uses out of their labels to obtain FDA approval but then market their drugs as "A" rated and fully substitutable for *all uses* on the pioneer label.[18] If, on the other hand, the Court upholds the Federal Circuit

ruling, it may encourage use code gamesmanship to slow down or prevent generic competition. Unless the Court can find some middle ground, it will be forced to tip the Hatch-Waxman balance in one direction or the other.

## B. Generic Substitution and Patent Infringement

As already noted, when a generic drug is approved by FDA it receives a code that is entered in the Orange Book to indicate whether it is approved as therapeutically equivalent to the pioneer drug (an "A" rating) or not (a "B" rating).[19] FDA considers drugs to be therapeutic equivalents if they are pharmaceutical equivalents[20] and are expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[21] Significantly, FDA states that any generic drug listed in the Orange Book with an "A" rating "can be substituted with the full expectation that [it] will produce the same clinical effect and safety profile as the prescribed product."[22] Thus, a therapeutically equivalent generic that is approved under a section viii statement and labeled for less than all the uses approved on the pioneer label receives an "A" rating[23] and becomes fully substitutable for the pioneer drug *even if the pioneer drug happens to be prescribed for a use that has been carved out of the generic label.*

Not only does FDA not see any contradiction in its generic rating practices, it fully acknowledges that a primary purpose for maintaining its Orange Book equivalency codes is to benefit the drug substitution decisions of "state health agencies, prescribers and pharmacists."[24] In 14 states, pharmacists are required by law to substitute "A" rated generics for pioneer prescriptions unless the doctor specifies otherwise.[25] In the remaining 36 states, pharmacists have the discretion to substitute generics unless the doctor designates "brand only."[26] Forty-seven states allow generic drug substitution if requested by the patient, which essentially means that the substitution decision is in the hands of medical insurers who impose low or no co-payment fees for generic drugs.[27] Pharmacists in 30 states (and D.C.) are required to follow FDA's Orange Book when making generic equivalency substitutions, three states publish their own formularies and 18 others define "generic equivalence" essentially to include any generic that is "A" rated by FDA.[28] In sum, a generic drug that is "A" rated is automatically substituted throughout the country regardless of the uses that may or may not be on the approved generic label.



As a practical matter, physicians, state pharmacies and health insurance companies have no idea what uses a generic drug has been approved for (or alternatively, which uses have been carved out of the label) because no compendium tracks such information.[29] More surprisingly, FDA does not even maintain a public database of the generic labels that it approves.[30] Because doctors typically write prescriptions for brand-name drugs and without any reference to the indication or condition being treated,[31] there is almost no way to determine what the prescribed drug is intended to treat when the substitution decision is made at the pharmacy. In reality then, the current system—which is grounded on Orange Book equivalency codes—is designed to ensure that "skinny labeled" generics will be routinely and automatically substituted for uses that may very well infringe pioneer patents.[32]

FDA is aware this is happening but claims to have no authority to "interfere" with private drug substitution decisions, even while it maintains an official compendium on which nearly all such decisions are based. State pharmacies and insurance carriers also know, but turn a blind eye because of the enormous financial pressure to move patients onto low-cost generic drugs. And because generics benefit financially from the system, they have little reason to say or do anything that might harm drug sales.[33] Incredibly, none of the entities invested in the current Orange Book scheme seem concerned that they may be actors in a collective fraud whereby patented uses are carved out of generic labels as a condition for FDA approval but are then substituted for those very same uses. Like the old joke about the Soviet government ("they pretend to pay us and we pretend to work"), the Orange Book pretends to protect patents and the manufacturers and sellers of skinny-labeled generics pretend they won't be infringed.

### C. Generic Substitution and Patient Safety

Patent infringement is not the only concern with skinny-labeled generics—patient safety is also at issue. On numerous occasions over the past decade, pioneers have challenged skinny-labeled generics before FDA on safety grounds but have lost in almost every case.[34] Invariably, the pioneer will point to the potential dangers to patients from foreseeable off-label use of the generic drug, but to no avail. FDA steadfastly defends the patent carve-out rules with the oft-repeated *non sequitur* that off-label use involves the "practice of medicine" over which it has no control.[35] Yet, when it comes to defending the Orange Book rating practice that enables such unsafe use, FDA has largely avoided the issue.

