

**Comments of the
Pharmaceutical Research and Manufacturers of America (PhRMA)**

on

FDA's Proposed Rule:

**“Applications for FDA Approval to Market a New Drug: Patent Listing Requirements
and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications
Certifying that a Patent Claiming a Drug is Invalid or Will not be Infringed”**

[Docket No. 02N-0417]

Of Counsel:

Bruce N. Kuhlik
Erika King
PHARMACEUTICAL RESEARCH
AND MANUFACTURERS OF
AMERICA
1100 Fifteenth Street, NW
Washington, DC 20005

Michael S. Labson
Christopher N. Sipes
COVINGTON & BURLING
1201 Pennsylvania Avenue NW
Washington, DC 20004-2401
Phone: (202) 662-6000
Fax: (202) 662-6291

*Counsel for the Pharmaceutical Research
and Manufacturers of America*

December 23, 2002

02N-0417

C27

Introduction

The Pharmaceutical Research and Manufacturers of America (“PhRMA”) submits these comments in response to the proposed rule FDA published on October 24, 2002 regarding the agency’s implementation of the patent listing and 30-month stay provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the “Hatch-Waxman Amendments”).¹ PhRMA is a voluntary, nonprofit association representing the country’s leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. PhRMA’s member companies invested more than \$30 billion in 2001 alone in discovering and developing new medicines. PhRMA companies are the source of nearly all new drugs that are discovered and marketed throughout the world.

As the leaders in the search for innovative new cures, PhRMA’s members hold the overwhelming majority of the new drug applications (“NDAs”) filed with FDA. The financial health of these companies, and their ability to continue to invest in future drug research and development, depend in critical part on the intellectual property that protects their inventions, including in particular patents. Accordingly, PhRMA and its members have a unique stake in the patent listing and stay provisions that are the subject of FDA’s proposed rule.

¹ 67 Fed. Reg. 65448 (October 24, 2002).

FDA's proposed regulation would make significant changes to current law. Since 1984, NDA and patent holders have had the opportunity to obtain a 30-month stay on FDA approval of an abbreviated new drug application ("ANDA") or 505(b)(2) application whenever the ANDA or 505(b)(2) applicant makes a paragraph IV certification challenging a listed patent. The proposed rule would eliminate this opportunity in certain circumstances. Generic drugs could be approved and enter the market without the innovator company's having had a fair opportunity to litigate the patent infringement issues raised by the generic product. FDA's proposal would also make several categories of patents ineligible for listing in the Orange Book. In short, the proposed regulation in its current form would have a substantial impact on the innovator drug industry that PhRMA represents.

The 30-month stay provisions are intended to give NDA and patent holders an opportunity to enforce their intellectual property rights prior to the approval and market entry of generic drugs, and are at the heart of the Hatch-Waxman scheme. FDA's stated intent is to ensure that innovator companies always have the opportunity for one 30-month stay on approval of an ANDA or 505(b)(2) application. As formulated, however, in some situations the proposed regulation could be manipulated by generic applicants to deprive NDA and patent holders of the opportunity to obtain even a single 30-month stay when their patents are challenged. As explained below, this apparently unintended consequence can be corrected by FDA in a final rule, without a significant adjustment to the legal theory put forward in the preamble to the proposed rule. The corrections are necessary, however, to effectuate the purpose of the statute, to be consistent with FDA's own stated goals, and to ensure that there

remains a meaningful opportunity to obtain an appropriate 30-month stay during the pendency of patent litigation.²

Detailed comments on these needed technical changes and other issues raised by the proposed rule follow. The 30-month stay provisions are addressed first.

I. How Many Times Can an Application's Approval Date Be Subject to a 30-Month Stay Period? [Proposed §§ 314.94(a) and 314.52(a)]

The proposed regulation should be modified to ensure that NDA and patent holders have one meaningful opportunity to obtain a 30-month stay. The Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") states that ANDA and 505(b)(2) applicants must provide notice to NDA and patent holders when an application is "amended to include" a paragraph IV certification. FDCA §§ 505(b)(3)(C) & 505(j)(2)(B)(iii). Under FDA's new proposed interpretation of this language, if an ANDA or 505(b)(2) application contains one paragraph IV certification and is amended subsequently to add another paragraph IV certification, the amendment would not be considered one to "include" a paragraph IV certification, because the application already contained a prior paragraph IV certification. No notice would therefore be required for the new paragraph IV certification, and no 30-month stay could arise based on the certification.

