The pioneer drug label innocuously read, "Take with or without food." But wending its way through the U.S. Patent and Trademark Office (USPTO) was a patent application designed to protect this "novel" method for administering the drug. The patent ploy was clever: any generic drug company attempting to sell the drug with this protected language on the label would be guilty of inducing infringement of the pioneer's patent. One generic, seeking to carve out the protected language from its label, argued to the Food and Drug Administration (FDA) that it was clearly a meaningless instruction whose only purpose was to keep generic drugs off the market. FDA did not disagree. Nonetheless, FDA denied the carve out request, claiming that the agency's hands were tied by the Federal Food, Drug, and Cosmetic Act (FDCA), which requires generic and pioneer labeling to be identical. Quipped one patent attorney familiar with the case, "Word is finally getting out that the label has become the new Orange Book!"

This is the story of how one small section of the FDCA, which requires identity between generic and pioneer labels, has morphed into a potent instrument to extend drug exclusivity—of how the law may compel generics to copy that which patents forbid.

**Patents and FDA—A Difficult Marriage**

Since enactment of the Hatch-Waxman Act in 1984, FDA has been at the vortex of pharmaceutical patent enforcement. Patents are critical to the business model for most pharmaceutical and biotechnology companies. They are the key to protecting drug market share and the monopoly revenues generated from patented drugs, in turn, fuel the enormous investment needed for new drug research and development. Any tinkering with the current patent system or the incentives established by Hatch-Waxman could threaten new drug pipelines and endanger U.S. healthcare. At least, this is what the pioneer manufacturers contend.

Generic manufacturers, of course, see it differently. They point to the high cost of patented medicines, but lay only part of the blame on a lax USPTO and pioneer-friendly Hatch-Waxman incentives. The real culprit, according to the generic manufacturers, is an entrenched FDA bureaucracy that lacks the political will to confront drug companies who are bent on using their patents to "game" the generic approval process and stifle price competition.

FDA finds itself at the center of this controversy due to its role as reluctant overseer of pioneer patents listed in the Orange Book. Although Hatch-Waxman imposes this administrative function on FDA, the agency has always taken the position that it has no authority to develop any expertise in patent law—that expertise lies solely in the province of the USPTO. When confronted with patent questions arising from Orange Book listings, FDA maintains that the agency's role is purely ministerial: FDA is required to list drug patents submitted by pioneer manufacturers.
applicants and to avoid, seemingly at all costs, any disputes raised by generics. Critics charge that FDA’s “see no evil” attitude toward drug patents sends the wrong message to pioneers and is the principal reason that the Orange Book has been exploited over the years to keep generics off the market. While the FDCA narrowly restricts Orange Book listings to patents that claim drugs or their methods of use, FDA has been unable to stop the listing of patents whose claims were only tangentially related to these core features. As a result, pioneers have been able to trigger multiple 30-month stays of generic approval by augmenting (or “ever-greening”) their Orange Book listings.

In 2003, in the face of Federal Trade Commission complaints and threatened legislation, FDA stemmed the aggressive listing practices of the prior two decades by adopting rules to limit pioneers to a single 30-month stay, clarifying the types of patents that would be acceptable for listing, and requiring pioneers to certify Orange Book submissions under penalty of perjury. The new rules hinted that henceforth, FDA staff would review patent claims to ensure eligibility for listing. The impact was immediate and unmistakable—the reforms diminished the versatility of the Orange Book as a tool for delaying generic entry. Thus, following the 2003 reforms, pioneers began looking beyond the Orange Book for new ways to extend their exclusivity rights.

### Drug Labels—Fertile Ground for Patentees

Pioneers soon discovered that drug labeling, particularly the lengthy patient package insert, could be fertile ground for extending exclusivity. Although it is difficult under the law to obtain a patent for printed matter, drug labeling can include instructions that induce others, such as doctors and patients, to infringe a manufacturer’s patent. For example, labeling instructions to “take with milk” would induce infringement of a method claim to administering the drug with casein. Drug labeling also can include descriptive language that provides evidence of direct infringement by the generic manufacturer. An example here might be a drug product described as having a particular molecular weight determined by a patented method (e.g., gel filtration chromatography). Generics would have to infringe the patented method of evaluating the drug’s molecular weight in order to meet the label’s literal language.