In the early carve-out case involving a generic version of Rebetol,[36] FDA explained that it is required to look only at the drug's *intended use* and not at any other use that may have been carved out of the generic label. Because its regulations define intended use as the "objective intent of the person legally responsible for the labeling of drugs,"[37] FDA reasoned that it could only look to what is stated on the label and not how it might foreseeably be substituted by pharmacists or used by patients. This analysis, however, overlooks two rather inconvenient facts: first, nearly all generic drugs are dispensed to patients based on what appears in the Orange Book and not what is on the label; and second, the "A" rating given by FDA to skinny-labeled generics guarantees the automatic substitution for uses *not* on the label. Thus, FDA plainly ignores the fact that patients who receive a substituted generic drug for a carved out use will be missing important information on the label or package insert that could put the patient at risk.

Even when pioneers have argued that a skinny-labeled generic would be missing important safety information linked to the carved out use FDA refused to act. In a 2008 decision involving Camptosar, FDA was petitioned not to approve generic labeling that omitted patent-protected information (for the first-line therapy) that was relevant to drug administration, drug-drug interactions and other warnings and precautions required on the pioneer label.[38] Although FDA had to acknowledge the obvious dangers to patients who might use the generic drug off-label without such information, it held such concerns to be irrelevant as long as the generic was only labeled for the unprotected (second-line) therapy.[39] With no sense of irony to such logic and as if its hands were tied by an Orange Book over which it had no control, FDA then concluded that the generic would be entitled to an "A" rating, thus ensuring it would be substituted and used for the protected first-line therapy but without the safety information required on the pioneer label.

Nothing in the legislative history of Hatch-Waxman suggests, even remotely, that Congress contemplated a generic drug substitution system that would diminish pioneer patent rights or promote the unsafe uses of generic drugs. When Hatch-Waxman was adopted in 1984, the Orange Book had already been in existence for four years. FDA had to revise its Orange Book rules to accommodate the new exclusivity rights and patent protection procedures that were part of the new legislation. However, it could not foresee how its "therapeutic equivalence" rating system and state drug substitution laws might evolve over time to impair the rights of patent owners and put potentially put generic drug users at risk.[40]

## IV. RESEARCH AND RESPONSE

### A. Create and maintain a database providing information on generic label carve-outs so the public can determine if a generic drug has been approved as "use equivalent" to the pioneer drug.

FDA maintains reams of drug information on various websites, yet compiles no data whatsoever on section viii approvals and labeling carve-outs. If a pharmacist (or insurance company) wants to make an informed drug substitution decision to ensure that an "A" rated generic is approved and labeled for a patient's intended use (both to ensure patient safety and to respect patent rights) there is no easy way of doing this under the current Orange Book system.

To illustrate, a pharmacist seeking to determine "use equivalence" would first need to determine whether an "A" rated generic drug is or is not skinny labeled. Because FDA does not make such data publicly available, the pharmacist would have to go to some unofficial source for this information. If the generic happens to be skinny labeled, the pharmacist would then have to determine the intended use of the drug, but since the intended use for the patient is rarely, if ever, noted on the written prescription it would mean contacting the prescribing physician for such information. As a last step, the pharmacist would then have to do a side-by-side comparison of the pioneer and generic labels to determine whether the use intended by the doctor is or is not an approved use for the generic drug. Then and only then could the pharmacist make a fully informed decision as to the attendant risks of drug substitution. Needless to say, few pharmacists or insurance companies are eager to follow such a convoluted and time-consuming verification process. It is (and has been) much easier for them to simply ignore the problem as an artifact of the 31-year-old Orange Book system.

### B. Require labeling changes for skinny-labeled generics.

While the Orange Book may be the underlying source of this problem, better labeling policies could provide a possible solution. For example, FDA could require skinny-labeled generics to state prominently on their labels what specific indications or other uses they are *not* approved for and perhaps why (e.g., exclusivity or patent). FDA could also maintain this information in an online database or even require "dear doctor" letters to be sent by generic manufacturers upon skinny-labeled drugs entering the market.[41] Not only would this prevent generic manufacturers and pharmacists from inadvertently inducing the infringement of patented uses when skinny-labeled drugs are substituted for the prescribed brand but also would alert them to the fact that the generic label may lack important prescribing or safety information for the condition being treated.[42] Moreover, this type of labeling reform would not prevent doctors from "practicing medicine" because skinny-labeled generics could still be prescribed for off-label use based on the doctor's professional judgment.