FDA's discussion of these issues focuses exclusively on amendments to ANDAs and 505(b)(2) applications that arise because of patents that are newly listed by

² PhRMA supports FDA's attempt to establish clearer rules on the operation of these complex provisions. Nonetheless, without the modifications described in these comments FDA's regulation could be manipulated to erode the opportunity to obtain any 30-month stay. However unintended this consequence might be, PhRMA would necessarily consider a legal challenge to prevent that outcome.

NDA holders. Indeed, FDA's entire proposal on 30-month stays is rooted in the concern that NDA holders should not be able to obtain multiple 30-month stays when litigation is brought on newly issued and listed patents. 67 Fed. Reg. at 65449. Nowhere does FDA address amended patent certifications that an ANDA or 505(b)(2) applicant makes on its own accord. These types of amendments are distinct, and present unique legal and policy concerns that FDA must address in a final rule.

If FDA does not clarify its approach to these and other related circumstances, ANDA and 505(b)(2) applicants may be able to game FDA's proposed rules to deprive NDA and patent holders of a meaningful opportunity to obtain even a single 30-month stay. The agency's change in interpretation of the Act itself shifts the balance of the Hatch-Waxman law. It deprives NDA and patent holders of a reasonable time period to adjudicate patent rights prior to agency approval for patents that do not issue before the filing of an ANDA. FDA must take care to ensure that it does not permit even further unintended erosion of the opportunity to obtain a 30-month stay. Such a result would be at clear odds with the Hatch-Waxman Amendments.

The importance of the stay provisions to the Hatch-Waxman scheme is clear from the face of the statute, as well as from the legislative history. A House of Representatives Report from 1984 explains that the stay

permits the commencement of a legal action for patent infringement before the generic drug maker has begun marketing. The Committee believes this procedure fairly balances the rights of a patent owner to prevent others from making, using, or selling its patented product and the rights of third parties to contest the validity of a patent or to market a product which they believe is not claimed by the patent.

H. Rep. 98-857, Part 1, 98th Cong., 2d Sess. at 28 (June 21, 1984). Senator Hatch recently explained:

a pioneer drug patent holder, whose patents are under challenge by a generic drug manufacturer, is accorded an automatic 30-month stay. This was not some giveaway to the innovator pharmaceutical industry. We inserted this mechanism to protect the intellectual property of companies that develop patented medications, companies, I might add, that were going to be afforded less intellectual property protections than any other industry as part of the 1984 law. . . . The public policy purpose for this stay is to allow time for the courts to determine the status of validity of drug patents and/or to decide whether valid patents are, or are not, infringed by a generic drug challenger.

148 Cong. Rec. S27342, S7344 (July 25, 2002) (remarks Sen. Hatch).³ The 30-month stay provisions are thus a key component of the careful compromise embodied in the law, and FDA must ensure that any regulatory actions it takes do not go too far in upsetting that legislative compromise.

FDA asserts in this rulemaking that its intent is to ensure that “the opportunity for one 30-month stay in the abbreviated application’s effective date always exists.” *Id.* at 65456. Indeed, FDA cites in the preamble to the proposed rule the agency’s prior acknowledgement that any result that would deprive NDA and patent holders of an opportunity to obtain a single 30-month stay “could not be reconciled with the Hatch-Waxman amendments’ intent to strike a balance between generic drug approval and

³ Senator Hatch further explained that “any discussion of the 30-month stay is incomplete if it does not include the fact that, under Hatch-Waxman, generic drug firms are given a unique advantage under the patent code that allows them to get a head start toward the market by allowing them to make and use the patented drug product for the commercial and ordinarily patent infringing purpose of securing FDA approval and scaling up production.” 148 Cong. Rec. at S7344.

encouraging future innovation.” 67 Fed. Reg. at 65455. The following sections discuss technical changes that must be made to the new proposed rules in order for FDA’s stated intent to be met.

A. Notice Should be Given when ANDA and 505(b)(2) Applicants Change Previous Patent Certifications.

Under the proposed rule, there is a serious potential for ANDA and 505(b)(2) applicants to avoid any 30-month stay. Assume, for example, that two patents are listed for Drug X, a patent on the drug substance in Drug X and a narrow formulation patent. Under the proposed regulation, an ANDA applicant could file a paragraph III certification on the drug substance patent and a paragraph IV certification of non-infringement on the formulation patent. The ANDA applicant would only have to provide notice to the NDA and patent holder on the formulation patent. If the NDA holder determines that the ANDA formulation does not infringe, it could not sue.