Artfully drafted composition claims can be used to protect a host of chemical or physical characteristics associated with a drug product’s ingredients. Patent-protected information might describe a particular formulation or pH level, or recite the stability characteristics, impurities, or molecular structures (e.g., hydration states or polymorphs) found in the drug.

By forcing generics to copy precise product descriptions, labeling can be used to reveal evidence of possible patent infringement or, alternatively, to force generics into admitting to FDA that their drugs may not be identical to the pioneer product.

Indeed, language protected by patent claims theoretically can appear in virtually any section of the drug label (see Table 1) as long as it is relevant to the kinds of information required by FDA rules and guidelines.

<table>
<thead>
<tr>
<th>Table 1: Required Sections of Drug Labels in Which Patents Can Appear</th>
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<tbody>
<tr>
<td><strong>Drug abuse and dependence</strong></td>
</tr>
<tr>
<td><strong>Over-dosage</strong></td>
</tr>
<tr>
<td><strong>Clinical pharmacology (including microbiology, mechanism of action)</strong></td>
</tr>
<tr>
<td><strong>Nonclinical toxicology</strong></td>
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<tr>
<td><strong>How supplied/storage and handling</strong></td>
</tr>
<tr>
<td><strong>Patient counseling information (e.g., pregnancy, nursing mothers)</strong></td>
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<tr>
<td><strong>Other FDA-required information for certain types of drugs or drug substances</strong></td>
</tr>
<tr>
<td><strong>Optional labeling permitted on animal pharmacology and clinical studies</strong></td>
</tr>
<tr>
<td><strong>Description (drug identity and characteristics)</strong></td>
</tr>
<tr>
<td><strong>Indications and usage</strong></td>
</tr>
<tr>
<td><strong>Dosage and administration (including monitoring recommendations, food effects, etc.)</strong></td>
</tr>
<tr>
<td><strong>Dosage forms and strength</strong></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td><strong>Warnings and precautions</strong></td>
</tr>
<tr>
<td><strong>Adverse reactions</strong></td>
</tr>
<tr>
<td><strong>Drug interactions (including absence of interactions)</strong></td>
</tr>
<tr>
<td><strong>Use in specific populations (e.g., pregnancy, pediatric use, geriatric use)</strong></td>
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</tbody>
</table>
For the skilled drafter, there virtually is no shortage of ways to intervene patent claims with labeling language to protect pioneer drug products. For example, method of use claims can protect label information describing novel pharmacokinetic features or different ways to administer drugs, or they may show up as protected warnings, contraindications, or in the instructions concerning adverse drug reactions. Consider the following patent claim that could be used to protect a newly-discovered adverse drug reaction associated with an approved drug:

A method of treating a patient for APPROVED INDICATION, the method comprising (a) determining whether the patient is undergoing treatment with COUNTER-INDICATED MEDICATION; and (b) administering the DRUG to the patient based on patient's treatment with COUNTERINDICATED MEDICATION.

In similar fashion, process claims may be used to protect key features of the manufacturing or quality control processes, or protect testing, screening, or handling operations needed to ensure drug purity or potency, all of which may be described on the label.

Laced with patent protected language, drug labels can be a powerful weapon against generic competition. Pioneers generally are permitted to amend or update product labeling even after generics are on the market. Indeed, FDA's philosophy always has been the more labeling information that can be made available to doctors and patients the better, provided the information is not misleading. Thus, a potent strategy to "re-protect" a drug that has been "genericized" might involve filing a patent application with claims specifically designed to appear on an amended pioneer label. Then, before the patent issues, the pioneer incorporates the protected language in a routine labeling amendment, which generics, by law, must copy. Later, when the patent issues the generics face imminent patent liability.

This strategy takes advantage of the fact that the label playing field is mainly one-sided in favor of the pioneer. Moreover, FDA does not scrutinize a pioneer’s intent when additional labeling text is sought. Consequently, pioneers are discovering that drug labels can be "ever-greened" with new patents just as the Orange Book was in years past.

