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May 3, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0087; Generic Drug Issues: Request for Comments

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit comments regarding the regulatory actions necessary to implement Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (Pub. L. No. 108-173). PhRMA represents 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. Investing more than \$30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

FDA recently revoked portions of its regulations governing the notice of certification of invalidity or non-infringement of a patent by Abbreviated New Drug Application (ANDA) and 505(b)(2) applicants. 69 Fed. Reg. 11309 (March 10, 2004). This action was necessary because the regulations, which were finalized in June 2003, were inconsistent with the new MMA provisions governing notice and the 30-month stay. For the reasons discussed below, PhRMA believes that additional regulatory revisions are necessary to implement and clarify the new MMA provisions relating to the 30-month stay of effectiveness period and the 180-day exclusivity period.

30-Month Stay

Administrative Penalty For Late Notice. The MMA requires ANDA and 505(b)(2) applicants submitting a paragraph IV certification to provide notice of invalidity or non-infringement to both the patent owner and NDA holder (a) within twenty days of notice that the ANDA or 505(b)(2) application has been filed by FDA, or (b) if the certification is in an amendment or supplement, at the time the applicant submits the amendment or supplement. 21 U.S.C. §§355(b)(3)(B), (j)(2)(B)(ii). These time limitations are designed to expedite the resolution of patent disputes by ensuring that the patent owner and NDA holder receive timely notice of a challenge to one or more of their patents and can, if warranted, commence a patent infringement suit.

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FDA should amend its existing regulations at 21 C.F.R. §§314.52 and 314.95 to incorporate these time limitations. In addition, FDA should fashion a regulatory mechanism to discourage ANDA and 505(b)(2) applicants from missing these important new notification deadlines. Although the MMA does not provide explicit penalties for failing to meet these deadlines, FDA has sufficient authority to implement by regulation its own administrative penalty, as it previously did for “late-listed patents,” i.e., patents submitted more than 30 days after issuance. See 21 C.F.R. §314.94(a)(12)(vi). Possible penalties for failing to meet the new notification deadlines might include: (a) delaying the substantive review of the ANDA or 505(b)(2) application until after notification is provided, or (b) creating an automatic regulatory presumption which could be used by the court hearing the patent infringement action that the ANDA or 505(b)(2) applicant “failed to reasonably cooperate in expediting the action” within the meaning of 21 U.S.C. §§355(c)(3)(C) and (j)(5)(B)(iii).

The MMA requires ANDA and 505(b)(2) applicants, respectively, to provide notice to each owner of the patent and the holder of the approved application. 21 U.S.C. §§355(j)(2)(B)(iii), (b)(3)(C). FDA regulations currently state that the names and addresses of each owner of the patent and the holder of the approved application may be obtained from the Patent and Trademark Office and the Center for Drug Evaluation and Research. 21 C.F.R. §314.52(a)(1), (2). ANDA and 505(b)(2) applicants, however, do not uniformly follow that practice. The result is that notice letters may be “received” by the appropriate corporate entity, beginning the 45-day clock, but take some time to reach the appropriate individual. Accordingly, companies must exercise constant vigilance in searching internally for notice letters and may lose considerable portions of the important 45-day window. FDA should amend 21 C.F.R. § 314.52 so that failure to address notice letters to the recipients designated in that rule will result in the 45-day clock not beginning until the designated individuals actually receive the notice letter.

Amendments and Supplements For ANDAs and 505(b)(2) Applications. The MMA states that a 505(b)(2) applicant cannot amend or supplement its application “to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.” 21 U.S.C. §355(b)(4)(A). Although this language is somewhat unclear, its intent was to codify existing FDA policies regarding the acceptance of amendments and supplements to ensure that 505(b)(2) applicants could not evade the new 30-month stay provisions by making creative use of amendments and supplements. See House Conf. Report 108-391 (Nov. 21, 2003) at 835. The MMA contains a similar provision applicable to ANDAs, which states that “an applicant may not amend or supplement an [ANDA] to seek approval of a drug referring to a different listed drug from the listed drug identified in the [ANDA] as submitted to the Secretary.” 21 U.S.C. §355(j)(2)(D)(i).