The proposed regulation would then permit the ANDA applicant to convert its earlier paragraph III certification to the drug substance patent to a paragraph IV certification without providing notice to the NDA or patent holder. No notice would be required because, under FDA’s new interpretation, the ANDA already “included” a prior paragraph IV certification. No 30-month stay could arise from the new paragraph IV certification, because there would be no notice and no way to trigger the statutory stay provisions. No 30-month stay would exist from the original paragraph IV certification, because the NDA and patent holders had not sued. Thus, no 30-month stay would apply, even though there was no prior stay on the approval of that ANDA. This result conflicts with FDA’s stated intent of ensuring that NDA holders have a *meaningful* opportunity to obtain one 30-month stay. At a

minimum, this must mean that NDA holders can litigate under a 30-month stay with respect to the patents listed at the time the ANDA is filed.

A similar situation might exist where two listed patents have substantially different expiration dates. The ANDA applicant could file a paragraph IV certification against a patent with an imminent expiration date, and a paragraph III certification against the second patent with a later expiration date. The applicant could then subsequently amend the paragraph III certification to a paragraph IV and circumvent the notice requirement, since the ANDA would already have included a paragraph IV certification.

This potential for abuse is real. Under FDA's proposal, there would be little reason for an ANDA or 505(b)(2) applicant ever to make more than one paragraph IV certification in an initial application. The applicant would have every incentive to select a single patent for a paragraph IV certification, make paragraph III certifications to the other patents, and later amend those paragraph III certifications to paragraph IV certifications for which no notice would be required and no stay could apply. NDA holders could do nothing to prevent such gamesmanship, because the law makes patent listing mandatory. NDA holders must list eligible patents and would have no discretion to forego the listing of narrow formulation or other patents that would be targets for initial paragraph IV certifications.

FDA must address this serious loophole in its proposed rule, and it can do so within the new statutory interpretation framework it has set forth. Specifically, FDA should provide that amendments to ANDA and 505(b)(2) applications that are made to change a patent certification that the applicant had already made relate back to, and substitute for, the original patent certification. That is, if an ANDA initially contains a paragraph IV

certification to one listed patent and a paragraph III certification to another, a later amendment to change the paragraph III certification to a paragraph IV would be considered to have been made with the initial application. Notice to the NDA and patent holders therefore would be required, just as it is for any paragraph IV certification made as part of an initial ANDA submission under FDCA § 505(j)(2)(B)(i).⁴ Under the statute (FDCA §§ 505(b)(3)(C) & 505(j)(2)(B)(iii)), notice is given when the application is amended (even if the amendment relates back to the earlier submission of the application), and receipt of the notice would start the 45-day period during which the NDA or patent holder could bring an infringement action and trigger a 30-month stay in connection with the patent that is the subject of the notice.

This approach is supported by FDA's existing regulations. FDA's current regulations provide that when an ANDA or 505(b)(2) applicant amends a previous patent certification, the new certification substitutes for the prior certification, and "the application will no longer be considered to contain the prior certification." 21 C.F.R. § 314.94(a)(12)(viii). When an ANDA or 505(b)(2) applicant converts a paragraph III certification to a paragraph IV certification, the amended certification should be deemed to relate back to and substitute for the original certification and trigger a new notice obligation.

This proposed "fix" would not prejudice generic applicants. It applies only when an ANDA or 505(b)(2) applicant itself changes a patent certification it previously

⁴ Alternatively, the change in patent certification could be viewed as an amendment to "include" a paragraph IV certification under FDCA § 505(j)(2)(B)(iii), since it would be treated as if it were made when the application was first submitted and no prior paragraph IV certification would exist. Again, notice would trigger a 45-day period to bring suit.

made. The fix would not affect FDA's proposed treatment of patents that are newly listed by NDA holders. In those instances, the ANDA or 505(b)(2) applicant would amend its application to add a new certification, not to change a prior certification. The new certification would not relate back and thus could not trigger a new notice requirement or a new stay, where there had not been an earlier paragraph IV certification. NDA holders could not abuse the approach described here, because the decision to *change* a prior patent certification would rest solely in the hands of ANDA and 505(b)(2) applicants.

PhRMA's proposed approach meets FDA's stated intent of ensuring that there remains one real opportunity for innovator companies to obtain a 30-month stay, while retaining FDA's proposed measures to address the concerns about operation of the 30-month stay provisions that the Federal Trade Commission raised in its report on *Generic Drug Entry Prior to Patent Expiration* (July 2002). Without modification along the lines described here, FDA's proposed regulation could be manipulated to erode the opportunity to obtain any meaningful 30-month stay.

