EXPANDING THE SCOPE OF THE HATCH-WAXMAN ACT'S PATENT CARVE-OUT EXCEPTION TO THE IDENTICAL DRUG LABELING REQUIREMENT: CLOSING THE PATENT LITIGATION LOOPHOLE

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INTRODUCTION

The Food and Drug Administration (FDA) has recently constructed a new roadblock to consumer access to generic drugs by narrowly construing the patent carve-out exception to the identical drug labeling requirement. Generic drug manufacturers often wait until a brand-name drug manufacturer's (or pioneer's) patent on the composition of its drug is about to expire before applying for FDA approval of the generic drug, so as to avoid patent infringement. As a result of the latest obstacle, however, generic drug manufacturers may still be susceptible after the patent on the drug's composition expires to patent infringement lawsuits based on active patents that cover language on the drug label.

Consider the following scenario. The pioneer's patent on the composition of its brand-name drug is about to expire, so a generic drug manufacturer applies for FDA approval to sell the generic drug. As required by law, the generic label is the same as the brand-name drug label, which reads in pertinent part, "take with orange juice."

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Upon notification of the generic drug application, the pioneer informs the generic drug company of the pioneer's active patent on a method for administering the drug with vitamin C, a vitamin found in orange juice. The generic drug manufacturer realizes its susceptibility to a patent infringement lawsuit because the generic drug label's instruction "take with orange juice" induces others (i.e., doctors and patients) to infringe the pioneer's patent on the method of administering the drug with vitamin C.

Rather than expose itself to a lawsuit for patent infringement, the generic drug manufacturer requests that the FDA make an exception to the identical labeling requirement and allow the patent-protected "take with orange juice" instruction to be deleted from the label as a patent carve-out. In its request, the generic drug company argues that the labeling instruction "take with orange juice" can be deleted without making the drug less safe or effective.

In the past, the FDA may have entertained the generic drug company's request and evaluated whether the patent carve-out would render the drug less safe or effective than the brand-name drug with its label. Recently, however, the FDA decided to limit the patent carve-out exception to patents in the Orange Book, a listing of patents that pertain to the listed drugs or their methods of use.\(^2\) The Orange Book may not always contain patents claiming drug labeling information, such as "take with orange juice," leaving the generic drug company with two options: litigate or wait until the method patent expires.\(^3\) Either way, consumer access to the generic drug is delayed.

Part I of this Comment discusses the development of the Orange Book restriction on the patent carve-out exception. Part II analyzes two current controversies involving old antibiotics and biological products that have arisen from the Orange Book limitation on the patent carve-out exception. Part III investigates whether limiting the scope of the patent carve-out to Orange Book listings is consistent with

\(^2\) See id. at 11 (explaining that the "labeling language sought to be carved out must be identified as deriving from a patent listed in the Orange Book"). The Orange Book is the common name for the FDA publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations." See CTR. FOR DRUG EVALUATION & RESEARCH (CDER), FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (2007), available at http://www.fda.gov/cder/orange/obannual.pdf [hereinafter Orange Book].

\(^3\) Mahn, supra note 1, at 11 (noting the "many types of patent claims that can protect language on drug labels that never appear in the Orange Book," including patents that claim manufacturing of the drug, verification of homogeneity or strength, or packaging).
the statutory language, legislative history, relevant case law, and the FDA's administrative record and agency decisions. Finally, Part IV proposes and evaluates alternative mechanisms that the FDA can employ to establish the appropriate scope of the patent carve-out exception.

I. THE ORANGE BOOK RESTRICTION ON PATENT CARVE-OUTS

Concerned with the cost of healthcare, Congress granted the FDA the authority to promulgate rules and regulations that will provide healthcare consumers with cheaper, generic drugs. The overwhelming administrative costs of creating this complex and intricate regulatory scheme have motivated a number of policy decisions that impose burdens on the generic drug applicants instead of on the FDA. Occasionally, the costs to the drug applicant outweigh the benefits of administrative efficiency. One such instance may be the FDA's decision to limit the scope of the patent carve-out exception to the identical labeling requirement.

The FDA generally requires the generic drug applicant to have the same labeling as the pioneer drug. The generic drug applicant may, however, request to omit language from the label if the language derives from a patent listed in the Orange Book. This Orange Book listing requirement eases the administrative burden on the FDA, because the agency need not review patents outside the Orange Book. The limitation may burden the generic applicants in ways not intended by Congress, however. To analyze the development and implications of the Orange Book restriction, Part I.A explains the legislation from which the FDA's authority derives; Part I.B discusses the exceptions to the identical labeling requirement; Part I.C fleshes out the impact of the Orange Book restriction on those exceptions; and Part I.D covers the results of a specific aspect of the Orange Book limitation based on use codes.

A. The Hatch-Waxman Act

In 1984, Congress passed a complex set of amendments to the Food, Drug, and Cosmetic Act (FDCA) that significantly changed the

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process of approving both new and generic drugs. Those amendments, known generally as the Hatch-Waxman Act (the Act), used both patent and food and drug laws 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." Congress wanted to expedite the process by which generics bring cheaper drugs to market while still creating incentives for pioneers to devote resources to research and development of new drugs. Accordingly, the Act provides pioneers with a limited extension of their patent terms and the generics with a shortened FDA approval process.

The Act offers three possible mechanisms by which a drug may secure FDA approval and reach the U.S. market: (1) a new drug application (NDA), (2) an abbreviated NDA (ANDA), or (3) a section 505(b)(2) application. The first pathway, the NDA, is used by a pioneer who wants to produce and sell a new drug for a particular use. The NDA is a lengthy document that includes, inter alia, safety and efficacy information, composition data, and substantial testing. Along with the NDA, the pioneer must also submit patent information for "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug." The FDA then publishes the patent information, along with patent expiration dates, in the Orange Book, to give notice to future generic holders.

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6 Andrx Pharm., Inc. v. Biovail Corp., 276 F.3d 1368, 1371 (Fed. Cir. 2002); see also AAIPharma Inc. v. Thompson, 296 F.3d 227, 230 (4th Cir. 2002) (quoting the description in Andrx of the balance struck by the Hatch-Waxman Act).
7 See H.R. REP. NO. 98-857, pt. 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647-48 (explaining the two-fold purpose of the Act: (1) "to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs" and (2) "to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket governmental approval" by granting "restoration of some of the time lost on patent life while the product is awaiting pre-market approval").
10 See id. § 355(a) (explaining the "[n]ecessity of effective approval of application").
11 See id. § 355(b) (outlining the filing and content requirements of an NDA).
12 Id. § 355(b)(1).
drug applicants that the patent may block introduction of generic products.

The Act relieves a generic, however, of the requirement to submit its own costly testing information to prove the safety and efficacy of an already NDA-approved drug. Instead, a generic may use the second pathway and file an ANDA for the same drug that has been approved by the FDA.\(^{15}\) To piggyback on the original NDA, the generic must demonstrate that its drug product is the "same" as the pioneer drug by submitting information to show that its product is pharmaceutically equivalent\(^{14}\) and bioequivalent\(^{15}\) to the pioneer approved drug.\(^{16}\) ANDAs are generally filed when a generic manufacturer wishes to duplicate an NDA holder’s drug product.

As a complement to the ANDA, the Act also implements a third mechanism, section 505(b)(2), for approved drugs that cannot be brought under an ANDA.\(^{17}\) Section 505(b)(2) is essentially a hybrid of an NDA and an ANDA. Under section 505(b)(2), an applicant submits reports of investigations of safety and effectiveness, but also relies on data not developed by the applicant.\(^{18}\) A section 505(b)(2) applicant can either submit an application for a new chemical entity or for changes to previously approved drugs.\(^{19}\) Section 505(b)(2) applications are meant for new drug products that are innovative or that offer a new therapeutic benefit or alternative.

\(^{15}\) See id. § 355(j)(1), (2)(A)(v).

\(^{14}\) See CDER, FDA, Drugs@FDA Glossary of Terms, http://www.fda.gov/cder/drugsatfda/glossary.htm#P (last visited Oct. 15, 2007) (defining pharmaceutical equivalents as drug products containing the same active ingredient(s), dosage form, route of administration, and strength or concentration).

\(^{15}\) See 21 U.S.C. § 355(j)(8)(B) (2000) (defining bioequivalent as a pharmaceutical equivalent whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions).

\(^{16}\) See id. § 355(j)(2)(A)(ii), (iv).


\(^{18}\) See 21 U.S.C. § 355(b)(2) (2000) (allowing an applicant to rely on investigations "not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted").

\(^{19}\) Id. Examples of changes that can be made with a section 505(b)(2) filing include changes in dosage, form, strength, or route of administration. Id.
For every patent listed in the Orange Book that relates to the NDA-approved drug, the ANDA or section 505(b)(2) applicant must include appropriate patent certifications and explain the basis for its belief that the application does not infringe any valid claim of an Orange Book-listed patent. The applicant may submit one of two types of possible certifications: (1) a "paragraph" certification explaining that the patent has not been filed (paragraph I), has expired (paragraph II), will expire (paragraph III), or is invalid or will not be infringed (paragraph IV); or (2) a “section eight” statement that the patent is a method-of-use patent that does not claim a use for which the applicant is seeking approval.

If an applicant certifies under paragraph IV that a patent is invalid or will not be infringed, then the applicant is required to notify the patentee and the NDA holder for the approved drug claimed by the patent as to why the patent is invalid or will not be infringed by the generic product. The patentee and NDA holder then have forty-five days to review the paragraph IV notice, during which time the FDA will take no action on the generic filing. If the patentee or NDA holder files an infringement suit within the forty-five-day period, FDA approval of the generic application is suspended for up to thirty months unless the matter is disposed of sooner by a court.

The FDA limits the second type of certification, section eight statements, to situations where "the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent." Therefore, a generic manufacturer filing a section eight statement must request FDA approval to change the generic drug’s labeling instructions to exclude the patented method of use listed in the Orange Book. Accordingly, the Act sets up a framework wherein a generic may deviate from the identical labeling requirement with the FDA’s approval.

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20 Id. § 355(j)(2)(A)(vii).
21 Id. § 355(j)(2)(A)(viii) (requiring a “statement that the method of use patent does not claim” the use for which the ANDA was submitted).
23 See 21 U.S.C. § 355(j)(5)(B)(iii) (Supp. IV 2004); 21 C.F.R. § 314.95(f) (2007) (explaining that the FDA will count the day following the date of receipt of the notice as the first day of the forty-five-day period).
26 See infra notes 30-31 and accompanying text. The section eight statement is just one type of situation where an applicant may invoke the labeling carve-out exception.
B. Labeling Carve-Out Exceptions

The FDA has the authority to approve ANDAs and section 505(b)(2) applications that omit labeling carried by the listed drug when such labeling is protected by patent or exclusivity. The Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." The Act also requires that an ANDA contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug." The Act specifies two exceptions to this requirement: ANDA labeling may differ from that of the listed drug because changes from the listed drug were approved pursuant to an ANDA suitability petition, or "because the new drug and the listed drug are produced or distributed by different manufacturers."