These limitations are necessary because, as revised by the MMA, the 30-month stay provision applies only to patents submitted to FDA before the date on which the ANDA or 505(b)(2) application (excluding an amendment or supplement to the application) was submitted. 21 U.S.C. §§355(c)(3)(C), (j)(5)(B)(iii). Without the

prohibition on the filing of amendments and supplements, the 30-month stay provision would be susceptible to gamesmanship by ANDA and 505(b)(2) applicants. This could happen, for example, where an innovator drug is approved in both an immediate release and extended release formulation, with additional patents covering the extended release formulation. After obtaining approval of an ANDA or 505(b)(2) application that references the immediate release formulation, the ANDA or 505(b)(2) applicant could try to supplement its application to seek approval of an extended release formulation without having to face any 30-month stay on the extended release patents. The applicant would argue that, under the new statutory provisions, a 30-month stay can only be triggered based on patents listed before the ANDA or 505(b)(2) application was filed, and since the original ANDA or 505(b)(2) application was submitted long before there even was an extended release product, the 30-month stay does not attach to the new patents covering the extended-release product.

In order to clarify that the provision on amendments and supplements is intended to prohibit this type of gamesmanship, FDA should amend its regulations to describe when a new 505(b)(2) application would be required. In addition, FDA should issue the guidance required by 21 U.S.C. §355(j)(2)(D)(iii) defining the term “listed drug.”

Non-concurrent 30-Month Stays. FDA should issue a guidance document or regulations clarifying that the new MMA provisions do not limit manufacturers to one 30-month stay per challenger but instead provide that 30-month stays apply only to those patents submitted to FDA prior to the submission of the ANDA or 505(b)(2) application. While the practical effect of this provision likely will be to preclude non-concurrent 30-month stays for most drug products, such non-concurrent 30-months stays still are possible in situations where the ANDA or 505(b)(2) applicant changes its patent certification. For instance, if an ANDA applicant submits two patent certifications in its original application -- a paragraph III certification to one patent and a paragraph IV certification to another -- then changes its paragraph III to a paragraph IV six months later, the ANDA applicant would be subject to two non-concurrent 30-month stays. PhRMA believes that there is widespread confusion regarding this issue that FDA guidance would help dispel.

180-Day Exclusivity

Define “First Applicant Date Certifications” and “Lawfully Maintained.”

PhRMA requests that FDA define the terms “first applicant date certifications” and “lawfully maintained” to clarify which paragraph IV certifications can qualify an applicant for 180-day exclusivity under Title XI of the MMA and to preclude ANDA applicants from “parking” their 180-day exclusivity. In the absence of such clarification, ANDA applicants could have an incentive to file premature and speculative paragraph IV certifications solely for the purpose of avoiding forfeiture of “first applicant” status, thereby resulting in unnecessary and costly patent litigation.

Under Title XI only those ANDA applicants that meet the definition of a “first applicant” can be eligible to earn the 180-day exclusivity. That definition requires that the ANDA applicant file a substantially complete application “on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug.” 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb). Title XI further mandates that at least one of the certifications filed on this first applicant date must then be “lawfully maintained” in order for a first applicant to remain eligible for the exclusivity period. There are a number of circumstances under which the ANDA applicant would fail to lawfully maintain a paragraph IV certification, such as when a court enters a final, non-appealable judgment that a valid and enforceable patent is infringed. In that case the paragraph IV certification is not maintained because it must be converted to a paragraph III certification. Under Title XI, an ANDA applicant that fails to lawfully maintain at least one first applicant date paragraph IV certification loses its status as a first applicant and, therefore, may become subject to the 180-day exclusivity of other first applicants who continue to lawfully maintain such certifications.