B. Notice Should Be Given When ANDA and 505(b)(2) Applicants Change the Formulation of a Product.

A similar issue and potential for abuse can be presented when an ANDA or 505(b)(2) applicant amends the formulation covered by the application. Suppose, for example, that an ANDA is filed for a drug product formulation that does not infringe, and the applicant files a paragraph IV certification on that basis. If the NDA or patent holder agrees that there is no infringement and does not sue, the ANDA applicant could then amend the application to use a drug product formulation that does infringe without having to give notice or risk a 30-month stay.

In order to avoid the potential for such gamesmanship, FDA should require that ANDA and 505(b)(2) applicants provide amended patent certifications whenever they make changes to the chemistry, manufacturing, and controls section of an application.⁵ As in the circumstances described in the preceding section, these would be amendments wholly of the ANDA or 505(b)(2) applicant's own doing, and unrelated to any patents being newly listed by the NDA holder. The amended patent certifications would substitute for and relate back to the prior patent certifications, and could trigger a new notice obligation in accordance with the approach proposed in the preceding section. In that way, the NDA and patent holder would retain one bona fide opportunity to obtain a 30-month stay.

C. A Single ANDA or 505(b)(2) Application May not be Used to Seek Approval of More than One Distinct Drug Product.

A further potential for abuse could occur under the proposed rule if the holders of ANDA and 505(b)(2) applications are permitted to file supplemental applications when they should instead be submitting new applications. For example, if an NDA holder develops a new patented dosage form that would be listed separately in the Orange Book, an ANDA applicant should be required to file a new ANDA for that dosage form, as opposed to a supplemental ANDA. Otherwise the applicant could avoid providing notice and becoming subject to a stay by amending an application that already "includes" a paragraph IV certification. FDA can ensure that this will not occur by making clear that separate ANDAs

⁵ This issue is the subject of a citizen petition currently pending before the FDA. See Docket No. 02P-0001, Citizen Petition Submitted by John B. Dubeck, Esq. on behalf of Biovail Corporation, January 2, 2002.

or 505(b)(2) applications are required for every drug product listed separately in the Orange Book.⁶

D. NDA and Patent Holders Should be Able to Learn About New Patent Certifications Even Where No 30-Month Stay Is Available.

When an ANDA or 505(b)(2) applicant amends an application to make a paragraph IV certification that does not trigger a notice requirement, NDA and patent holders should be able to learn about the paragraph IV certification even if it does not trigger the opportunity to obtain a 30-month stay. This would arise, for example, where an ANDA applicant makes a paragraph IV certification to a newly listed patent and had already made a prior paragraph IV certification. FDA assumes in the preamble to the proposed rule that NDA and patent holders will somehow learn about all subsequent paragraph IV certifications, even when no notice is provided, and will be able to enforce their rights by seeking a court injunction and/or damages. 67 Fed. Reg. at 65455. This is not accurate. For example, if the first paragraph IV certification did not trigger litigation, or if that litigation is over, there may be no mechanism for an NDA or patent holder to learn about the subsequent paragraph IV certification until a generic product has already entered the market.

FDA should prevent such stealth paragraph IV certifications by posting paragraph IV certifications on its Web site, or otherwise making the information public. This approach would be entirely consistent with FDA's implementation of the Freedom of

⁶ While ANDA applicants may be permitted to include, for example, several strengths in a single *initial* ANDA submission, they should not be permitted to file originally for one strength and then amend to add another, if the result would be to deprive the NDA and patent holders of an opportunity to sue under a 30-month stay with respect to the new strengths. FDA therefore must require that new strengths be submitted through a separate ANDA, or otherwise ensure an opportunity for a 30-month stay on the new strengths.

Information Act (“FOIA”). When an ANDA or 505(b)(2) applicant makes an initial paragraph IV certification, it must provide notice to the NDA and patent holders, even under FDA’s proposed regulation. That notice is a form of public disclosure of the existence of the ANDA or 505(b)(2) application. Accordingly, there is no basis under FDA’s FOIA regulations to exempt from public disclosure the fact that a subsequent paragraph IV certification has been made. Disclosure of the subsequent paragraph IV certification – for example, on FDA’s Web site – merely indicates what was already publicly disclosed when notice was given of the earlier paragraph IV certification, namely that a particular ANDA has been filed. Moreover, under its existing rules, FDA has required ANDA filers to provide notice of all paragraph IV certifications and hence has not deemed the filing of such notices to be confidential as to the affected NDA and patent holders.