The FDA implemented generic labeling regulations that fleshed out the acceptable labeling differences between the proposed labeling in the ANDA and NDA as a result of distribution by "different manufacturers":

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 "omission of an indication or other aspect of labeling protected by patent" is known generally as the patent carve-out exception to the identical labeling requirement.

The regulations further provide that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, the FDA

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27 A listed drug is defined as a "new drug product that has an effective approval...for safety and effectiveness....Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's [Orange Book]." 21 C.F.R. § 314.3(b) (2007).
29 Id. § 355(j)(2)(A)(v).
30 See id. § 355(j)(2)(C) (enabling applicants to file suitability petitions for changes in "route of administration, dosage form, or strength" that differ from the listed drug).
31 Id. § 355(j)(2)(A)(v).
must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." Whether omission of protected information renders a drug less safe and effective is a fact-intensive inquiry that depends on the specific drug and the labeling at issue.

The seminal case sanctioning the FDA’s application of the carve-out exception, albeit to a nonpatented use that was accorded exclusivity, is *Bristol-Myers Squibb Co. v. Shalala* (*BMS*). In *BMS*, the U.S. Court of Appeals for the D.C. Circuit addressed whether the Hatch-Waxman Act allowed the FDA to approve an ANDA for a generic drug even though the label of the generic drug would exclude an indication that appeared on the pioneer drug. Applying the first step of the *Chevron* analysis, the court concluded that Congress directly addressed this issue. In its discussion of congressional intent, the court cited the legislative history of § 355(j) as "unusually strong support" for allowing generic labels to exclude indications approved for the pioneer: "The Report accompanying the House bill expressly noted that it 'permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved.'" Accordingly, the *BMS* court held that the Hatch-Waxman Act permits the FDA to approve an ANDA for a generic drug with labeling that differs from that of the pioneer drug.

Even though the court in *BMS* upheld the FDA’s authority to approve generic drugs with labeling different from the referenced listed drug, the courts have not yet spoken to labeling differences resulting

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33 Id. § 314.127(a)(7).
34 91 F.3d 1493, 1500 (D.C. Cir. 1996).
35 See id. at 1499 ("The crux of the dispute is whether 21 U.S.C. § 355(j)(2)(A)(v) permits the agency to approve an ANDA for a new generic drug even though the label of the generic product will not include one or more indications that appear on the label of the pioneer drug upon which the ANDA is based.").
36 See *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984) ("When a court reviews an agency’s construction of the statute which it administers, it is confronted with two questions. First, always, is the question whether Congress has directly spoken to the precise question at issue.... If the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency’s answer is based on a permissible construction of the statute.").
37 See *Bristol-Myers Squibb*, 91 F.3d at 1500.
39 Id. at 1501.
from information protected by patent.\textsuperscript{40} The \textit{BMS} court specifically held that the patent carve-out exception applies to an omission of an indication on the label,\textsuperscript{41} but neither the courts nor the FDA have formally addressed how the patent carve-out exception applies to "other aspect[s] of labeling protected by patent."\textsuperscript{42} In fact, the FDA's current policy effectively renders this second half of the patent carve-out exception virtually meaningless.\textsuperscript{43}

\section*{C. The Orange Book Restriction}

The FDA has recently limited the patent carve-out exception to patents listed in the \textit{Orange Book}.\textsuperscript{44} According to the FDA's current policy, a generic manufacturer seeking to carve out patent-protected language from its label must show, first, that the language derives from a patent listed in the \textit{Orange Book}, and, second, that the carve-out will not "render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."\textsuperscript{45} The \textit{Orange Book} restriction is a new FDA policy with potentially unintended consequences.

To appreciate the consequences of the \textit{Orange Book} restriction, it is important to understand the contents of the \textit{Orange Book}, how those contents are regulated, and the \textit{Orange Book}'s purpose. As described above,\textsuperscript{46} every NDA must contain patent information regarding the

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\item The FDA recently stated that "[t]he courts have upheld FDA's authority to approve generic drugs with labeling that omits . . . information protected by patent." Decision Letter from Gary J. Buehler, Dir., Office of Generic Drugs, CDER, FDA, to Applicant (Mar. 1, 2004) (citing Purepac Pharm. Co. v. Thompson, 238 F. Supp. 2d 191 (D.D.C. 2002), aff'd, 354 F.3d 877 (D.C. Cir. 2004)). \textit{Purepac} did not, however, involve a proposed omission of patented labeling information; rather, the issue in \textit{Purepac} was whether a section eight statement was appropriate with respect to a listed use patent that did not cover any approved indication for use of the listed drug. 238 F. Supp. 2d at 200.
\item In \textit{BMS}, the generic sought omission of a supplemental indication on which the pioneer had obtained three-year exclusivity. 91 F.3d at 1496.
\item \textsuperscript{21} C.F.R. § 314.94(a)(8)(iv) (2007).
\item See infra note 187 and accompanying text (discussing the impact of the \textit{Orange Book} restriction on the "other aspect[s] of labeling" language).
\item See Mahn, supra note 1, at 11 (explaining the FDA's current patent carve-out policy).
\item See \textit{id.} (quoting \textsuperscript{21} C.F.R. § 314.127(a)(7) (2007)).
\item See supra note 12 and accompanying text (describing the required patent submissions of an NDA applicant).
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drug for which the applicant seeks approval.\textsuperscript{47} Once the FDA approves an NDA, the applicant then has thirty days to amend its patent submissions to ensure that they list only those patents "that claim[] the drug substance (active ingredient), drug product (formulation and composition), or approved method of use."\textsuperscript{48} If the applicant obtains a patent for an approved drug after the FDA accepts the NDA, the owner must list the new patent information within thirty days after the patent is issued.\textsuperscript{49} The FDA lists all of these patent submissions in an addendum to the \textit{Orange Book}.\textsuperscript{50}

Three aspects of the \textit{Orange Book} are particularly important to understanding the effect of this restriction on the patent carve-out exception. First, the \textit{Orange Book} lists only the following types of patents: drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents.\textsuperscript{51} Importantly, the \textit{Orange Book} excludes many other types of patents that pertain to a given drug, including patents claiming off-label methods of use, methods of manufacturing, drug packaging, intermediates, or metabolites.\textsuperscript{52} Moreover, Congress at times may exclude certain types of otherwise listable patents from the \textit{Orange Book}. As described below,\textsuperscript{53} these unlisted patents may be the subject of bona fide carve-out requests.

Second, the FDA does not take it upon itself to review the patent submissions. The duty to ensure that the \textit{Orange Book} lists patents that actually claim approved drugs lies with NDA holders.\textsuperscript{54} That is not to

\textsuperscript{47} See 21 U.S.C. § 355(b)(1) (2000) (requiring the applicant to file "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 with 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").

\textsuperscript{48} 21 C.F.R. § 314.53(c)(2) (2007).


\textsuperscript{51} 21 C.F.R. § 314.53(b)(1) (clarifying the "[p]atents for which information must be submitted and patents for which information must not be submitted").

\textsuperscript{52} \textit{Id.}

\textsuperscript{53} See infra Parts II.A (discussing the statutory exclusion of patents claiming old antibiotics from the \textit{Orange Book}), II.B (discussing the importance of process patents for biological generics).

\textsuperscript{54} See Watson Pharm., Inc. v. Henney, 194 F. Supp. 2d 442, 445 (D. Md. 2001) ("In making its decision to list a patent . . . it is entirely appropriate and reasonable for the FDA to rely on the patentee's declaration as to coverage, and to let the patent infringement issues play out in other, proper arenas . . . .").
say that parties, including ANDA applicants, cannot dispute the accuracy or relevance of patent information listed in the Orange Book. The FDA will relay such complaints about Orange Book listings to NDA holders, but unless the NDA holder “withdraws or amends its patent information in response to FDA’s request, the agency will not change the patent information in the list.” The FDA views its role with respect to patent listing in the Orange Book as “ministerial” and is unwilling to undertake any kind of review of the submissions by the NDA holders or the challenges by the generic drug companies. Under the current patent carve-out framework, the Orange Book listing by the NDA holder dictates whether a generic can carve out language from its label.

Third, the FDA does not enforce the penalties for withholding patents from the Orange Book. Section 505(b)(2) allows the FDA to withdraw its approval for a previously approved drug if the NDA holder fails to submit relevant patents to the Orange Book. No case or controversy could be identified, however, where the FDA invoked this section. The penalties for improperly listing a patent in the Orange Book, on the other hand, seem to deter pioneers effectively from “ever-greening” the Orange Book. Since 2003, the NDA applicant or holder must “verify under penalty of perjury” that its submission of patent information is “accurate and complete.”

55 21 C.F.R. § 314.53(f).
57 See Mahn, supra note 1, at 11 (describing the penalty of withdrawing FDA approval from pioneers who fail to list patents as “draconian . . . and unlikely to ever be employed”).
58 21 U.S.C. § 355(e)(4) (2000) (providing the FDA with the authority to withdraw approval of a drug if the required patent information “was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information”).
59 See Mahn, supra note 1, at 9 (suggesting that the amendments to the Hatch-Waxman Act by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 “diminished the versatility of the Orange Book as a tool for delaying generic entry”).
60 21 C.F.R. § 314.53(c)(2)(ii)(R) (2007). The FDA cracked down on inappropriate Orange Book submissions after the court in Purepac rejected the agency’s reliance on the regulations and general declaration as a reasonable basis for denying a patent carve out. See Applications for FDA Approval To Market a New Drug: Patent Submission and Listing Requirements, 68 Fed. Reg. at 36,682 (explaining that the “need for accurate and detailed information related to the approved methods of use claimed in the patent being submitted for listing is underscored by the decision in [Purepac].”
similar avenue of policing exists for patents withheld from the *Orange Book*.\footnote{Actions may be brought directly against the FDA under the Administrative Procedure Act (APA), 5 U.S.C. §§ 701–706 (2000), on the grounds that the agency’s action was arbitrary or capricious or not in accordance with the law. See Andrx Pharm., Inc. v. Biovail Corp., 276 F.3d 1368, 1379 (Fed. Cir. 2002) ("[T]he APA provides an appropriate mechanism for reviewing the lawfulness of the FDA’s action.").}

The limited types of patents in the *Orange Book*, the failure of the FDA to review patent submissions, and the absence of utilized penalties for withholding patents from the *Orange Book* make the *Orange Book* a poorly suited limitation on patent carve-outs. An insufficiently policed collection of select patents will undeservedly bar generics from FDA approval—a result that flies in the face of the Act’s underlying purpose.