### C. Add "use equivalency codes" to the Orange Book.

Another option would be for FDA to revise its Orange Book by adding a "use equivalency code" to indicate which generics are approved with skinny-labeling and thus, have only limited substitutability for the pioneer drug.[43] With online access, the Orange Book could easily be expanded to include information on "patent carve-out" codes to indicate the protected uses that the generic is not approved to treat. These codes would alert pharmacists and others about pioneer patent rights and possible safety issues that need to be considered before making any substitution decisions. With this additional information in hand, physicians could then be asked about the intended use of the drug being prescribed so pharmacies, insurance companies and patients would have complete information and safety assurance before any generic substitution decisions are made. Generic labels would also include a statement about the carved out use to draw attention to the fact that important prescribing or safety information may be missing from the label.[44]

### D. Create a second carve-out option for "skinny-labeled" generics to address patent concerns.

Although the foregoing suggestions address pioneer concerns over the *full* substitutability of skinny-labeled generics, they do not address generic concerns about Orange Book use codes that may be used unfairly to prevent *any* substitutability for non-patented uses. The problem here is with FDA's patent certification rules. Currently, a generic manufacturer that wants to carve out a patent-protected use has only one option: carve out the use code as listed in the Orange Book or submit a Paragraph IV certification with all pioneer uses shown on the generic label. But FDA has the authority to create a second carve-out option, for example, one that would permit the generic to submit a proposed label that it believes will not

infringe the use patent (irrespective of the listed use code) *along with* a Paragraph IV certification claiming non-infringement of the patent.[45] Under this option, FDA still would need to make a safety and effectiveness evaluation of the carved out label as it does currently with all section viii filings, only now it would let the courts decide whether the carved out label infringes the pioneer drug. If a court finds that the generic label with the omitted language avoids infringement, FDA could add the omitted language as a new "use code" to the Orange Book with court assurance that it represents the proper scope of the patented use. The pioneer would be assured of its day in court to litigate its use patents prior to generic entry and the generic manufacturer would have an opportunity to challenge an overbroad or incorrect use codes listed in the Orange Book. Undoubtedly there are approaches to these issues that FDA could consider as well.[46]

## V. IMPACT OF POLICY RECOMMENDATIONS

In the age of the Internet there is almost no excuse for FDA not maintaining a database that includes information on generic label carve-outs so the public can determine whether a generic drug has been approved as "use equivalent" to the pioneer. Such a database would provide quick answers to use equivalence questions for skinny-labeled generics, giving much-needed assurance that the correct decision has been made to use a generic substitute rather than the pioneer drug. Requiring skinny-labeled generics to state on their labels what specific indications or other uses they are *not* approved for as well as including this information in the Orange Book in the form of "use equivalency codes" would ensure protection for all patented uses and provide additional measures for patient safety.

## VI. CONCLUSION

Caraco, in effect, is asking the Supreme Court to order Novo Nordisk to list a narrow use code in the Orange Book so that Caraco can carve the patented use out of its label in order to obtain FDA approval and an "A" rating for its drug, so that it can be marketed with the knowledge that its drug will be sold and used in an infringing manner. Framed in this way, it is difficult to imagine the Court siding with this argument. For one thing, it undercuts Constitutionally protected patent rights; for another, it subverts a core tenet of Hatch-Waxman, which is to provide pioneers with the opportunity to litigate drug patents that will be infringed by the sale of a generic drug prior to FDA approval.

Instead, the Court might decide that the counterclaim statute was designed only to prevent pioneers from obtaining any *undeserved* opportunities to litigate patents prior to generic entry, which is what would occur if a listed patent does not claim the pioneer drug or an approved use. But in *Caraco* the patent is properly listed and arguably, the pioneer is simply ensuring that it has the opportunity to enforce its rights against a generic drug that will be approved and marketed as fully substitutable for the patent-protected use. In the end, the Court may well decide that the regulatory scheme at issue in *Caraco,* just like the one in *Pliva*, makes "little sense" but it is up to FDA or Congress but not the courts to resolve.