FDA’s FOIA regulations state that the agency “will not publicly disclose the existence of an application or abbreviated application before an approvable letter is sent . . . *unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged.*” 21 C.F.R. § 314.40(b) (emphasis added). In the case of an ANDA or 505(b)(2) application with a prior paragraph IV certification, the applicant did previously disclose or acknowledge the existence of the application. Accordingly, there is no bar on FDA’s publication of any subsequent paragraph IV certifications for such applications.

This proposed approach of FDA publication of subsequent paragraph IV certifications is one way of addressing the concern that NDA and patent holders should be able to learn about all paragraph IV certifications challenging listed patents. Other

approaches would no doubt work as well. PhRMA is supportive of other approaches that would effectively address this issue.

II. What Patents Must Be Listed in the Orange Book? [Proposed § 314.53(b)]

Proposed § 314.53(b) would delineate what patents must and must not be listed in the Orange Book. PhRMA agrees that it is beneficial to establish clearer rules regarding patent listing. The proposed rule provides helpful guidance in this regard for NDA, ANDA, and 505(b)(2) sponsors alike, and, if adopted, should reduce considerably the number of disputes that will arise with the agency or between private parties over the listing of patents.

At the same time, PhRMA has concerns regarding three issues under the new proposed rules for patent listing: the listing of patents that claim different forms of a drug substance; the listing of patents that claim integrated drug delivery systems; and the listing of patents that claim a method of using an approved drug product to administer a metabolite. Comments on these issues follow. FDA specifically requested comments on the listing of product-by-process patents, and that topic is also addressed below.

A. FDA Should Clarify in its Preamble that Patents Claiming a Form of a Drug Substance that is the “Same” as the Active Ingredient in the NDA Are and Always Have Been Listable.

The proposed rule would require the listing of patents that claim the form of the drug substance that is the subject of a pending or approved NDA, or that claim a different form of the drug substance where the different form is the “same” as the active ingredient that is the subject of the NDA within the meaning of section 505(j)(2)(A)(ii) of the FDCA. The proposal reflects a reasonable and sensible reading of the statute. Indeed, it would be improper for FDA to consider different forms of a drug substance to be the “same” active

ingredient under the ANDA approval provisions of the Act, and yet somehow not to be the same for determining whether a patent may be listed under the Act's closely related patent listing provisions. The proposal is also consistent with court decisions holding that patents on different drug forms may be listed, court decisions which FDA has cited with approval in the past.⁷ The agency's past reliance on these decisions belies its contention in the preamble (67 Fed. Reg. at 65450) that it "implicitly" did not accept the reasoning in those cases.

FDA is incorrect when it suggests at several points in the preamble (67 Fed. Reg. at 65449, 65451, 65452, 65453) that the proposal reflects a change in prior FDA policy. The proposal would at most confirm prior agency policy and cannot fairly be characterized as a substantive change.⁸

⁷ See *Zenith Labs., Inc. v. Abbott Labs.*, Civ. No. 96-1661, 1996 WL 33344963 (D.N.J. Aug. 7, 1996); *Ben Venue Labs., Inc. v. Novartis Pharm. Corp.*, 10 F. Supp. 2d 446 (D.N.J. 1998)); Response from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Hugh L. Moore et al., Lord, Bissell & Brook, dated November 21, 2000 ("Woodcock Letter"), at 5 n.13 (denying citizen petition that sought to delist patents claiming a different form of paroxetine hydrochloride than the form in Paxil, as marketed, and citing these two court cases with approval).

⁸ FDA's policy is best shown in its denial of a citizen petition regarding two patents claiming anhydrate forms of paroxetine hydrochloride, listed by SmithKline Beecham Corporation ("SmithKline") (now GlaxoSmithKline) for its drug Paxil (paroxetine hydrochloride). Apotex, Inc. sought to de-list the patents on the ground that Paxil, as marketed, contains only the hemihydrate form of paroxetine hydrochloride. SmithKline supported the listing of the patents, among other reasons, on the ground that the hemihydrate and anhydrate forms of the drug were asserted by Apotex and considered by FDA to be the same. Letter from Bruce N. Kuhlik, Covington & Burling, Counsel for SmithKline, to Docket No. 00P-0499, dated June 13, 2000, at 6-8. FDA denied the Apotex citizen petition. Woodcock Letter, *supra* note 7, at 1. The only possible reading of this decision is that it was FDA's policy at the time to permit the listing of patents claiming different forms of a drug substance. FDA denied the citizen petition with full knowledge that the patents at issue claimed forms of the drug substance not present in the marketed NDA formulation. If it were FDA's policy at the time that patents are listable only if they claim the form of the drug substance actually present in the marketed drug product, the agency surely would have clarified the applicable standards for patent listing and requested that the NDA holder re- (continued...)