\section*{D. The Use Code Requirement}

Alongside the *Orange Book* restriction, the FDA now also requires generics to identify the specific “use code” in the *Orange Book* to be carved out from the label for all method-of-use patents.\footnote{See Mahn, supra note 1, at 11 (explaining the FDA’s requirement that “Orange Book carve outs involving use patents can occur only at the ‘use code’ level”).} The FDA assigns use codes to method-of-use patents for approved products and lists them numerically in the *Orange Book* section on use codes.\footnote{See FDA Approval To Market a New Drug: Patent Submission and Listing Requirements, 68 Fed. Reg. at 36,683 (describing how use codes are listed and assigned).} According to the FDA, the purpose of use codes is to “alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use.”\footnote{Id.} Descriptions of the use code are limited to 240 total characters “[d]ue to the limitations of [the FDA’s] database system and software constraints.”\footnote{Id.} For instance, the FDA assigned the use code U-258 to an approved indication for the “treatment of neurodegenerative diseases.”\footnote{See Patent and Exclusivity Information Addendum: Patent and Exclusivity Lists, supra note 50 (defining the patent use codes).} The NDA holder provides the FDA with the exact use code description for publication in the *Orange Book*.\footnote{See FDA Approval To Market a New Drug: Patent Submission and Listing Requirements, 68 Fed. Reg. at 36,677 (asking the NDA holder to give the FDA the “exact use code description to be published in the Orange Book”).} The FDA now requires carve-out requests to correspond to a use code, de-
spite the NDA holder’s interest in assigning a broad use code to relevant patents.

The implications of this requirement are best illustrated using an example. Suppose the FDA approved drug X to treat both Huntington’s disease and Alzheimer’s disease. Further assume that the NDA holder of drug X holds a patent on a method of treating Huntington’s disease with drug X, but the patent on a method of treating Alzheimer’s disease expired. Pursuant to the NDA holder’s request, the Orange Book lists the Huntington’s patent under use code U-258: treatment of neurodegenerative diseases (perhaps because no use code for Huntington’s disease exists). Suppose a generic submits an ANDA with a section eight statement requesting approval to treat Alzheimer’s patients with drug X, but not Huntington’s patients. The generic requests a patent carve-out exception to omit the language on the label associated with treating solely Huntington’s disease, but the use code broadly encompasses treatment for all neurodegenerative diseases. The FDA’s current patent carve-out policy would deny the generic its carve-out because omission of the entire use code leaves the label without any indication. Therefore, the generic will not market drug X for Alzheimer’s disease, even though the patent expired, because of the use code limitation on the carve-out policy.

The use code should not restrict the patent carve-out exception because the purpose of the use code will be skewed, and the use code does not adequately represent the scope of patents. The purpose of use codes is to “allow interested parties, including ANDA applicants, to determine the particular medical uses of brand-name drugs asserted by the various use patents listed in the Orange Book.” Because the purpose of use codes is essentially informative, pioneers are encouraged to be forthright in their listings so that a drug use does not go unnoticed. By using the use code as a limitation on the patent carve-out exception, the FDA (inadvertently) motivates pioneers to strategize in selecting what information to provide. Recall that the FDA “relies exclusively on the NDA holder’s statements regarding a patent’s coverage” to assign the use code to the method of use pat-

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68 This example is an adaptation of an example in Mahn, supra note 1, at 12 n.21, which provides an example of a use code for nausea that does not distinguish between postoperative and postradiation treatments.

ents. Instead of appropriately assigning the use code, pioneers may
be motivated to assign an extremely broad use code to its method of
use, thereby optimizing patent protection.

According to the FDA, use codes “are not meant to substitute for
the applicant’s review of the patent and the approved labeling.”
Ironically, the FDA now uses these very same use codes in exactly the
manner the agency cautioned applicants not to use them. The FDA
substitutes the use codes for its own review of the patent and labeling
that the applicant seeks to carve out. This Comment does not suggest
that the FDA should engage in extensive patent review, but the agency
should look into alternative modes of patent carve-out review that ex-
tend beyond use codes. The benefits of administrative efficiency
gained from use code restrictions do not warrant the costs to the
ANDA or section 505(b)(2) applicants and to the public.

II. CURRENT CONTROVERSIES WITH RESTRICTING PATENT
CARVE-OUTS TO THE ORANGE BOOK

The impact of the Orange Book restriction on the patent carve-out
exception can perhaps be best understood by considering the types of
patents that are excluded from the Orange Book. In at least one in-
stance, Congress has denied Orange Book entry of patents that claim an
entire category of drugs (e.g., old antibiotics). The FDA has also re-
fused an Orange Book listing to categories of patents (e.g., patents
claiming off-label methods of use, drug packaging, intermediates, or

70 Id. at 198 n.10. The court recognized that the agency’s “self-abnegation” as to
patent review “creates the possibility for conflict between NDA holders and ANDA ap-
plicants over the proper scope of a particular use patent.” Id. at 205.

71 The Orange Book’s purpose is also essentially informative, and the FDA eventu-
ally imposed content restrictions on the Orange Book to reduce the number and types
of patent entries. See CDER, FDA, GUIDANCE FOR INDUSTRY: LISTED DRUGS, 30-MONTH
STAYS, AND APPROVAL OF ANDAS AND 505(B)(2) APPLICATIONS UNDER HATCH-
WAXMAN, AS AMENDED BY THE MEDICARE PRESCRIPTION DRUG IMPROVEMENT AND
MODERNIZATION ACT OF 2003, at 3 (2004) (restricting the types of patents that may be
listed in the Orange Book); cf Purepac, 238 F. Supp. 2d at 208 (criticizing the FDA for
assuming that every patent in the Orange Book belongs there).

72 FDA Approval To Market a New Drug: Patent Submission and Listing Re-

73 See infra Part IV (discussing possible solutions that maintain the level of patent
review required of the FDA while ensuring a proper scope to the patent carve-out ex-
ception).

74 See infra Part II.A (describing the FDA’s refusal of a patent carve-out for the
drug azithromycin).
metabolites) even if those patents pertain to Orange Book listed drugs. The exclusion of these manufacturing patents likely affects certain types of drugs (e.g., biological drugs) more than others (e.g., small molecule drugs). In both cases, Congress and the FDA were motivated by the overriding policy interests of bringing cheaper generic drugs to market and encouraging development of new drugs. Yet, the patent carve-out restriction to the Orange Book arguably controverts the intent of the legislature and agency by preventing generics from coming to market and encouraging research in old drugs. Part II.A explores the problems encountered by ANDA applicants of unlisted, generic old antibiotics, and Part II.B discusses the implications of the Orange Book restriction for biological generics.

A. The Old Antibiotics

Prior to the enactment of the Food and Drug Administration Modernization Act (FDAMA) of 1997, section 507 of the FDCA regulated the marketing of antibiotic drugs. As a result, antibiotics were not eligible for the exclusivity and patent protections afforded to nonantibiotic drugs under section 505 of the Act. In 1997, Congress repealed section 507 and subjected antibiotic drug approvals to section 505 of the FDCA. This revision made antibiotics eligible, for the first time, for section 505's patent and nonexclusivity provisions.

Section 125 of the FDAMA also contains a transition provision affecting certain "old antibiotics"—antibiotics for which an applicant

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75 See infra Part II.B (detailing how a process patent impeded FDA approval of a carve-out request for the biological drug enoxaparin).
76 See infra Part II.B.
78 An antibiotic drug is
any drug . . . composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for use by man containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy microorganisms in dilute solution . . . or any derivative thereof.

submitted a marketing application to the FDA prior to repeal of section 507. The transition provision exempts old antibiotics from the exclusivity and patent protections otherwise available under section 505, including patent listing and certification. Therefore, patents claiming old antibiotics and their methods of use are not eligible for listing in the Orange Book.

The exclusion of patents claiming old antibiotics from the Orange Book recently led the FDA to refuse a potentially bona fide patent carve-out from a generic label of azithromycin. Patients use azithromycin to treat certain bacterial infections, such as bronchitis and pneumonia. Azithromycin is characterized as an old antibiotic, because the FDA approved Pfizer's NDAs for oral capsules and tablets of Zithromax (azithromycin) before 1997. Therefore, the Orange Book does not list Pfizer's patents relating to the drug azithromycin and its methods of use.

Pfizer changed its formulation from capsules to tablets in the mid-1990s because the "tablets do not have a food effect." In a letter accompanying its NDA, "Pfizer explained that the tablets are bioequivalent to the capsule formulation and... 'can be taken without regard to meals.'" Upon FDA approval of the tablet formulation, Pfizer decided not to market the capsules. Instead, Pfizer marketed oral tablets of azithromycin and included the food effect in its drug label. Under the "Precautions" section of the Zithromax drug label, the "Information for Patients" states, "ZITHROMAX tablets and oral suspension can be taken with or without food."

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81 Id. § 125(d)(2), 111 Stat. at 2325.
82 See REPEAL OF SECTION 507, supra note 78, at 2 (discussing the exemption of all old antibiotics from the patent listing, patent certification, and exclusivity provisions in section 505).
83 Id.
85 See CDER, FDA, Drugs@FDA: FDA Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/drugsatfda (enter search term "Zithromax"; follow "Zithromax" link) (last visited Oct. 15, 2007) (revealing that five Zithromax NDAs were approved prior to 1997).
87 Id. at 29,330.
88 Pfizer, supra note 84, at 15. Note that this drug label was revised in January 2004.
Pfizer’s patent protection for the drug in the U.S. market expired in November 2005, coinciding with the emergence of generic products.\textsuperscript{89} These generics recently became vulnerable to potential patent litigation as a result of the Patent and Trademark Office’s 2006 reissue of a patent on a “Method of Administering Azithromycin” assigned to Pfizer.\textsuperscript{90} The ’889 patent claims “[a]n oral dosage form of azithromycin . . . which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect.”\textsuperscript{91} Now Pfizer can sue generics for inducing infringement\textsuperscript{92} of the ’889 patent. By including the phrase “take with or without food” on the azithromycin drug label, the generic may be guilty of inducing consumers to administer an oral dosage of azithromycin without an adverse food effect.

Concerned about potential litigation, one generic requested a patent carve-out exception from its azithromycin drug label.\textsuperscript{93} The generic argued to the FDA that the “take with or without food” instruction was superfluous and would be protected by patent if issued.\textsuperscript{94} The FDA did not suggest that the instruction was meaningful, but denied the carve-out nonetheless, “claiming that the agency’s hands were tied by the [FDCA].”\textsuperscript{95} The FDA did not reach the question of whether the omission would render the product less safe or effective than its pioneer counterpart, because the Orange Book did not list the ’889 patent.

A generic’s frustration with the FDA’s decision regarding azithromycin is exacerbated by the agency’s allowance of patent carve-

\textsuperscript{89} See CURRENT PATENTS GAZETTE (Apr. 28, 2006) (announcing that “Teva and Sandoz each launched their generic versions of a tablet formulation of azithromycin in November 2005”).


\textsuperscript{91} U.S. Patent RE39,149 col.23 l.25–29.


\textsuperscript{93} See Mahn, supra note 1, at 8 (describing the FDA’s response to the patent carve-out request of “take with or without food” without specifying that the scenario involved Pfizer or azithromycin). Mr. Mahn later explained that Pfizer’s azithromycin was the drug discussed in his article. Telephone Interview with Terry G. Mahn, Managing Principal, Fish & Richardson P.C., in Washington, D.C. (Nov. 7, 2006).

\textsuperscript{94} Mahn, supra note 1, at 8.