## SOURCES


**1** Pliva Inc. v. Mensing, 131 S. Ct. 2567, 2581 (2011).

**2** Caraco Pharmaceutical, et al. v. Novo Nordisk A/S, et al., 601 F.3d 1359 (Fed. Cir. 2010), *cert. granted*, 79 U.S.L.W. 3403 (U.S. June 27, 2011) (No. 10-844).

**3** U.S. Food and Drug Admin., Ctr. for Drug Evaluation and Research, Approved Drug Products with Therapeutic Equivalence Evaluations, 31st Ed. (2011) ("Orange Book"). The rules governing Orange Book information are set forth in 21 C.F.R. § 20.117.

**4** Pub. L. No. 98-417, 98 Stat. 1585 (1984).

**5** The act is designed to "strike a balance between 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." Caraco Pharm. Labs, Ltd. v. Forest Labs., Inc., 527 F.3d 1278, 1282 (Fed. Cir. 2008) (citations and brackets omitted), *cert. denied*, 129 S. Ct. 1316 (2009).

**6** U.S. Dep't of Health and Human Servs., ASPE Issue Brief: Expanding the Use of Generic Drugs ("ASPE Issue Brief") 1, 6 (2010), *available at* http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml (last visited July 29, 2011).

**7** Drugs no longer protected by composition or formulation patents may undergo costly research and development to better target their effectiveness, thereby breathing new life into their use for "personalized medicine." A 2009 National Institutes of Health study found that less than 60 percent of all drugs were effective in patients taking them. Diagnostic "biomarkers" can improve a drug's effectiveness by, among other things, identifying patients who are likely to respond to treatments, assessing disease states or mechanisms of action, optimizing dosages, monitoring patient responses and determine toxicity risk or adverse reactions. Method of use patents are the principal means of protecting drug/biomarker discoveries.

**8** FDA adopted its Orange Book regulations in 1980. *See* Therapeutically Equivalent Drugs; Availability of List, Proposed Rule, 44 Fed. Reg. 2932 (Jan. 12, 1979) ("Orange Book Proposed Rule"); Therapeutically Equivalent Drugs; Availability of List, Final Rule, 45 Fed. Reg. 72,582 (Oct. 31, 1980) ("Orange Book Final Rule").

**9** 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. Orange Book Preface at iv.

**10** 21 U.S.C. § 355 (j)(2)(A)(vii); 21 C.F.R. § 314.94 (a)(12)(i).

**11** 21 U.S.C. § 355(j)(2)(A)(viii); 21 C.F.R. § 314.94(a)(12)(iii).

**12** Form FDA 3542 requires applicants to verify "under penalty of perjury" that patent submissions on the form are true and correct and that a "willfully and knowingly false statement is a criminal offense under 18 U.S.C. § 1001."

**13** 21 C.F.R. § 314.127(a) (7).

**14** 21 C.F.R. § 314.53(f) states, "unless the application holder withdraws or amends its patent information … the agency will not change the patent information in [the Orange Book]."

**15** 21 U.S.C. § 355(j)(5)(C)(ii)(I).

**16** Novo Nordisk is alleged to have listed a use code in the Orange Book that covers both a patent-protected combination therapy and a non-patent-protected monotherapy for its drug.

**17** Caraco Pharmaceutical, et al. v. Novo Nordisk A/S, et al., 601 F.3d 1359, 1366 (Fed. Cir. 2010).

**18** It is not entirely clear whether a decision in favor of the petitioner will actually speed up generic entry in situations involving improper use codes. Arguably, the time it will take for a trial court to review the scope of a use code under the counterclaim statute may not be much different than the time it now takes for a court to conduct a Markman hearing on the scope of patent claims in Paragraph IV litigation. In both situations, the court has to review the patent claims and determine their meaning in the context of the drug's labeling. Whereas the counterclaim statute would require a revision and re-listing of the use code that was overbroad in scope, a Markman hearing could achieve the same objective as long as FDA were willing to take cognizance of the court's claim construction and apply that, rather than the listed use code, to any carve-out analysis for the generic label. FDA has shown that it has the authority to disregard Orange Book information that conflicts with court rulings (e.g., in cases where a decision on non-infringement or invalidity automatically lifts the 30-month stay but the blocking patent remains in the Orange Book pending appeal) so there is really nothing to stop FDA from using the claim construction rendered by a court in place of an overbroad use code.