FDA must clarify this point in the preamble to its final regulation, both to correct the administrative record and to avoid raising inappropriate implications about patents on different drug forms that were listed previously based on perceived agency policy and prevailing court decisions.

B. No Further Rules are Necessary to Identify Listing Criteria for Product-by-Process Patents.

The proposed rule appropriately provides that product-by-process patents must be listed. As FDA recognizes in the preamble, product-by-process patents are properly classified as product, not process, patents. 67 Fed. Reg. at 65452 (citing *In re Bridgeford*, 357 F.2d 679, 682 (CCPA 1966)). It would be improper to treat a product-by-process patent as an unlistable process patent. *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 970 F.2d 834, 845 (Fed. Cir. 1992) (“Though using only process terms, a product-by-process applicant sought rights to a product, not a process.”).

In the preamble, the Agency invited comment “on ways to ensure that only appropriate product by process patents are listed, while maintaining the act’s restriction against listing process patents.” 67 Fed. Reg. at 65452. The same listing criteria used for other product patents should be used for product-by-process patents. The pertinent inquiry is whether or not the patent claims the approved drug product (in the case of product-by-process patents claiming drug products) or a form of the drug substance that is the “same” as the approved drug (in the case of product-by-process patents claiming drug substances). *See id.* at 65464 (proposed 21 C.F.R. § 314.53(b)). If a product patent claims a drug – whether

certify against those standards, precisely as FDA did in the Biovail and Pfizer cases discussed in the preamble.

defined structurally or in terms of a process – and the drug is the same as that in a pending or approved NDA, the patent should be listed.⁹ The certification provided by the NDA holder will be sufficient to cover these points. There is no need for FDA to establish additional mechanisms to distinguish product-by-process patents from process patents. Indeed, it is difficult to envision any additional measures FDA could impose that would not plunge the agency inappropriately into complicated issues of patent law and introduce listing criteria alien to the statute.

C. Patents Claiming Drug Delivery Systems Are Listable.

A patent claiming a drug delivery system that is an integral part of the drug product is listable. Such patents differ from patents claiming only packaging and containers, which FDA explains in the preamble to the proposed rule are “distinct from the approved drug product” and do not “claim the drug.” 67 Fed. Reg. at 65451. Examples of integrated drug delivery systems include, but are not limited to, asthma inhalation devices, nasal inhalers, trans-dermal patches, and pre-filled syringes. Patents claiming such integrated drug delivery systems claim the drug product, and should be listable, even if ordinary packaging and container patents are not. We do not understand FDA to be calling for a different approach in its proposed regulation.

⁹ This is true whether or not the process specified in the patent is the approved manufacturing process for the drug product. So long as the product claimed by the patent is the approved product, and an ANDA or 505(b)(2) application could be approved employing the process described in the patent, the patent should be listable.

D. Patents Claiming an Approved Method of Using a Drug Product to Administer a Metabolite are Listable.

The proposed regulation would prohibit the listing of patents that claim metabolites and not an approved drug substance or drug product. Proposed 21 C.F.R. § 314.53(b). We do not construe this proposed regulation to prohibit the listing of a patent that claims a method of using an approved drug product to administer a metabolite. Such a patent claims an approved method of use of an approved drug product, and would be listed under proposed 21 C.F.R. § 314.53(b).

III. What Does the Patent Declaration Say? [Proposed § 314.53(c)(2)(i)]

A. FDA's Proposed Claim-by-Claim Declaration Requirements are Improper.

The proposed rule would significantly expand the information that an NDA sponsor must include in the patent declaration that is submitted with an NDA by requiring detailed information on each claim of a patent. This claim-by-claim declaration requirement is improper. Under the statute, patents – not claims – are submitted to the FDA for listing, and ANDA and 505(b)(2) applicants must provide a certification “with respect to each listed patent” – not a certification only to particular claims. FDCA §§ 505(b)(1), 505(b)(2)(A), 505(c)(2), 505(j)(2)(A)(vii). If a patent contains one claim that meets the requirements for listing, the patent must be listed. The proposal to require expansive claim-by-claim patent declarations thus goes beyond the statutory language and would not serve any statutory purpose.