\textsuperscript{95} Id.
out requests for food effects of other listed drugs. The FDA recently approved a patent carve-out of labeling information relating to the bioavailability of metaxolone when taken with or without food. Because the Orange Book listed the relevant patent by use code, the FDA proceeded to the safety and efficacy prong. While the FDA's decision to delete label information on the effect of administering the drug with or without food depends on the specific facts of that case, the FDA found that metaxolone was safely and effectively administered without the food effect labeling. Arguably, the bioavailability data of metaxolone was equally, if not more, important to safety and efficacy than the "take with or without food" instruction for azithromycin. The metaxalone example therefore highlights the potential inconsistencies in the types of information deleted from labels due to the Orange Book restriction on the patent carve-out exception.

Depending on how Pfizer and generic drug companies react, the FDA's refusal even to consider the safety and efficacy of generic old antibiotics with carved-out labels may impede public access to generic azithromycin. This end result presumably diverges from Congress's intent. In its repeal of section 507, Congress clearly intended for old antibiotics not to benefit from the patent protections of section 505. Congress limited the patent protections solely to new antibiotics (1) to speed up the entry of generics for old antibiotics into the marketplace

96 See Decision Letter from Gary J. Buehler, supra note 40, at 1 ("[T]he FDA has determined that labeling corresponding to the use (U-189) listed in [the Orange Book] for [the listed '128 patent] may be carved out of the metaxalone labeling.").

97 See id. at 1 (identifying the Orange Book use code and proceeding to address the question of the drug's safety and efficiency).

98 See id. at 4 (finding that the omission of food effect labeling will not render use of metaxalone less safe or effective).

99 See Citizen Petition of King Pharmaceuticals, Inc. at 11-17 (Mar. 18, 2004) (describing why deletion of the bioavailability information would render metaxalone less safe and effective). The FDA allowed ANDA applicants to delete the bioavailability information from the label because of (1) the long history of the safe use without the bioavailability information, (2) the isolated placement of the bioavailability data in the Clinical Pharmacology section of the label, and (3) the lack of information on the clinical effect of the increased bioavailability of the drug when taken with high fat meals. See Decision Letter from Gary J. Buehler, supra note 40.

100 In Eon Labs, Inc. v. Pfizer, Inc., Eon Labs, a manufacturer of generic Zithromax, pleaded its belief that Pfizer would assert claims of infringement of the '889 patent based, in part, on Pfizer's counterclaim against Teva for infringement of the '889 patent. Eon's Complaint for Declaratory Judgment at 4-5, Eon Labs, Inc. v. Pfizer, Inc., No. 05 Civ. 002(LAP), 2005 WL 2848952 (S.D.N.Y. Oct. 28, 2005)

101 See supra note 82 and accompanying text (describing the CDER's policy toward patent protections of old antibiotics pursuant to congressional intent).
and (2) to encourage research and development in new antibiotics to fight the public health crisis due to antibiotic resistance. By forbidding an *Orange Book* listing of old antibiotics, the Act (inadvertently) afforded old antibiotics a patent protection that, in some ways, exceeds the patent protection afforded to other drugs under section 505.

The FDA’s refusal to omit the azithromycin “take with or without food” instruction illustrates how the *Orange Book* restriction may unduly limit the patent carve-out exception. The azithromycin example is unique; but for its being an old antibiotic, the FDA would have required Pfizer to list the ’889 patent in the *Orange Book*. The FDA requires NDA holders to list patents claiming methods of administering drugs, like the ’889 patent, in the *Orange Book*. The FDA also requires *Orange Book* listing of patents relating to new antibiotics. However, many old antibiotics are profitable drugs and not all of their patents have expired. Perhaps azithromycin will not remain the only example of an old antibiotic with newly enforceable, unlisted patents that inhibit generics from obtaining labeling carve-outs.

**B. Biological Products**

As mentioned above, the *Orange Book* may not list process-of-manufacturing patents. Generally, such patents are not the subject of carve-out requests because most patent carve-out requests pertain to small molecule drugs. Small molecule drugs are not typically de-

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104 If the FDA changes its patent carve-out policy for old antibiotics, azithromycin might be the only recognized example of the *Orange Book* restriction’s effect. See Mahn, *supra* note 1, at 12 n.19 (“FDA is in the process of reviewing the patent carve-out policy for old antibiotics.”).

105 See *supra* note 52 and accompanying text.

106 In this Comment, “process-of-manufacturing patents,” also referred to as “process patents,” will be used generally to include both methods of manufacture and methods to analyze drug products.

107 As used in this Comment, the term “small molecule” refers to a “discrete chemical entity that generally would contain no more than fifty nonhydrogen atoms,
fined by features deriving from methods of manufacture; rather, they are usually described by their specific, well-defined physical and chemical properties. For example, the drug label for Zithromax describes its active ingredient, azithromycin (a small molecule drug), by its chemical name, molecular formula, molecular weight, and structural formula.\footnote{Dudzinski, \textit{supra} note 17, at 154.} Drug labels for small molecules do not typically contain information on methods of manufacture.

In the rare event that an important element of a small molecule is defined by a patented analytical method, the generic will probably "design around"\footnote{See Pfizer, \textit{supra} note 84.} that method. When evaluating sameness, the FDA requires identity of the pharmacological activity, rather than absolute chemical identity.\footnote{An example of "design around" is the tweaking of an element of a purification process (i.e., using a different resin in a column) to avoid patented methodology, while still isolating, purifying, and characterizing a drug product that is the "same" as that of the pioneer.} The methodology to characterize small molecules is so sophisticated that a generic can define the small molecule using an unprotected method and thereby establish pharmacological identity. Therefore, the fact that process patents are ineligible for listing in the \textit{Orange Book} does not substantially thwart generics of small molecules from reaching the marketplace.

Process patents play more crucial roles, however, in the manufacture and characterization of biological products\footnote{In this Comment, the term "biological products" refers broadly to drugs that are obtained from biological sources, including complex carbohydrate-based, nucleic acid-based, and protein-based therapeutics, as well as "biologics," which are "viruses, therapeutic serums, toxins, anti-toxins, or analogous products." Dudzinski, \textit{supra} note 17, at 147 (quoting Biologics Control Act of 1902, Pub. L. No. 57-244, Ch. 1378, 32 Stat. 728 (1902)).}—large, complex molecules derived from living cells. Due to the nature of their source, biological therapeutics are heterogeneous mixtures of components often identified by their manufacturing process.\footnote{See id. at 148-49 (describing the regulatory focus on manufacturing control as opposed to control of the final product); see also CTR. FOR BIOLOGICS EVALUATION \& RESEARCH \& CDER, FDA, FDA GUIDANCE CONCERNING DEMONSTRATION OF COMPARABILITY OF HUMAN BIOLOGICAL PRODUCTS, INCLUDING THERAPEUTIC BIOTECHNOLOGY-DERIVED PRODUCTS (1996) ("Because of the limited ability to characterize the identity and structure and measure the activity of the clinically-active component(s), a biological product was often defined by its manufacturing process.").} For example, a
biological therapeutic might be defined as "drug X obtained by chemical process Y and characterized by signature group Z." The "active ingredient"\textsuperscript{113} is typically not any one particular type of molecule; rather, certain "signature aspects" of the composition of molecules define the drug's biological activity. Process patents, unlisted in the Orange Book, likely claim the parameters that describe biological drugs.

Process patents can therefore delay or inhibit biological generics from entering the marketplace more often than small molecule generics. Since the FDA limits carve-out exceptions to Orange Book-listed patents, the FDA will not approve carve-out exceptions for a generic biological drug based on a process patent. If the drug label describes a patented method of manufacture directly (chemical process Y in the example), then the company applying for FDA approval of a generic must either challenge the patent or wait until the patent expires, even if the FDA does not require the method-of-manufacture for sameness. If the drug label describes a signature characteristic of the drug obtained by a patented method (signature characteristic Z in the example), then the generic has another option: it can try to design around the protected method.

Because pioneers define biological products in terms of the process and its associated signatures, generics cannot easily design around process patents for biological products. Biological therapeutics are rarely characterized fully. Manufacturers continually develop new methods of defining the active ingredient, so alternative processes to identify a certain characteristic are not always available. Furthermore, pioneers can continually update their drug labels to include new information about the drug based on newly developed, patented analytical methods.\textsuperscript{114}

Now, if the FDA required new information for sameness, it might make sense that a company interested in developing a generic version of the drug would have the formidable task of finding or developing an alternative method to measure the newly added information on the drug label. The problem is that the generic must design around the patented method (or challenge the patent's validity) irrespective of whether the FDA requires the new characteristic for a sameness de-

\textsuperscript{113} The FDA defines active ingredient as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease." 21 C.F.R. § 210.3(b) (7) (2007).

\textsuperscript{114} See Mahn, supra note 1, at 10 ("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.").
termination. Even if the FDA did not require the signature characteristics for sameness, an ANDA or section 505(b)(2) applicant still would have to satisfy the identical labeling requirement (without being susceptible to patent infringement) and, again, the FDA would not approve carve-outs for unlisted process patents. Therefore, the generic really has three options: (1) design around, if possible, (2) challenge the process patent’s validity, or (3) wait until the patent expires. Even though an ANDA or section 505(b)(2) applicant may successfully produce a generic drug that is the “same” as the pioneer drug without infringing a patented method of manufacture, the applicant remains susceptible to litigation because its label describes the patented method of making or signature thereof.

A recent example of a process patent impeding an ANDA applicant from FDA approval of a carve-out request involves a biological drug called enoxaparin. In 1993, the FDA approved Aventis’s NDA for Lovenox (enoxaparin sodium) to inhibit blood clots. Enoxaparin is a low molecular weight heparin (LMWH) derived from porcine intestinal source heparin. A heparin is “composed of a core protein with a number of linear polysaccharide chains extending from the protein.” A manufacturer of enoxaparin must break down the large carbohydrate chains into smaller chains through enzymatic or chemical depolymerization. A complex mixture of sugars comprises the final product, and which sugar or combination of sugars makes up the active ingredient is unknown.

Because of the difficulty of characterizing biological drugs, the label for Lovenox describes enoxaparin by its method of manufacture (i.e., “obtained by alkaline depolymerization”) and its signature characteristics (i.e., “acid group at the non-reducing end” and “molecular weight distribution”). Aventis recently added another signature characteristic, generally known as a “structural fingerprint,” to its de-

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117 Id.
118 See id. at 7 (describing the various depolymerization processes of LMWHs).
119 See id. at 10-11 (acknowledging that enoxaparin is not “fully characterized”).
scription of enoxaparin. The new label reads in pertinent part, "About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide chain." Around the same time Aventis updated the Lovenox label with the 1,6 anhydro derivative fingerprint, Aventis obtained Patent '316, which claims a method of manufacturing polysaccharides with a 1,6 anhydro derivative on the chain's reducing end. The Orange Book does not list Patent '316.