**19** "A" ratings are assigned to drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products. "A" rated drugs are those for which actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. "B" ratings are assigned to drug products that FDA, at the time, considers *not* to be therapeutically equivalent to other pharmaceutically equivalent products. "B" rated drugs, 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. Orange Book Preface at xiii and xvii.



**20** 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 vi-vii.

**21** *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.

**22** *Id*.

**23** ANDAs approved under a Suitability Petition because they differ in dosage, strength, route of administration or the active ingredient in a combination drug approval, receive a "B" rating in the Orange Book. *See* 21 C.F.R. § 314.93.

**24** Orange Book Preface at iv.

**25** *See* Steven C. Schachter, M.D., *State Laws or Statutes Governing Generic Substitution by Pharmacists.* Epilepsy.com/Professionals, Apr. 25, 2007, http://professionals.epilepsy.com/page/statutes_by_ pharmacists.html (last visited July 29, 2011). In Massachusetts, a 2009 law actually requires doctors to defend, in writing, any prescription designated "brand only" (or "dispensed as written") before state reimbursement for a brand can be approved. Mass. Gen. Laws ch. 112, § 12D.

**26** *Id*.

**27** *Id.*

**28** *See* Wan-Chih Tom, Pharm.D., and Kayla Dotson, Pharm.D., State Regulations on Generic Substitution, Pharmacist's Letter, April 2009, http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PL&pt=2&dd=220901&AspxAutoDetectCookieSupport=1#CHART1186 (last visited July 29, 2011).

**29** Pioneer drug labels, but not generic labels, are listed in the *Physicians' Desk Reference*.

**30** The Orange Book does not contain copies of approved drug labels. Drugs@FDA contains copies of approved pioneer labels and, in some cases, label information for the first approved generic.

**31** According to a 2007 study, physicians referred to medications by their brand names more frequently than by their generic names when writing prescriptions, a finding consistent with a 1999 study which found that physicians wrote 86 percent of prescriptions using the brand name of the drug. Michael A. Steinman, et al., *What's in a Name? Use of Brand Versus Generic Drug* Names *in United States Outpatient Practice*. 22 J. Gen. Internal Med. 646 (2007), and Dong-Churl Suh, *Trends of Generic Substitution in Community Pharmacies*, 21 Pharmacy World Sci. 260-65 (1999). Nevertheless, generics today account for about 75 percent of all prescriptions filled. ASPE Issue Brief at 2.



**32** In fact, state laws drafted to respect pioneer patents often fall short in their implementation. In Massachusetts, for example, the list of "interchangeable" drugs includes all drugs that are "A" rated in the Orange Book but specifically *excludes* any drug product that is "protected by a pioneer patent." Mass. Department of Public Health, Regulation 720.060. Because neither the state public health agency nor the FDA maintains a list of "A" rated drugs that are subject to use patent protection the Massachusetts exclusion, although well intentioned, is meaningless.

**33** Generics are not entirely without risk though as they may be inducing the infringement of patents when they promote their drugs as being fully substitutable for patent protected uses. *See* Terry G. Mahn, *Skinny Labeling and the Inducement of Patent Infringement*, Update, November/December 2010, at 39-43.

**34** *See e.g.*, FDA April 6, 2004, Decision Letter, Docket No. 2003P-032/1CPI (denying Citizen Petition) at 18 ("Rebetol Decision").