FDA asserts (67 Fed. Reg. at 65453) that requiring submission of a claim-by-claim declaration would ensure that applicants submit only appropriate patents for listing. The agency offers no support for its assertion that the new declaration rules would promote

appropriate patent listings. The agency's suggestion (67 Fed. Reg. at 65454) that "precise identification" of patent claims may reduce infringement disputes also cannot support the agency's new proposed requirements. This rationale reflects an inappropriate attempt by the agency to influence patent infringement litigation, and is unrelated to the role assigned the agency under law with respect to patent listing.¹⁰

So long as FDA requires the applicant to declare that at least one claim of the patent supports listing, the statutory listing criteria are met. Requiring declarations to additional claims provides no further assurances for the propriety of the patent listing and merely increases the administrative burdens on applicants.

B. FDA Should Modify the Proposed Drug Substance Acknowledgement of "Sameness" Requirement.

For drug substance claims, FDA's proposed rule would require NDA sponsors to state whether the claim covers the active ingredient in the approved or pending NDA, or an active ingredient that is the "same" as the active ingredient in the approved or pending NDA. If the claim is for an active ingredient that is the "same" as the active ingredient in the NDA, the sponsor must "acknowledge that an ANDA or 505(b)(2) application containing the same active ingredient that is claimed by the patent is the 'same' for ANDA or 505(b)(2) approval purposes." This proposed pre-condition to the listing of patents claiming different drug forms is overbroad.

¹⁰ Whatever requirements the agency adopts for the declaration would not limit the claims that could be asserted in patent infringement litigation. NDA and patent holders remain free to assert all the claims of a listed patent in an infringement action whether or not a particular claim could have been listed with FDA standing alone. Of course, any patent whether listed or not can be enforced upon the marketing of an infringing product.

FDA itself states that different drug forms of a drug substance (*e.g.*, polymorphs or hydration forms) *may* be the same active ingredient, and that whether they *are* the same active ingredient “is a scientific determination” based upon characteristics such as dissolution, solubility, and bioavailability. 67 Fed. Reg. at 65452. It is ultimately FDA’s responsibility to determine whether different forms of a drug substance are or are not the “same” for purposes of ANDA approval. NDA holders should not be put in the position of having to state unequivocally that two drug substance forms are the same for purposes of ANDA and 505(b)(2) approval in order to list a patent. At most, NDA sponsors should be required to acknowledge that FDA has indicated that an ANDA or 505(b)(2) application containing the form of active ingredient claimed in a listed patent is or may be the same as the reference listed drug for purposes of approval.¹¹

In contrast to the blanket acknowledgement that FDA has proposed, this modified declaration would reflect the inherent scientific uncertainty associated with different drug forms. Any acknowledgement that is required should be without prejudice to raising a later argument that an ANDA or 505(b)(2) application containing a different form of a drug substance should not be approved, for example, because of possible health consequences. If FDA were later to determine in a particular case that a form of the drug substance was not and could not be the same for purposes of approving ANDA and 505(b)(2)

¹¹ For these same reasons, FDA should not require that NDA holders submit additional information regarding the basis for an assertion that drug substances are the same active ingredient. FDA invited comment on this issue in connection with its proposed rules for what patents must be listed. 67 Fed. Reg. at 65451.

applications, the agency would presumably direct the NDA holder to delist patents claiming that drug substance form.¹²

C. FDA Should Clarify the Requirements for Providing Notice to the NDA Holder and Patent Owner.

FDA invited comment on whether the agency's current regulations regarding the notice that ANDA and 505(b)(2) applicants must provide to NDA holders and patent owners could or should be amended. FDA certainly has the authority to amend its regulations in this regard. The statute expressly provides that ANDA and 505(b)(2) applicants must include in their notice to NDA and patent holders a "detailed statement of the factual and legal basis" for an assertion that a patent is invalid or not infringed. FDCA §§ 505(b)(3)(B) & 505(j)(2)(B)(ii). This legislative language gives the agency all the authority it needs to establish reasonable rules to implement the notice requirement for paragraph IV certifications.

Moreover, it could be quite helpful for the agency to clarify the elements of a proper paragraph IV notification. The quality of paragraph IV notifications in practice is at best highly variable. Additional guidance from FDA on this issue would promote consistency and help ensure that paragraph IV notifications communicate meaningful information regarding the basis for an assertion that a listed patent is invalid or not infringed. ANDA and 505(b)(2) applicants should be required to include in a paragraph IV notice (1) an explanation of the relationship between the claims, as construed by the ANDA/505(b)(2)

¹² Of course, a finding of non-bioequivalence with regard to a particular ANDA would not necessarily establish that the form of the active ingredient in the proposed generic could not be the same as the approved drug for purposes of ANDA submission in other cases.

applicant, and the aspects of the drug product for which approval is being sought, and (2) if applicable, an analysis of the legal bases upon which the patent claims might be deemed invalid or unenforceable based upon the construction of the claims provided by the ANDA/505(b)(2) applicant.