Aventis's major patent on Lovenox expired in December of 2004. In 2003, both Amphastar and Teva submitted ANDAs for generic versions of enoxaparin, which Aventis heavily contests. In August 2005, Momenta, in an exclusive collaboration with Sandoz (generics division of Novartis) to jointly develop and commercialize generic enoxaparin, submitted an ANDA for "technology-enabled" M-Enoxaparin. Momenta has developed its own technology to analyze and sequence complex mixtures of sugars. According to Momenta, the technology enables the company to develop a generic version of enoxaparin that "will demonstrate chemical 'sameness' to Lovenox and meet the FDA requirements for generic marketing approval." Momenta's technology does not detect 1,6 anhydro derivatives, however.

Even if Momenta can prove that its generic M-Enoxaparin is the same as Lovenox, Aventis will almost certainly sue Momenta for patent

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122 Id. at 2.
124 See Feliza Mirasol, Generics To Challenge Lovenox, 268 CHEMICAL MARKET REP., Sept. 5-11, 2005, at 28, 28 (noting that "despite the December 2004 expiration of Lovenox's major patent, the fight has just begun for Sanofi-Aventis").
125 See Citizen Petition, supra note 116 (requesting that "the FDA refrain from approving any ANDA citing Lovenox® as the reference listed drug unless the manufacturing process used to create the generic product is determined to be equivalent to Aventis' manufacturing process ... [or] the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15% and 25% of its polysaccharide chains").
127 Id.
infringement based on the labeling language describing the 1,6 anhydro derivative. Under current analytical technology, Momenta cannot determine whether M-Enoxaparin has the 1,6 anhydro derivatives—the structural fingerprint—without infringing Aventis’s patent. Yet, the FDA has not determined that enoxaparin needs the structural fingerprint for a sameness determination.129 Without having demonstrated that the structural fingerprint actually bears the clinical significance necessary for sameness, Aventis has delayed the entry of generic enoxaparin into the marketplace by implanting process patent language into its drug label.

Momenta’s hands are further tied because the FDA will not approve a carve-out request based on an unlisted patent. Regardless of whether the omission of the language would actually render the drug less safe or effective, the FDA will deny a carve-out request by Momenta because the Orange Book does not list the patent claiming production of enoxaparin with an 1,6 anhydro derivative on its reducing end. Notably, Aventis was not required to demonstrate to the FDA that alternative manufacturing processes cannot achieve enoxaparin that is legally or clinically the “same” as Lovenox. Rather, the FDA imposes the burden on Momenta to demonstrate that its enoxaparin possesses Aventis’s structural fingerprints. The FDA’s current policy misplaces this burden, especially considering that the FDA may not even require structural fingerprints for sameness.

The enoxaparin example is a precursor to problems that biological generics may incur due to the Orange Book restriction on the patent carve-out exception. Enoxaparin is an anomaly, however, because Teva, Amphastar, and Momenta all applied for FDA approval of generic enoxaparin using ANDAs. Generally, the FDA does not approve generic biological products via ANDAs for two reasons: (1) the Orange Book does not list pioneer biological products, and (2) generics cannot meet the stringent same active ingredient requirement of ANDAs.130 The FDA has approved very few NDAs for biological prod-

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129 The FDA could find that generic M-Enoxaparin is the “same” as Lovenox even though the generic biological product exhibits heterogeneity. The FDA deemed generic menotropin products to be the same as Perganol, so long as the degree of batch-to-batch variation in the generic is similar to variation in the reference listed drug. See Serono Labs. v. Shalala, 158 F.3d 1313, 1318 (D.C. Cir. 1998) (noting the FDA’s determination).

130 Generic menotropin is a biological therapeutic approved via an ANDA. Id.
ucts. In the few instances when the FDA has approved an NDA for a biological product, the generic applicant has preferred a section 505(b)(2) application, and not an ANDA, though some support FDA approval of biological generics through section 505(b)(2). Nevertheless, section 505(b)(2) subjects applicants to the same patent and Orange Book requirements as ANDAs. Therefore, the enoxaparin example illustrates the arguably negative consequences of the Orange Book-restricted patent carve-out exception on both ANDA and section 505(b)(2) applicants of biological generics.

Yet only a handful of biological drugs are currently subject to the Hatch-Waxman Act. The FDA approves most biological therapeutics, including glycoproteins and monoclonal antibodies, as biologics via Biologics License Applications, or BLAs. The Public Health Service Act of 1944 (PHSA) codifies the segregated regulatory system for biologics. Currently, no established statutory or regulatory pathway provides the FDA with the authority to utilize an abbreviated approval process for generic versions of BLA products. The FDA could, in theory, "recharacterize BLAs as NDAs" or "interpret Hatch-Waxman and section 505(b)(2) to authorize a form of abbreviated biologics licensing application (ABLA)," in which case the labeling sameness requirement would apply to all biological generics. Realistically, however, the FDA is probably not going to do much in this area without direction from Congress.

131 But see Dudzinski, supra note 17, at 219 (noting that insulin and human growth hormone were approved under NDAs).

132 See id. ("The application of section 505(b)(2) to those therapeutic proteins approved under an NDA, like insulin and growth hormone, seems rather noncontroversial . . . .").

133 See id. at 198-220 (analyzing "Section 505(b)(2) as a mechanism for FDA approval of generic biologics").

134 In fact, "Aventis questions . . . whether the generic drug approval model (i.e., the ANDA process) is appropriate for [enoxaparin] even though they have officially fallen under CDER's jurisdiction." Citizen Petition, supra note 116, at 8. Decisions as to which biological products are approved under NDAs and BLAs have been somewhat arbitrary over the years. See Dudzinski, supra note 17, at 145-49, 152-54, 158-60, 175-78 (providing a thorough overview of regulatory history in the area of biologics and protein-based therapeutics).


136 See id. (establishing no provision that would permit approval of a follow-on, or generic, protein product using an abbreviated application, but allowing the Secretary to prescribe requirements for exceptions).

137 Dudzinski, supra note 17, at 219-20.
The next two years should present the FDA with a reasonable opportunity to change its patent carve-out policy as applied to biological products. Congress is currently grappling with the creation of a pathway for biological generics. Legislation now moving through Congress may or may not have a labeling sameness requirement, however, so the patent strategy discussed here may only affect the few albeit profitable biological drugs approved via NDAs. Regardless of whether Congress passes legislation using one of the existing pathways or crafting a new pathway for biological generics, the FDA should create new regulations that contemplate the detrimental impact of the *Orange Book* restriction on patent carve-out exceptions in the biological generic context.

III. LACK OF JUSTIFICATIONS FOR THE *ORANGE BOOK* LIMITATION

In addition to the potentially undesirable consequences of the *Orange Book* restriction on the patent carve-out exception, the FDA may not actually have the authority to implement such a restriction. The text of the Hatch-Waxman Act clearly makes an exception to the identical labeling requirement for different manufacturers, and, read alongside the other same labeling exceptions, it provides only one limitation to that exception: the generic drug must be as safe and effective as the pioneer drug. The legislative history recognizes that different manufacturers must "design around" the pioneer manufacturer and provides a nonexhaustive list of instances where labeling differences would be apt, none of which depend on the patent's *Orange Book* status. The judicial constructions of the Act and its early administrative record envision a broad scope for the carve-out exception. The FDA itself has previously required only that labeling changes not render the generic drug less safe and effective than the pioneer drug. This lack of statutory, judicial, and agency support suggests that the FDA should rethink its approach to the patent carve-out policy.

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138 See Senate Advances Biogenerics Bill, CHEMICAL & ENGINEERING NEWS, July 2, 2007, at 20 (discussing legislation currently before the Judiciary Committee that would give the FDA authority to approve less-expensive generic versions of biological medicines).
139 See infra Part III.A.
140 See infra Part III.B.
141 See infra Part III.C–D.
142 See infra Part III.C.
A. The Text of the Hatch-Waxman Act

The FDA’s recent treatment of patent carve-outs arguably conflicts with the Hatch-Waxman Act. The plain meaning of the different manufacturer exception does not expressly allow for an Orange Book restriction on patent carve-out requests. Moreover, the FDA should consider only safety and efficacy when evaluating a patent carve-out, so that the agency’s treatment of the different manufacturer exception is internally consistent with its treatment of other labeling exceptions in the Act.

The Hatch-Waxman Act makes an exception to the identical labeling requirement for instances where the generic manufacturers or distributors differ from those of the pioneer. The Act requires an ANDA to provide information showing that the “labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under [a suitability petition] or because the new drug and the listed drug are produced or distributed by different manufacturers.”143 The statute itself provides no further information on how to implement the different manufacturer exception.

At first glance, the different manufacturer exception appears to swallow the identical labeling requirement. The pioneer and generic drug manufacturers are typically different entities, so, according to the plain meaning of the exception, the identical labeling requirement does not seem to apply to them. This interpretation of the Act does not seem reasonable, however, because of the importance of keeping labels of the same drug nearly identical. Therefore, the different manufacturer exception must be read more narrowly.

One way to interpret the exception more narrowly is to place more emphasis on which changes in the label are actually required. The generic manufacturer has the burden to show that its label is identical to the pioneer’s except “for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers.”144 Accordingly, the same labeling requirement does not apply to “required” changes in labeling information, but the question becomes: Which types of changes are “required” because different manufacturers produce or distribute the pioneer and generic drugs? Broadly interpreted, manufacturers could request any number

144 Id. (emphasis added).
of labeling changes based on differences in production and distribution, but not all of them will be "required." The statute itself does not address this question in the context of the different manufacturer exception.

The Act does, however, address the types of changes required for the other exception to the identical labeling requirement—differences approved under a suitability petition. An applicant submits a suitability petition along with an ANDA for a generic drug "which has a different active ingredient or whose route of administration, dosage form, or strength differs from that of a listed drug." The FDA will approve the petition so long as it finds the drug as "safe and effective" as the listed drug. For suitability petitions, FDA approval hinges on the safety and effectiveness of the generic drug under the conditions prescribed on its label. Therefore, the "required" changes under a suitability petition are those changes requested by the ANDA applicant that do not render the generic drug less safe or effective than the pioneer drug.

Drawing on the Act's treatment of the other exception (suitability petitions), the different manufacturer exception should extend to changes requested by the applicant because of differences in production and distribution that do not affect the safety and efficacy of the drug. This interpretation of the exception makes the Act's treatment of exceptions to the identical labeling requirement internally consistent. FDA approval of the labeling changes due to different manufacturers should therefore depend on whether the FDA deems the generic drug as safe and effective as the pioneer drug in the context of its proposed label.

The FDA seemed to agree at one point. Pursuant to the Hatch-Waxman framework, the FDA had instituted a mechanism for generics to request patent carve-outs that appeared to revolve solely around the safety and effectiveness of the generic drug. Under that previous mechanism, an ANDA applicant proposed a generic product with la-

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140 Id. § 355(j)(2)(C).
146 Id. ("The Secretary shall approve such a petition unless the Secretary finds—(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or (ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an ANDA.").
147 See 21 C.F.R. § 314.127(a)(7) (2007) (requiring that omissions of an aspect of labeling protected by patent "not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use").
beling that differs from that of the reference listed drug, and the applicant argued to the FDA that the proposed labeling rendered the drug as safe and effective as the concurrently approved labeling of the listed drug. The FDA then assessed, in the context of an ANDA, the safety and effectiveness of the generic drug's proposed labeling.