**35** Bristol-Myers Squibb Co. v. Shalala (BMS) 91 F.3d 1493 (D.C. Cir. 1996). FDA acknowledges that it "does not regulate ... the possible substitution of a generic drug for the pioneer by doctors or pharmacists." See Federal Trade Comm'n v. Simeon Mgmt. Corp., 391 F. Supp. 697, 706 (N.D.Cal.1975) (act does not "interfere in or regulate the practice of medicine between the physician and the patient"); Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503 (1972) (Notice of Proposed Rulemaking) ("the new drug provisions apply only at the moment of shipment in interstate commerce and not to action taken subsequent[ly] ... Once the new drug is in a local pharmacy ... the physician may, as part of the practice of medicine, lawfully ... vary the conditions of use from those approved in the package insert").

**36** Rebetol Decision at 22.

**37** See 21 C.F.R. § 201.128.

**38** See e.g., FDA July 28, 2008, Decision Letter, Docket No. FDA-2008-P-0069 (denying Citizen Petition) at 12-13 ("Camptosar Decision").

**39** FDA reached a similar decision in a 2010 citizen petition decision involving the drug Lyrica. There, FDA indicated that class warning information on the pioneer label about suicidal behavior could be carved out of the generic label as long as the drug was not being approved for a use in the class. FDA July 30, 2010, Decision Letter, Docket No. FDA-2010-P-0087 (denying Citizen Petition).

**40** *See* Orange Book Proposed Rule at 2933("All persons involved in drug product selection obviously need accurate complete and understandable information regarding prescription drug products.") At the time of Hatch-Waxman passage, most state laws required a pharmacist to obtain physician consent before a generic substitution could be made. Today, no state law requires such consent.

**41** FDA uses black box label warnings to inform patients about unapproved uses for certain drugs usually due to safety concerns. *See e.g.,* Prescribing Information for Botox, BLA No. 103000 (revised June 23, 2011) and NovoSeven, BLA No. 103665 (revised Aug. 6, 2010).

**42** Pediatric uses are often carved out of pioneer labels during the exclusivity protection period with an added "warning" to ensure patient safety, for example: "Due to [pioneer] exclusivity rights this drug is not labeled for such use in those pediatric patients."

**43** When the carved out use patents expire, the generic label and Orange Book code could be changed.

**44** FDA has shown flexibility in allowing minor changes in generic labeling beyond a literal carve-out of the patent use code to ensure that important information is properly conveyed to the patient. See e.g., FDA June 30, 2010 Decision Letter, Docket No. FDA-2010-P-0087 (denying Citizen Petition) re Lyrica (pregabalin)).



**45** Despite long-standing FDA "policy" in this area, the legislative history of Hatch-Waxman indicates that a patent certification is required of all ANDAs and the use of a "section viii" patent statement does not eliminate this requirement. For example, the House Report provided an illustration of how section viii was intended to operate by stating that if a listed drug is approved for two indications and the applicant is seeking approval for indication No. 1 and not indication No. 2 because it is protected by a use patent, then the applicant must make the appropriate patent certification and a statement explaining that it is not seeking approval for indication No. 2. H.R. Rep. No. 98-857, pt. 1, at 22 (1984) (emphasis added). The House Report also stated that an ANDA is incomplete and cannot be approved if it omits the required patent certification. *Id.* at 26 (emphasis added).

**46** If "use equivalency" codes are adopted and listed in the Orange Book, pioneer manufacturers would have no incentive to overreach on their use codes because skinny-labeled generics would not be given "full substitutability" for the pioneer drug.

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**Terry G. Mahn** is the Managing Principal of Fish & Richardson's DC office, and the Regulatory and Government Affairs Practice Group Leader. His FDA practice involves pharmaceutical and medical device approvals with special emphasis on drug exclusivities and patent protection under Hatch-Waxman. Mr. Mahn is experienced in a wide range of FDA product approvals including small molecule drugs, biologics, and medical devices. Client work includes gene and cell therapies, anti-hypertensives, ophthalmics, anti-inflammatories, immunologics, antibiotics, anti-anxieties, hormone therapies, and medical gases. He provides advice and counseling to clients on the scope and applications of 271(e)(1) safe harbor; Orange Book practice and patent litigation under 271(e)(2); marketing exclusivities for pioneers and generics; and patent term extensions. Mr. Mahn speaks regularly at industry conferences and has published numerous articles on patent issues and Hatch-Waxman. He is an Advisory Board Member for BNA's Pharmaceutical Law & Industry Report.

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