Patent "Carve Outs"—Favoring the Pioneer

The critical question for generics is whether the Hatch-Waxman requirement for identical labeling admits an exception where the labeling language raises issues of patent infringement. While there is authority in the statute and FDA’s regulations for a patent "carve out," the scope of the carve out is a topic of current debate.

Hatch-Waxman created an accelerated process for generic drug approvals premised on the notion that the generic essentially is an identical copy of the referenced pioneer drug. The safety and effectiveness clinical studies requirement was eliminated because generics would contain the same active ingredient as the approved product and would duplicate other important features, in particular, labeling instructions, dosage form, route of administration, and strength. Even so, certain of these features could be changed by a generic upon FDA approval of a suit-ability petition or "because the new drug and the listed drug are produced or distributed by different manufacturers." Thus, Hatch-Waxman accepted the possibility that generics might have to "design around" certain features in the pioneer product in order to produce and distribute a competing drug.

In 1992, FDA implemented generic labeling regulations to "flesh out the statutory exceptions" for differences due to distribution by "different manufacturers" to the labeling identity requirement.

Such differences between the applicant’s proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

The administrative record indicates that, at the time of promulgation, FDA regarded the patent carve out as a fairly broad exception, unlimited by the nature of the patent claims that might appear on the label. Although FDA initially had proposed narrow carve out language limited to approved "indications," the agency expanded the exception in response to an industry objection that "non-approved conditions discussed on a label could also be protected by patent." Because patents to nonapproved conditions were not to be listed in the Orange Book, FDA appeared willing to accept the rationale that generics could omit language from pioneer drug labels protected by claims.
of patents that were not eligible for listing and, hence, not subject to the generic certification requirement.\textsuperscript{16}

The generic labeling regulations soon became the focus of litigation in Bristol-Myers Squibb v. Shalala.\textsuperscript{17} Bristol-Myers Squibb (BMS) challenged the labeling carve out regulations as being beyond FDA's statutory authority because the objective was to delay generic competition by forcing generics to label their drug with an indication protected by three-year exclusivity rights. In siding with FDA, the D.C. Circuit observed that "whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference" under the statute.\textsuperscript{18} Generics need not copy pioneer labeling verbatim, the court ruled, but are free to choose the indications to promote. To hold otherwise would permit pioneers to unjustly extend their drug monopolies.

Reading both BMS v. Shalala and FDA's administrative record narrowly, the agency recently said FDA will apply the patent carve out exception only for patents listed in the Orange Book.\textsuperscript{19} According to FDA, this will prevent the proliferation of generic labels to the confusion of doctors and patients and, moreover, is consistent with the agency's historical approach toward patents. But FDA's logic does not necessarily stand scrutiny, because it is one thing to turn a blind eye toward the ministerial act of Orange Book listing, and another when it comes to determining the scope and language of a bona fide labeling carve out.\textsuperscript{20} In this respect, FDA has simplified its role even further by determining that Orange Book carve outs involving use patents can occur only at the "use code" level—meaning that if the specific language to be carved out does not have it own use code in the Orange Book it cannot be omitted from the generic labeling.\textsuperscript{21} At some point, FDA's discomfort with reading patents will collide directly with the agency's responsibility to facilitate generic market entry.

One other important limitation on labeling carve outs is that the omitted language must not "render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."\textsuperscript{22} This additional restriction suggests a possible further strategy for extending exclusivity—a pioneer need only invent, patent, and label an incremental improvement in safety or effectiveness of its drug to put generics at risk. Such a strategy could be justified on the grounds that the public clearly benefits from any improvements in the safety and effectiveness of pioneer products.