Recently, the FDA departed from its precedent and inserted a preliminary step to the safety and effectiveness evaluation. This step requires that the omitted language derive from an Orange Book-listed patent. The basis for this restriction is not in the text of the statute itself. At best, the statute is silent as to this limitation. At worst, the limitation does not comport with the statutory provisions that authorize the process for generic drug approval.

While no current controversy exists in the courts, an aggrieved party could, under the Administrative Procedure Act (APA), challenge an FDA denial of a patent carve-out based on the Orange Book restriction as being inconsistent with the Hatch-Waxman Act. The aggrieved party would likely argue that there is no reason to believe on the face of the Hatch-Waxman Act that Congress intended differences resulting from different manufacturers to be acceptable only when the differences derive from patents listed in the Orange Book. The success of this statutory challenge will likely depend on the court's tools of statutory interpretation and the level of deference awarded to the FDA. On the one hand, a textualism-centered court applying a Chevron analysis may find the Hatch-Waxman Act silent or unambiguous as to the breadth of the different manufacturers' exception and defer to the FDA. On the other hand, a court using other tools of statutory interpretation, such as legislative history, and deferring to the FDA under Skidmore may find the Orange Book restriction outside the exception's scope.

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148 According to section 706(2)(C) of the APA, a reviewing court may reverse the FDA's decision if it is "in excess of statutory jurisdiction, authority, limitations, or short of statutory right." 5 U.S.C. § 706(2)(C) (2000).


150 Since the FDA applies the Orange Book restriction in informal adjudications (i.e., decision letters to individual applicants), the court may apply Chevron or Skidmore (persuasive) deference to the FDA's interpretation of the Hatch-Waxman Act. See United States v. Mead, 533 U.S. 218, 229 (2001) (holding that Skidmore, and not Chevron, deference applies to statutory constructions announced in classification ruling letters issued by the Customs Service).
B. The Legislative History of the Hatch-Waxman Act

While the legislative history of the Act's labeling exceptions is meager, the comments in the House Report are consistent with a view that the different manufacturer exception was intended to have a broad scope. Congress anticipated that generic drug manufacturers would seek FDA approval of labels that differ from those of the pioneer. The House Report explained that "[t]he Committee recognizes that the proposed labeling for the generic drug may not be exactly the same."  

The congressional reports condoned specific differences in the labeling due to different manufacturers as well. For instance, members of Congress expected different manufacturers to delete from their labels information pertaining to an indication for which approval was not being sought. The report accompanying the House version of the Hatch-Waxman Act expressly noted that the Act "permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved." In BMS, the D.C. Circuit Court understood the House Report to suggest that Congress regarded labeling changes as a necessity for ANDAs accompanied by a section eight statement.

The legislative history also lists instances outside of indications where the proposed labeling for the generic drug may not be exactly the same as that of the reference listed drug. This list is clearly by way of example and is not exhaustive. The congressional report provides "an example" where "the name and address of the manufacturers would vary as might the expiration dates for the two products." Congress clearly intended the different manufacturer exception to apply to technical differences between manufacturers, such as names, addresses, and expiration dates.

The report approves another seemingly technical difference between manufacturers that is much more indicative of the breadth and substance of the carve-out exception:

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152 Id. at 21, reprinted in U.S.C.C.A.N. at 2654.
153 See supra notes 34-41 and accompanying text.
154 See supra notes 30-31 and accompanying text (describing statutory exceptions to the labeling requirements).
Another example is that one color is used in the coating of the listed drug and another color is used in that of the generic drug. The FDA might require the listed drug maker to specify the color in its label. The generic manufacturer, which has used a different color, would have to specify a different color in its label.\textsuperscript{156}

While an exception based on different colors between drugs may seem no more substantive than different names and addresses between manufacturers, the color specification example implies that the carve-out exception may extend to differences based on a combination of FDA requirements and intellectual property law.

Generic drug manufacturers purposefully change the color of generic drugs to avoid trademark infringement suits. Colors may receive trademark protection if they possess secondary meaning, so a pioneer can sue a generic for trademark infringement if the generic drug and brand-name drug have the same color.\textsuperscript{157} Furthermore, if a generic drug has the same color as the pioneer drug, the pioneer may sue the generic manufacturer for inducing pharmacists to illegally substitute a generic drug for the brand-name drug.\textsuperscript{158}

Congress presumably recognized that generic manufacturers may need to color their drugs differently from those of the pioneer for intellectual property reasons.\textsuperscript{159} Congress also understood that generics must follow FDA requirements, such as color specifications. Therefore, the House Report notes a difference in manufacturing (color changes) necessitated by intellectual property concerns that falls within the different manufacturer exception. In doing so, the legislative history supports the extension of the labeling exception to attempts by generics to "design around" the pioneers. Congress apparently intended the different manufacturer exception to broadly encompass changes in labeling, including those compelled by intellectual property protection.

\textsuperscript{156} Id.
\textsuperscript{157} See Qualitex Co. v. Jacobson Prods. Co., 514 U.S. 159, 163 (1995) (holding that color can be a trademark when the "color has attained 'secondary meaning' and therefore identifies and distinguishes a particular brand").
\textsuperscript{158} See Inwood Labs., Inc. v. Ives Labs., Inc., 456 U.S. 844, 846 (1982) (discussing "the circumstances under which a manufacturer of a generic drug, designed to duplicate the appearance of a similar drug marketed by a competitor under a registered trademark, can be held vicariously liable for infringement of that trademark by pharmacists who dispense the generic drug").
\textsuperscript{159} Notice that Inwood was tried concurrently with the enactment of the Hatch-Waxman Act.
A broad reading of the different manufacturer exception is also consistent with the Act's purpose, as stated in the legislative history of the Act, to limit the monopolization of certain drugs by brand-name manufacturers.

[T]he purpose of Title I of the Bill is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs . . . .

The purpose of Title II of the Bill is to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket government approval. The incentive is the restoration of some of the time lost on patent life while the product is awaiting pre-market approval.\[160\]

The goal to "make available more low cost generic drugs" is furthered by a broad reading of the different manufacturer exception, and is both separate and distinct from the incentive for research and development—namely, "restoration of some of the time lost on patent life."

The FDA's Orange Book restriction conflicts with both of the stated purposes of the Hatch-Waxman Act, and would confer substantial additional rights on pioneer drug patent owners that Congress quite clearly did not intend to confer. Diverging from Title I's purpose, an NDA holder can maintain its exclusivity by exploiting the Orange Book limitation on the patent carve-out exception in a variety of ways.\[161\]

For example, the NDA holder can amend its label to include information protected by newly acquired patents.\[162\] Or the NDA holder can assign a use code that overstates the patent's scope, thereby inhibiting a generic from obtaining FDA approval for an unprotected indication.\[163\] In addition, the NDA holder could withhold patents from the Orange Book to inhibit the FDA from approving carve-outs.\[164\] In all these cases, the NDA holder can use the Orange Book restriction against any competitor seeking approval to market an off-patent drug

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\[161\] See Mahn, supra note 1, at 11-12 (describing ways in which NDA holders can "ever-green" the drug label).

\[162\] See id. at 10 ("[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.").

\[163\] See supra Part I.D (providing an example where an NDA holder's broad use code eliminated the carve-out exception for a generic).

\[164\] See Mahn, supra note 1, at 11 ("[P]ioneers have a strong incentive to opt out of the Orange Book in order to eliminate the carve out option . . . .").
for an approved use not covered by a patent. NDA holders can essentially bar generic manufacturers from entering the market, a result that does not advance the purpose of making available "more low cost generic drugs."

The *Orange Book* restriction does not advance the purpose of Title II of the Hatch-Waxman Act either. Congress explicitly stated that the incentive created by the Act was patent term restoration, and the Act describes a detailed protocol to increase "some of the time lost on patent life." The *Orange Book* restriction is not the type of incentive for research and development that Congress had in mind. In fact, the *Orange Book* restriction creates a disincentive to perform research and development that would yield new drugs and new methods of use.\(^\text{165}\) Since pioneers can use patent carve-outs as a tool to delay generic drug entry, they are encouraged to research and develop patentable, incremental improvements on old drugs that can be added to a drug label, as opposed to new drugs and methods.\(^\text{166}\) There is no evidence that Congress intended the Act to enable a pioneer to extend its exclusivity merely by manipulating entries in the *Orange Book* and updating labeling instructions.

Also noteworthy is the lack of support for the *Orange Book* restriction in the Act's legislative history. Nowhere in the reports did Congress envision limiting the types of features that the generic could "design around" to features protected by patents in the *Orange Book*. Also absent from the legislative history is the suggestion that the FDA should deny or even delay an ANDA because of an existing patent claiming some aspect of the labeling that is tangential to the drug's safety and effectiveness. To the contrary, congressional reports indicate that Congress intended drug labels to reflect differences between the generic and pioneer drugs, including those stemming from intellectual property concerns.

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\(^\text{165}\) *See Mahn, supra* note 1, at 12 n.25 ("Restricting patent label carve outs to listed patents ironically enhances the power of unlisted patents relative to listed patents, as a tool to monopolize drug marketing. This result would encourage a pioneer to invest more on the search for minor, albeit patentable improvements that could be used to protect an aspect of labeling, and less on developing new methods of use and drug products.").

\(^\text{166}\) *Id.*
C. Agency’s Regulations and Rulings

Not only do the statute and legislative history seem to approve of, or at least not condemn, carve-out requests deriving from unlisted patents, but the FDA also designed its rules to allow the agency to approve such requests. When crafting the original labeling regulations in 1992, the FDA contemplated approval of bona fide carve-out requests besides those included in section eight statements. The administrative record indicates that the FDA actually changed a draft regulation to specifically condone nonindication carve-out requests derived from unlisted patents. A 2002 decision from the FDA also demonstrates that, pursuant to its own rules, the agency approved a carve-out request deriving from unlisted patents.

The original version of the generic labeling rules proposed by the FDA specified that only an “omission of an indication protected by patent” (and not any “other aspect of labeling”) was an acceptable difference in labeling.\(^{167}\) A prognostic comment convinced the agency, however, that the scope of the proposed labeling rule was too narrow. The comment that struck a chord with the FDA expressed the concern that ANDA applicants may be exposed to litigation based on “a possible claim of inducement or infringement where a nonapproved, but patented, method of administration is discussed in the innovator’s label.”\(^{168}\) Importantly, the Orange Book does not list patents for “non-approved” conditions. The FDA “agree[d] in part with the comment” and, accordingly, amended the provision to include any “other aspect of labeling protected by patent.”\(^{169}\)

At least initially, the FDA apparently viewed unlisted patents as a bona fide source of information to be carved out of a label. And the amended provision gave the agency flexibility to approve the omission of language protected by claims of patents ineligible for Orange Book


\(^{168}\) Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,962 (Apr. 28, 1992). The comment also warned the FDA that the proposed rules did not account for instances in which the “labeling refers to more than one method of use and 'some but fewer than all of the methods of use are entitled to nonpatent exclusivity.'”\(^{169}\) Id.