The importance of these interpretations is illustrated by the following example. An innovator drug company obtains approval of a New Drug Application (NDA) for a novel drug product that is protected by two patents: (1) a compound patent expiring in Year 6; and (2) a formulation patent expiring in Year 15. If an ANDA applicant believed that a loss in infringement litigation concerning the compound patent nonetheless might confer a benefit of allowing it to “park” its exclusivity, it would have an incentive to challenge both the compound and formulation patents prior to Year 6, even if it felt there was only a legitimate basis for challenging the formulation patent. It essentially would take its chances against the compound patent, filing a premature and speculative paragraph IV certification, secure in the knowledge that, even if it lost on the compound patent as expected, it could “park” its 180-day exclusivity until it was ready to market.

Without the “lawfully maintained” language, this is exactly what could happen under the new MMA forfeiture provisions. If the ANDA applicant filed early and prevailed in patent infringement litigation on the formulation patent, but lost on the compound patent, the applicant still would avoid suffering a potential “forfeiture event” under 21 U.S.C. §355(j)(5)(D)(i)(I). This is because the adverse decision on the compound patent would not be considered a triggering event for purposes of the failure to market forfeiture provision. See 21 U.S.C. §355(j)(5)(D)(i)(I)(bb). On the contrary, because that forfeiture provision becomes operative only when there has been a triggering event for *each patent* that was the subject of a paragraph IV certification qualifying the ANDA sponsor for “first applicant” status, the adverse decision on the compound patent actually would block the 75-day forfeiture clock from starting. In other words, it would allow the ANDA applicant to “park” its 180-day exclusivity until the compound patent expires.

This result, however, can be avoided by proper implementation of the “lawfully maintained” provision. In particular, FDA should confirm that its existing regulations (21 C.F.R. §314.94(a)(12)(viii)) require that when an ANDA applicant has litigated and lost a

patent infringement case, it must amend its paragraph IV certification to a paragraph III certification, at which point it no longer will be considered to have “lawfully maintained” a paragraph IV certification with respect to that patent. Therefore, the applicant can no longer use that particular certification as a basis to qualify as a “first applicant.” This will help ensure that 180-day exclusivity will not act as an incentive for ANDA applicants to initiate premature and inappropriate patent challenges.

In the scenario above, for example, the requested clarification would result in forfeiture if the applicant failed to market within 75 days after the court’s finding of invalidity or non-infringement of the formulation patent (or, if later, 75 days after ANDA approval or 30 months from ANDA filing). This is because, following the adverse decision against the ANDA applicant on the compound patent, the compound patent no longer would be considered a patent for which the ANDA applicant “lawfully maintained” a paragraph IV certification. The only relevant patent for purposes of the forfeiture provision would be the formulation patent. The result, as intended by Title XI of the MMA, is that the court’s finding of invalidity or non-infringement on the formulation patent would thus potentially start the 75-day forfeiture clock. In this way, essentially wasteful litigation concerning the compound patent, with the outcome all but certain to be a finding adverse to the ANDA sponsor, could no longer be used to block the forfeiture clock from starting.

Multiple First Applicants. FDA should clarify how forfeiture will work in a situation involving multiple first applicants. In particular, FDA should state that a first applicant that fails to lawfully maintain at least one first applicant date paragraph IV certification loses its status as a first applicant and, therefore, may become subject to the 180-day exclusivity of other first applicants who continue to lawfully maintain such certifications.

Expiration of All Patents. FDA should clarify that under the new MMA provisions, 180-day exclusivity cannot extend beyond the expiration of all patents covering the innovator drug product. FDA’s position on this issue has been that 180-day exclusivity is extinguished when the relevant patents expire (see 21 C.F.R. §314.94(a)(12)(viii)). FDA should clarify that the new “expiration of all patents” forfeiture provision does not change this result. In the terms of the new Title XI, the first applicant’s paragraph IV certifications are converted to paragraph II certifications upon expiration of the patents, which triggers the loss of “first applicant” status and thus any remaining 180-day exclusivity.

Thank you for your consideration of these comments.

Sincerely,



Scott M. Lassman
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