**Ever-Greening the Label**

FDA's current patent "carve out" policy involves a straight-forward, two-step examination. First, the labeling language sought to be carved out must be identified as deriving from a patent listed in the Orange Book (thus, only drug composition and use claims are eligible for label omission); and, second, the protected language may be carved out only upon a finding by FDA that the generic will be as safe and effective as the pioneer drug for all nonpatent protected conditions of use.\textsuperscript{23}

Generics argue, however, that step one—Orange Book listing—is an overly narrow reading of FDA's authority and threatens to convert drug labels from purely medical aids into instruments for extending drug monopolies. They contend that FDA rules give pioneers broad latitude to update labeling language under a legitimate guise of informing doctors and patients of new information about the drug, regardless of whether the new information is related to safety or efficacy. As a result, generics assert that the current process invites patent abuse, stifling generic entry and threatening competitive drugs already on the market.\textsuperscript{24}

As noted, there are many types of patent claims that can protect language on drug labels that never appear in the Orange Book.\textsuperscript{25} Patents that never reach the Orange Book can protect language describing how the drug is made, how it is to be stored, how it is to be verified for purity or potency, or how it is to be packaged. In some cases, patents work indirectly through labeling language, such as the case where a manufacturer "characterized" certain structural information on its large molecule drug, which a generic could validate only by using its patented test method. Another concern is that once generics are on the market,\textsuperscript{26} pioneers have a strong incentive to opt out of the Orange Book in order to eliminate the carve out option and force generics to amend their labels\textsuperscript{27} with infringing language. Although there are theoretical penalties for pioneers who fail to list patents, they are draconian (i.e., withdrawal of FDA approval) and unlikely to ever be employed. Moreover, even if such sanctions were to be threatened, the delays inherent in the administrative process serve the ultimate goal of delaying generic entry.\textsuperscript{28}

A solution proposed by generics is for FDA to broaden the agency's carve out policy to encompass all patents, whether or not listed in the Orange Book, thereby removing the incentive for pioneers to game the Orange Book. Another suggestion is to require
pioneers to disclose whether patents protect labeling changes or pending applications—much like most standards organizations now require—so FDA can make informed decisions as to whether the amendments are for competitive gain or for consumer health. Until FDA implements such policies, generics argue, pioneers will have strong incentives to “ever-green” their labels to the detriment of generic entrants. △

Ramon Tabtiang, Ph.D., an Associate in the Boston, MA, office of Fish & Richardson P.C., provided invaluable assistance in the preparation of this article.

1. The Orange Book identifies drug products approved on the basis of safety and effectiveness by FDA under the FDCA. Drugs on the market approved only on the basis of safety (covered by the ongoing Drug Efficacy Study Implementation review or pre-1938 drugs) are not included in the Orange Book. The main criterion for inclusion is that the product be the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. FDA, Center for Drug Evaluation and Research (CDER), Approved Drug Products with Therapeutic Equivalence Evaluations, 26th Edition, Preface (Jan. 26, 2006), http://www.fda.gov/cder/ob/docs/preface/preface.pdf, and other guidelines on labeling.


4. Patients listed in the Orange Book prevent generic drug approval unless the generic applicant certifies that the patents are expired, invalid, or not infringed. See also Mahn & Deal, Orange Book Gaming, FDLI Update, May/June 2001, at 8.

5. FDA made clear that certain previous listing practices would no longer be tolerated including the listing of patents for off-label uses, drug packaging, metabolites, and intermediates not found in the final drug. By enforcing the statutory requirement that certain listed patents claim drugs or their methods of use, FDA entry tends to be speeded, as these patents typically are the first to expire in the panoply of patents obtained by innovators to protect their products. E.g., 21 C.F.R. § 314.55 requires that new drug application (NDA) applicants submit method of use patents to describe the pending method of using and the “related patent claim.” The regulation also provides that a listing can be rejected if FDA determines that a patent is “not eligible for listing.” FDA staff continue to dispute whether this regulation requires them to read and interpret submitted patents.

6. In re Nagg, 367 F.3d 1336 (Fed. Cir. 2004) (concluding that inventions are “not … entitled to patent a known product by simply attaching a set of instructions to that product.”).

7. 21 C.F.R. § 201.257 permits any chemical and physical information as long as it is “appropriate.”

8. The generic might be approved under statutory exceptions that allow certain labeling differences, but the regulatory process may create a discoverable paper trail that supports a charge of patent infringement under the doctrine of equivalents if the generic argues that the drug is nonetheless bioequivalent.