\(^{169}\) Id. The FDA did not specify the part of the comment with which it agreed, but the amendment allows the agency to extend the different manufacturer exception in both instances. Id.
listing. Evidently, the FDA originally supported a broad scope of the patent carve-out currently contravened by the Orange Book restriction.

The FDA’s recent decision to apply the Orange Book requirement to all carve-out requests (i.e., both “omission of an indication" and “other aspect[s] of labeling protected by patent”) suggests that the FDA no longer supports a broad exception. The 2003 Modernization Act strictly limited the types of patents eligible for listing in the Orange Book, and the FDA apparently believes that this subset of patents is the only source of bona fide patent carve-outs. The FDA provides no reasoning as to why it narrowed the scope of the exception, nor any justification for the change in its approach. In fact, the Orange Book restriction and the logic behind it are wholly undocumented.

Furthermore, the FDA’s current treatment of patent carve-out requests is both new and inconsistent with previous decisions. In 2002, the FDA approved labeling changes originating from an unlisted patent. In its Citizen Petition, GlaxoSmithKline (GSK) requested that the FDA deny ANDAs for crystalline generic cefuroxime axetil, in part because generics could not meet the same labeling requirement. The package insert for GSK’s cefuroxime axetil drug (Ceftin) described the active ingredient as being “in the amorphous form.”

GSK contended that “approving a drug product wholly or partially composed of the crystalline form of cefuroxime axetil would flout the requirement that the labeling of an ANDA product be the same as that of the reference listed drug.” The FDA rejected GSK’s argument and approved the labeling changes proposed by ANDA applicants: “Consistent with this regulatory scheme, FDA may approve a generic cefuroxime axetil tablet product whose labeling states that the active ingredient is wholly or partially in crystalline form.”

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170 See Mahn, supra note 1, at 10-11 ("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.").

171 See Decision Letter from Dennis Baker, Assoc. Comm’r for Regulatory Affairs, FDA, to Donald O. Beers et al., at 1 (Feb. 15, 2002) (responding to citizen petitions and petitions for stay of action that requested FDA denial of approval of any ANDA for wholly or partially crystalline generic cefuroxime axetil).

172 Id. at 17.

173 Id.

174 Id. (emphasis added).

175 Id. at 18.
The FDA approved the labeling change even though the Orange Book does not list patents covering cefuroxime axetil. Cefuroxime axetil is an old antibiotic, so patents claiming the drug and its methods of use are ineligible for Orange Book-listing.\textsuperscript{176} The agency recognized that the Orange Book did not contain cefuroxime axetil patents, but this fact did not inhibit the agency from delving into the safety and efficacy of generic cefuroxime axetil (in step two of its current patent carve-out inquiry). The agency ultimately found the crystalline form as safe and effective as the amorphous form of the drug and consequently approved the patent carve-out.\textsuperscript{177}

Interestingly, the FDA never explicitly invoked the patent carve-out exception, though that is exactly what the agency approved. Rather, the FDA acknowledged that the different manufacturer exception extended beyond its own list of examples:

The plain language of § 314.94(a)(8)(iv) explicitly recognizes that these differences listed in the regulation are examples; therefore, § 314.94(a)(8)(iv) recognizes that there are other differences in labeling between generic drug products and reference listed drugs that are permissible due to the fact that the generic drug product and reference listed drug product are produced or distributed by different manufacturers.\textsuperscript{178}

The FDA did not categorize the requested labeling change as a patent carve-out request, even though the generics effectively "designed around" the pioneer's patents on the physical form of the drug. The agency focused on the safety and efficacy of the generic drug and approved an omission of language protected by patents not listed in the Orange Book.

What exactly motivated the FDA to add the Orange Book as a gatekeeper to the patent carve-out exception is unknown. At least until 2002, the FDA seemed to support a fairly broad interpretation of the patent carve-out exception. The change in its treatment of carve-out requests likely derives from the agency's refusal to engage in patent

\textsuperscript{176} The FDA originally approved GSK's Ceftin on December 28, 1987. See Drugs@FDA: FDA Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/drugsatfda (type in Ceftin; then follow Ceftin NDA #050605 hyperlink) (last visited Oct. 15, 2007). When discussing certification requirements in response to the PDI Petition, however, the agency did note that GSK's "patent was not required to be listed in the Orange Book because cefuroxime axetil is an antibiotic drug that was approved under section 507 of the Act." Decision Letter from Dennis Baker, supra note 171, at 31.

\textsuperscript{177} See Decision Letter from Dennis Baker, supra note 171, at 7-16.

\textsuperscript{178} Id. at 18.
Rather than reviewing patents to determine whether a patent's scope covers labeling language, the FDA decided to use the patent's *Orange Book* status as the threshold to the safety and efficacy inquiry. As discussed below, a compromise may be had where the FDA need not engage in additional patent review, and the patent carve-out exception can extend to patents not listed in the *Orange Book*.

D. Judicial Constructions

No court decision to date specifically addresses the scope of the patent carve-out exception. A number of cases, however, discuss the FDA's authority to extend exceptions to the identical labeling requirement. The majority of these cases involve an ANDA submitted for an unprotected indication, where the applicant proposed labeling instructions omitting language pertaining to a protected indication. An analysis of each court's language in these cases suggests that the court supports a broad scope for the carve-out exception generally.

*BMS* is the earliest case addressing the FDA's authority to approve ANDAs even though the label of the generic drug would not include an indication that appears on the label of the pioneer drug. In *BMS*, the court interpreted labeling requirements of the Hatch-Waxman Act: "[T]he statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference." First, the court interprets the statute to say *expressly* that the touchstone of the identical labeling requirement is the safety and efficacy of the drug in the context of its own label. Second, the court notes that the difference in the number of indications between the pioneer and generic drug labels is a "matter of indifference." The generic drug manufacturer should be free to choose which indications to promote, and the specific nature of those differences is not relevant to the analysis. According to *BMS*, Hatch-Waxman does not concern itself with the omit-
ted language, because the focus of the exception is on the information provided on the label.

Extending this logic to patent carve-outs, the FDA should not concentrate on the source of the omitted, protected information. Whether the omitted information derives from a listed or unlisted patent is irrelevant. So long as the generic drug label does not render the drug less safe or effective than the pioneer drug, the generic should satisfy Hatch-Waxman's (and consequently the FDA's) labeling requirements. The *Orange Book* restriction is arguably contrary to the BMS court's interpretation of Hatch-Waxman. If so, under a *Chevron* analysis, the FDA may be stepping out of bounds by departing from the BMS court's interpretation of exceptions to the identical labeling requirement.\(^{182}\)

A broad view of the same labeling requirement was also supported in *Zeneca v. Shalala*.\(^{183}\) Zeneca had challenged the FDA's decision to allow Genesia to add a sulfite warning on the label of its generic product.\(^{184}\) Zeneca urged the court to narrowly interpret the labeling exception, but the court declined to do so, citing *BMS*.\(^{185}\) The *Zeneca* court noted the importance of "harmony" among the different provisions: "Given that a generic manufacturer is permitted to substitute certain inactive ingredients,... it follows that these different ingredients must be identified in the labeling."\(^{186}\)

Applying *Zeneca*’s reasoning to the patent carve-out exception, the FDA’s *Orange Book* limitation may not be in "harmony" with other provisions. The "other aspect of labeling protected by patent" language is basically superfluous\(^{187}\) if it is limited to the *Orange Book*-listed patents, because the *Orange Book* primarily lists patents claiming the drug itself or indications. The FDA provides a specific labeling exception for


\(^{184}\) Id. at *10.

\(^{185}\) See id. ("[T]he Court of Appeals for the District of Columbia Circuit took a much broader view of the same labeling requirement.").

\(^{186}\) Id. at 11.

\(^{187}\) Besides being superfluous, this severe limitation on the meaning of "other aspect of labeling" is also contrary to the FDA's purpose in adding the language. See supra notes 167 to 170 and accompanying text (discussing the comment in the administrative record that motivated the FDA to add the "other aspect of labeling" provision).
“omission of an indication,” and generics do not submit ANDAs until the drug patents expire. Extending the exception to “other aspect[s] of labeling protected by patent” provides no additional protection. To harmonize the “other aspect of labeling” provision with the Orange Book listing requirements, the FDA should extend the exception broadly to labeling changes due to different manufacturers, as BMS and Zeneca suggest.

The assumption that the Orange Book should contain all patents that would be subject to a bona fide carve-out request is flawed, and case law suggests such an assumption will not fare well in courts. In Purepac, the FDA denied an ANDA for a generic drug based on an improperly listed patent. The FDA argued that the Orange Book “should” only contain patents claiming approved uses, and that assumption somehow absolved the agency of the responsibility of reviewing a patent that the ANDA applicant contended did not belong in the Orange Book. The court criticized the FDA for using its construction of a “legal fiction” to ignore crucial facts and found that the FDA’s decision violated the APA. An assertion by the FDA that old antibiotics would be in the Orange Book but for Congress will probably not excuse its denial of carve-out requests from ANDA applicants of old antibiotics. The reasoning from Purepac implies that courts will not tolerate the FDA’s assumption that the Orange Book necessarily contains the types of patents that would comprise bona fide carve-out requests.

Another case worth discussing—not for its discussion of labeling, but for its underlying proposition—is Warner-Lambert. The central question in Warner-Lambert was whether submitting an ANDA seeking approval to make, use, or sell a drug for an approved use was an act of infringement under 35 U.S.C. § 271(e)(2)(a) if any other use of the

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188 Purepac Pharm. Co. v. Thompson, 258 F. Supp. 2d 191, 208 (D.D.C. 2002), aff’d, 354 F.3d 877 (D.C. Cir. 2004). The FDA improperly listed Pfizer’s ‘479 patent covering gabapentin’s unapproved use for treating neurodegenerative diseases in the Orange Book, and then denied Purepac’s ANDA for gabapentin to treat epilepsy—the approved use—because only approved method-of-use patents may be listed in the Orange Book. Id.
189 Id.
190 Id.
191 Id. at 212.
192 See Warner Lambert, Inc. v. Apotex Corp., 316 F.3d 1348, 1354-55 (Fed. Cir. 2003) (holding that “it is not an act of infringement to submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved under the NDA”).
drug is claimed in a patent, or, in the alternative, if “it is only an act of infringement to submit an ANDA seeking approval to make, use, or sell a drug if the drug or the use for which FDA approval is sought is claimed in a patent.” 193 Warner-Lambert asserted that “a patent claiming a use of a drug is infringed by the filing of an ANDA irrespective of whether approval is sought to market the drug for the patented use.” 194 The Federal Circuit disagreed. The Court engaged in statutory interpretation and found that “Congress intended to draw a distinction in the Act between those indications for which an ANDA applicant is seeking approval and those for which it is not when determining if certification is necessary.” 195 Warner-Lambert therefore stands for the proposition that an ANDA applicant need not file a paragraph certification for that which it is not asserting.