It would also be helpful for FDA to specify the rules regarding service of paragraph IV notices upon NDA and patent holders. There have been instances in which a notice of a paragraph IV certification was served upon an NDA holder but did not reach the proper location within the corporation in a timely manner, and the opportunity to bring a suit within the 45-day period and obtain a stay was inadvertently lost. These situations could be avoided if FDA were to require each NDA and patent holder to identify an agent to receive service of all patent notices from ANDA and 505(b)(2) applicants, just as FDA requires the identification of an agent for foreign patent owners, and to require ANDA and 505(b)(2) applicants to serve all notices on that agent by registered mail.

IV. FDA Has Adopted an Appropriate Implementation Plan.

PhRMA supports FDA's proposal to apply the proposed rules prospectively only. Indeed, prospective application of those aspects of the proposed regulation that truly are new (e.g., the 30-month stay provisions) would be required as a matter of administrative law. As the D.C. Circuit has explained, there is a basic "distinction between rules which create new legal obligations and those which simply restate or clarify existing statutes or regulations." *Chemical Waste Mngt. v. EPA*, 869 F.2d 1526, 1534 (D.C. Cir. 1989).

Whereas interpretive rules clarifying existing law may be applied retroactively where reasonable, legislative rules establishing new rights and obligations, or significantly changing prior agency policy, may not. *See Williams Natural Gas Co. v. FERC*, 3 F.3d 1544, 1554

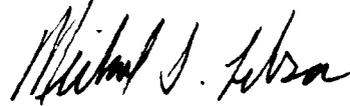
(D.C. Cir. 1993); *National Medical Care Inc. v. Shalala*, No. 95-0860, 1995 U.S. Dist. LEXIS 10074, *4 n.2 (D.D.C. June 6, 1995); *Alvarado Parkway Institute v. Mendex*, 789 F. Supp. 1190, 1195-96 (D.D.C. 1992).

Prospective application of the new rules also makes good sense as a matter of policy, and is consistent with FDA's approach in prior cases. As FDA explains in the preamble, retrospective application of the changes "would risk upsetting legitimate expectations held by those who had relied on our earlier interpretation of the act." 67 Fed. Reg. at 65457. FDA followed the same approach when it adopted a new interpretation of "court decision" for purposes of 180-day exclusivity and ANDA approvals. As the agency explained in its March 2000 guidance, "applicants who have made certain business decisions in good faith reliance upon an FDA regulation should not be penalized for their actions." Guidance for Industry: Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act at 4; *see also Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d 30, 45 (D.D.C. 2000) (indicating that it would be "inequitable to penalize" company that had endured lengthy litigation in reliance upon FDA regulation that had been upheld by circuit court).

Conclusion

PhRMA supports the agency's attempts to bring greater clarity to this important but highly complex area. Nevertheless, the proposed rule as currently formulated raises a number of significant issues with the potential to affect new drug innovation adversely. It is critical that FDA address these issues as it considers a final regulation.

Respectfully submitted,



Michael S. Labson
Christopher N. Sipes
COVINGTON & BURLING
1201 Pennsylvania Avenue NW
Washington, DC 20004-2401
Phone: (202) 662-6000
Fax: (202) 662-6291

Of Counsel:

Bruce N. Kuhlik
Erika King
PHARMACEUTICAL RESEARCH
AND MANUFACTURERS OF
AMERICA
1100 Fifteenth Street, NW
Washington, DC 20005

*Counsel for the Pharmaceutical Research
and Manufacturers of America*

December 23, 2002

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW WASHINGTON, DC
WASHINGTON, DC 20004-2401 NEW YORK
TEL 202.662.6000 LONDON
FAX 202.662.6291 BRUSSELS
WWW.COV.COM SAN FRANCISCO

MICHAEL S. LABSON
TEL 202.662.5220
FAX 202.778.5220
MLABSON@COV.COM

9150 '02

DEC 23 11:02

December 23, 2002

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, Maryland 20852

Re: Docket No. 02N-0417

Dear Dockets Management Branch:

Enclosed please find two copies of the Comments of the Pharmaceutical Research and Manufacturers of America (PhRMA) on FDA's proposed rule on "Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying that a Patent Claiming a Drug is Invalid or Will Not be Infringed" (Docket No. 02N-0417).

Thank you for your assistance.

Best regards,



Michael S. Labson

*Counsel for Pharmaceutical
Research and Manufacturers
of America*

Enclosures