10. In 2006, FDA issued new labeling procedures to standardize labeling formats and clarify the information to be included on drug labels. See FDA, Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products—Implementing the New Content and Format Requirements (Jan. 18, 2006), available at http://www.fda.gov/cder/guidance/001556d.pdf; 21 C.F.R. § 201.56 (stating that labeling shall contain a summary of the essential scientific information needed for the safe and effective use of the drug. It shall be informative and not misleading”).

11. FDCA §§ 505(j)(2)(A)(ii) and 505(j)(2)(C)(ii) enable applicants to file suitability petitions for changes in “route of administration, the dosage form, or the strength.”

12. 21 C.F.R. § 314.127(a)(7).

13. Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Mary Macdonald, Associate Director, Regulatory Affairs, Apotex Corp. et al. (June 11, 2002) (Docket No. 02-0191) (hereinabove Transmorrol Letter).

14. 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).


16. FDCA § 505(j)(2)(A)(v). The regulation’s open-ended language, “other aspects of labeling,” suggests that the rule was intended to do more than implement section 505(j)(2)(A)(viii), the narrow exception to the generic certification requirement for Orange Book listed patents. Sections 505(j)(2)(A)(v) and 505(j)(2)(G) are cited in support of the regulation, but do not concern Orange Book listings.

17. 91 F.3d 1493 (D.C. Cir. 1996).


19. This policy effectively eliminates any patent carve out for “old antibiotics” because these drugs are not eligible for Orange Book listing. An “old antibiotic” is one whose active moiety was submitted for approval prior to November 21, 1997, under section 507 of the FDCA. FDA, CDER, Guidance for Industry and Reviewers: Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act (May 1998), available at http://www.fda.gov/cder/guidance/index.htm. Curiously, FDA has approved a labeling change so that a generic could carve around an unlisted patent to a formulation of cefuroxime axetil, but the agency did so without explicitly invoking the patent carve out regulation. Letter from Dennis Baker, Associate Commissioner for Regulatory Affairs, FDA, to Donald O. Beers et al. (Feb. 15, 2002) (Docket Nos. 00P-1150 & 01P-0428). FDA is in the process of reviewing the patent carve out policy for old antibiotics.

20. FDA already engages in a rudimentary patent analysis when reviewing and verifying that an NDA applicant has correctly certified a patent for listing in the Orange Book (see 21 C.F.R. § 314.53), and when reviewing a generic applicant’s Paragraph IV certification and/or Section viii statements in view of patent claims and label language.

21. An example of this would be an approved indication for treating nausea, which is given Orange Book use code “U-330,” if the listed patent claims nausea treatment for only one condition (e.g., postoperative) but the drug is approved also to treat nausea under a nonapproved condition (e.g., preoperative), the protected language can only be carved out by carving out all use code U-330—which includes the nonapproved condition the generic would be trying to keep.

22. 21 C.F.R. § 314.127(a)(7).

23. Id. FDA has approved carve outs of protected conditions where the carve out does not alter effectiveness for the principal patient population. For example, FDA allowed a carve out for a generic version of tramadol because the carve out only pertained to treatment of a small minority of tramadol-intolerant patients. See Transmorrol Letter, supra note 13, at 8. Conversely, FDA has disapproved carve outs that affect the principal patient population. E.g., Letter from Dr. Steven K. Galson, Acting Director, CDER, FDA, to Mr. Labon et al., Wyeth Pharmaceuticals (Sept. 20, 2004) (Docket No. 003P-0518).


25. Restricting patent label carve outs to listed patents irrationally enhances the power of unlisted patents, relative to listed patents, as a tool to monopolize drug marketing. This result would encourage pioneers to invest more on the search for minor, albeit possible improvements that could be used protect an aspect of labeling, and less on developing new methods of use and new drug products.

26. Once ANDAs are on file with FDA, no 30-month stay is available for new patent listings, decreasing the incentive to file new patents in the Orange Book.

27. 21 C.F.R. § 314.150(b)(10) (requiring that generics amend labels whenever the label of the reference listed drug changes, but with a patent carve out with the same apparent scope as 21 C.F.R. § 314.127(a)(7)).

28. FDCA § 505(j)(2)(C), 21 C.F.R. § 314.150(b)(2)(ii)(B) (providing for withdrawal of approval of an NDA for failure to submit patent information after notice).