The logic behind Warner-Lambert holds significance in the patent carve-out context. When an ANDA applicant seeks to carve out protected language from a label, the applicant is not seeking FDA approval to make, use, or sell the drug as described in the omitted language. Therefore, the ANDA applicant should not have to certify that a listed patent protects the omitted language. According to Warner-Lambert, Apotex did not have to certify that patents covering the omitted indications either were not filed, were expired, will expire, or were not infringed, because Apotex did not seek FDA approval for the omitted indications. Similarly, an ANDA applicant should not have to certify that the Orange Book lists patents covering omitted language when the applicant does not seek FDA approval for the omitted language. Limiting generics to language omissions protected by listed patents essentially restricts generics to language omissions that are subject to generic certification requirements. Applying Warner-Lambert, generics should not be required to certify patented language that they seek to omit.

IV. POSSIBLE SOLUTIONS

A couple of solutions have been proposed to guide the FDA in finding the appropriate scope of the patent carve-out exception. The generics, unsurprisingly, call for a broad carve-out policy that encom-

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193 Id.
194 Id. at 1355.
195 Id. at 1361.
passes all patents, irrespective of the *Orange Book* listings. Such an unfettered policy does not address what is perceived to be the agency’s concern about patent review: the FDA has made it clear that it does not want to review patents. Presumably, the FDA’s desire to maintain its ministerial role drives the agency to limit patent carve-outs to the *Orange Book*. As long as the generics request carve-outs based on language protected by patent, there has to be some verification process to determine if that language is indeed protected. Currently, the FDA has assumed the responsibility, in a way, by limiting the patent carve-out to the agency-compiled *Orange Book*. The FDA assumes that the language is protected because the language derives from an *Orange Book*-listed patent.

A solution that better balances the proper scope of the carve-out exception with the responsibilities of the FDA is to require the ANDA or section 505(b)(2) applicant to profess, under penalty of perjury, its belief that the language is claimed by a patent, listed or unlisted. This approach is consistent with the FDA’s implementation of a number of Hatch-Waxman Act provisions. The FDA’s policies frequently place the onus on the NDA holder to reasonably abide by the regulations. One example is the submission of the use code. Another example is the submissions to the *Orange Book*. Part of the FDA’s motivation in placing the burden on the applicants is convenience, but another part also presumably derives from its trust in the system. For those same reasons, the FDA should seriously consider placing the onus of unlisted patent carve-out requests on the applicant. The potential abuses of the system are no different than those available to the pioneers in the use code and *Orange Book* listing context.

A second suggestion proposed by generics requires pioneers to disclose relevant patents when amending labels. The FDA can then make a judgment call as to whether the label updates are genuinely

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196 See Mahn, *supra* note 1, at 11 (“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*.”).

197 See Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,345 (Oct. 3, 1994) (“FDA does not have the resources or the expertise to review patent information for its accuracy and relevance to an NDA.”); Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,909 (proposed July 10, 1989) (“Because the FDA has no expertise in the field of patents, the agency has no basis for determining whether a use patent covers the use sought by the generic applicant.”).
for consumer health or for competitive gain. This suggestion is good, but incomplete. The agency would initially use the patent submissions as a red flag, but what standard would the FDA apply in accepting or denying the label amendments? From the FDA's standpoint, this suggestion has two undesirable attributes. First, in order to assess whether the amendments are designed to extend exclusivity or for consumer health, the FDA would have to engage in the review of patents listed or unlisted in the Orange Book. Second, the agency's workload would increase in amount and difficulty if the FDA had to inquire into the purpose of the amendments and the intent of the NDA holders.

Perhaps a better way to stop NDA holders from updating the label to inhibit generics from entering the marketplace is to limit drug label updates to those that improve the safety and efficacy of the drug. In addition to requiring NDA holders to submit relevant patents, the FDA can require that any request for label amendments be a "good faith" assertion that those amendments are more than incremental improvements that need to be communicated to doctors and patients. That way, when the generic submits an ANDA with language carved out, the generic must rebut the presumption that the language is necessary for the safety and efficacy of the drug. This approach front-loads the determination of safety and efficacy onto the NDA holders and may slightly increase the FDA's workload when pioneers request labeling amendments.

Yet the FDA's presumption of necessity may result in less work overall. This good faith approach may discourage NDA holders from submitting updates that fail to provide more than incremental improvements to the drug's safety and efficacy. Furthermore, generics will only challenge the presumption when they can make a particularly strong showing that the language omission does not affect safety and efficacy. Finally, the good faith approach focuses the FDA on the proper inquiry for the agency—the safety and efficacy of the drug in light of the labeling change—and excludes patent review, which is outside the agency's expertise.

This good faith approach to labeling amendments would require the FDA to change its philosophy toward labeling changes, which

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198 See Mahn, supra note 1, at 11-12 ("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.").
could benefit the FDA and the public in other ways as well. Currently, the FDA includes updates to labeling information liberally, with the idea that more is better. Product inserts are already long and cumbersome for doctors and patients to read, and changes in labels often times lead to consumer confusion. Limiting the insert to updates that are truly important to the safety and efficacy of the drug may lessen consumer confusion and better highlight the important information, while potentially reducing the workload of the FDA.

The utility of both of these suggestions hinges on the threat of real penalties. According to these proposals, ANDA applicants will have to swear under penalty of perjury that they are omitting language deriving from a patent, and NDA holders must submit in good faith that the labeling amendments improve the safety and efficacy of the drug to an extent that warrants notification to the consumer. The penalty of perjury, in combination with other measures, has reportedly quashed Orange Book ever-greening. The success of this penalty in the Orange Book context should make the FDA feel comfortable requiring a similar declaration from generics in the patent carve-out context.

A good faith requirement is much more difficult to enforce because NDA holders can always argue that they believe the label change to be more than an incremental improvement. Yet, the good faith approach rightfully places the time delay in the administrative process for the safety and efficacy determination on the NDA holder instead of the generic. The NDA holder will need to be more cautious about submitting labeling amendments under the good faith requirement, and the FDA may need to spend more time scrutinizing the labeling updates and relevant patents before making a determination.

If the FDA continues to restrict the patent carve-out exception to the Orange Book, then the agency should, at the very least, subject NDA holders to real penalties if they fail to list patents in the Orange Book. Pioneers are likely to withhold patents from the Orange Book so that the agency cannot approve proposed carve-outs. The Orange Book restriction creates incentives for pioneers to exclude patents from the

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199 See supra note 59 and accompanying text.
200 See Mahn, supra note 1, at 11 ("[P]ioneers 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 with infringing language.").
Orange Book without much of a loss.\textsuperscript{201} As mentioned above, the withdrawal of FDA approval is the only current penalty for withholding patents, and such a “draconian” penalty is not likely to be employed.\textsuperscript{202}

In anticipation of future abuses, the FDA should set up a mechanism whereby a generic can challenge the pioneer’s failure to submit to the FDA a patent for inclusion in the Orange Book. Once the pioneer receives notice, the FDA can set a time frame during which the pioneer should respond. After looking at the complaint and response, the FDA should make a ruling as to whether the patent should be submitted. If the FDA finds that the patent qualified for Orange Book listing, then the FDA can impose a fine (or whatever other penalty the agency deems fit) upon the pioneer for withholding the patent. While this mechanism does require the FDA to engage in some patent review, the level of review is no more intensive than the analysis the FDA already performs for Orange Book submissions.\textsuperscript{203}

The FDA should return to interpreting the patent carve-out exception broadly, while staying removed from the patent arena. By requiring ANDA applicants to declare, under penalty of perjury, that the information they seek to carve out is protected under patent, the FDA can focus on the central inquiry of the safety and efficacy of the drug in the context of its label. By implementing a good faith requirement to label updates, the FDA will discourage label updates unnecessary to doctors and patients. Fewer label changes also means fewer carve-out requests. Further, instituting a mechanism to challenge the absence of patents from the Orange Book should keep the Orange Book listing up to date. These provisions acting in concert will hopefully return the patent carve-out exception to the broad scope intended by Congress.

CONCLUSION

The inherent assumption of the FDA’s Orange Book limitation is that all of the desirable carve-outs will derive from patents listed in the Orange Book. In the words of the Purepac court, “it is simply misguided

\textsuperscript{201} See id. at 12 n.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.”).

\textsuperscript{202} See supra note 57 and accompanying text.

\textsuperscript{203} See Mahn, supra note 1, at 12 n.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.”).
to suggest that this situation must actually exist merely because it is supposed to exist." And the situation does not exist. The FDA probably based its current framework for evaluating a patent carve-out on its experience with requests to omit a patented use of a drug, which should be listed in the Orange Book, from a generic label. This restriction ignores two facts: (1) "other aspect[s] of labeling protected by patent" are not necessarily in the Orange Book and (2) Congress may have reasons unrelated to the patent carve-out exception for designating certain patents ineligible for the Orange Book.

The FDA should recognize the legitimacy of carve-outs based on unlisted patents in at least two scenarios—old antibiotics and biological products. The FDA is currently reevaluating its policy toward old antibiotics. The agency likely already recognizes the unfortunate situation of generics submitting ANDAs for old antibiotics, since it approved a patent carve-out request for an old antibiotic before its adoption of the Orange Book restriction. Therefore, the new policy toward old antibiotics may not subject this category of drugs to the Orange Book restriction. The FDA’s policy toward biological generics has only just begun. Patents on many of the first biological products (e.g., interferons, interleukins, and erythropoietin) are beginning to expire, and Congress will likely create a mechanism for approval of biological generics during the next few years. Having seen the effect of the Orange Book restriction on at least one potential biological generic (enoxaparin) will hopefully inform the FDA’s patent carve-out policy for biological generics.

The unintended consequences of a narrow interpretation of the patent carve-out are only part of the reason that the FDA should

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205 See supra Part II.A (discussing Congress’s decision not to list old antibiotics in the Orange Book).
206 See supra note 104 and accompanying text.
207 See supra Part III.C (discussing the approval of the old antibiotic cefuroxime axetil).
208 See Heidi Ledford, The Same but Different, 449 NATURE 274, 276 tbl. (2007) (cataloguing the patent expiration dates of prominent biologic drugs).
209 See Congressional Fix for Follow-On Biologics Unlikely Until 2008, WASH. DRUG LETTER, June 26, 2006, at 26 (reporting that, according to one Senate staffer, legislative proposals amending the FDCA will be entertained in 2008); see also Senate Advances Biogenerics Bill, supra note 138, at 20 (discussing proposed bills).
strongly consider reevaluating its policy. The *Orange Book* limitation is not clearly supported by the text or legislative history of the Hatch-Waxman Act, the FDA's own regulations and decisions, or the courts' opinions relating to exceptions to the labeling requirement.

The FDA probably decided to limit patent carve-outs to those listed in the *Orange Book* to avoid patent review, but the FDA need not engage in further patent analysis to maintain the appropriate breadth of the patent carve-out exception. The FDA should place the burden on the ANDA or section 505(b)(2) applicant to identify the patents and declare, under penalty of perjury, that those patents protect the carved-out language. The generic will likely bear the responsibility gladly in exchange for FDA consideration of its patent carve-out under the safety and efficacy standard.