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Phone 317 276 2000

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

Re: Docket No. 2004N-0087; 21 CFR Part 314; Generic Drug Issues; Request for Comments;

Dear Sir or Madam:

Eli Lilly and Company (Lilly) appreciates the opportunity to submit comments to the above-referenced docket regarding the implementation of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA).

Title XI of the MMA includes changes to the 30-month stay, the 180-day generic exclusivity period, and the bioavailability and bioequivalence testing requirements of 21 U.S.C. § 505(a), (b) and (j). The Food and Drug Administration (FDA) has asked for public comments to identify issues raised by these statutory changes, and for suggestions on how to resolve the issues and what additional regulatory actions might be appropriate. Lilly's comments focus only on the changes to the 180-day generic exclusivity period, where the correct interpretation and action by FDA will be crucial to ensuring appropriate implementation of the MMA.

The statutory provisions for first-filing generic applicants to achieve and maintain the right to the 180-day exclusivity period have been completely rewritten in Section 1102 of the MMA. The MMA also introduces a number of very important "forfeiture provisions," whereby a "first applicant" loses its right to the 180-day period if any event of forfeiture occurs with respect to that applicant. Collectively, these provisions – requirements for generic filers to *achieve, maintain, and not forfeit* their status as "first applicants" – operate to circumscribe opportunities for the 180-day exclusivity period.

Achieving and Maintaining "First Applicant" Status

Under Section 1102, every generic applicant filing a substantially complete application on *the first applicant date*¹ that contains at least one Paragraph IV certification meets the initial requirements to be a "first applicant" for a drug.² Hence, unlike the prior law, multiple generic applicants can initially achieve the status of "first applicants." This definition is significant because only those ANDA filers who meet the definition of a "first applicant" are even eligible for the 180-day exclusivity period.

There are two aspects to the statutory definition of "first applicant" that are absolutely critical. One is the "first day" requirement for "containing" at least one Paragraph IV certification. The other is the requirement to "lawfully maintain" the paragraph IV certification(s) made on the first day.

Under Section 1102, the Paragraph IV certifications contained in the application *on the first applicant date* represent the set of Paragraph IV certifications from which at least one certification must thereafter be "lawfully maintained" in order for the applicant to retain "first applicant" status. Once a generic applicant that initially had achieved "first applicant" status no longer lawfully maintains at least one of those "first applicant date" Paragraph IV certifications, its first-applicant status is lost. This occurs whenever a first applicant fails to maintain at least one "first applicant date" Paragraph IV certification continuously up until the time of first commercial marketing. Under Section 1102 an applicant that loses its first-applicant status

¹ Defined as "...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..."

² 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb)

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is no longer entitled to a 180-day exclusivity period and, perhaps, becomes subject to the 180-day exclusivity period of other first applicants who have continuously maintained their status.

There are a number of circumstances under which a “first applicant” can no longer “lawfully maintain” a Paragraph IV certification. Under current FDA regulations, a Paragraph IV certification cannot be maintained once a court enters a final, non-appealable judgment that a valid and enforceable patent is infringed. In this situation, the Paragraph IV challenger has reached a Paragraph III outcome. By FDA regulation, this Paragraph IV certification must be converted to a Paragraph III certification (stating “the date on which such patent will expire”), thereby allowing approval for marketing not earlier than the stated patent expiration date.³ Other circumstances requiring conversion of Paragraph IV certifications – and therefore a failure to “lawfully maintain” – are when the patent is delisted from the Orange Book (converts to a Paragraph I certification) and when the patent expires (converts to a Paragraph II certification).

How Failure to Retain a Paragraph IV Certification Operates in Practice

An example will illustrate the impact of the “contains and lawfully maintains” requirement that must be satisfied in order to retain “first applicant” status:

The “Belated Certification” Example

Orange Book:	Patent 1: Polymorph Patent, Expires in 1 year. Patent 2: Polymorph Patent, Expires in 5 years.
First Applicant 1:	Paragraph IV Certification on both Patent 1 and Patent 2
First Applicant 2:	Paragraph IV Certification on Patent 1. Paragraph III Certification on Patent 2.

One year after the patent challenges are made, Patent 1 expires and the FDA requires that the Paragraph IV certifications for this patent be converted to Paragraph II certifications (“such patent has expired”) for both first applicants. As to Patent 1, neither first applicant “lawfully maintains” the Paragraph IV certification.

On Patent 2, First Applicant 1 is sued and will eventually mount a “successful defense,” demonstrating it did not infringe the patent, and seek to market under its 180-day exclusivity period. Just prior to the expiration of Patent 1, however, First Applicant 2 makes a belated Paragraph IV certification to Patent 2, so that for a few days it has Paragraph IV certifications challenging both patents.

What happens to the “first applicant” status of First Applicant 2 on the expiration date of Patent 1? On that date First Applicant 2 no longer retains its “first applicant” status. Once First Applicant 2 must switch its only “first applicant date” Paragraph IV certification to a Paragraph II certification, as required under required under FDA regulations, it no longer qualifies under the requirement to “contain and lawfully maintain” a Paragraph IV certification dating back to the first applicant date.

Even though First Applicant 2 belatedly filed a Paragraph IV certification on Patent 2 it cannot in effect piggyback on the successful defense of First Applicant 1 that challenged both patents on the first applicant date. First Applicant 2 is treated in exactly the same manner as all other generic applicants making Paragraph IV certifications with respect to Patent 2 after the first applicant date.

Hence, the qualifications for retaining “first applicant” status require that at the time the first applicant seeks to begin marketing as a first applicant, that applicant must have at least one remaining Paragraph IV certification from the set of Paragraph IV certifications that were originally contained in its generic drug application as filed on the first applicant date. Those Paragraph IV certifications originally contained that cannot be “lawfully maintained,” either because of patent expiration (forcing a Paragraph II conversion) or because of an unsuccessful defense (forcing a Paragraph III conversion), must be disregarded in determining continuing qualification for “first applicant” status.

Forfeiture of the 180-Day Exclusivity Period

³ 21 C.F.R. § 314.94(a)(12)(viii)

The discussion above illustrates the importance of the statutory provisions on qualifying for first applicant status based on “first applicant day certifications”, and then “lawfully maintaining” those certifications continuously up until the time of first commercial marketing. Another important prerequisite for the 180-day exclusivity is that first applicant must avoid becoming subject to any of the “forfeiture provisions.”

Section 1102 adds a number of very important “forfeiture provisions,” whereby a first applicant loses its right to the 180-day exclusivity period if any one of those provisions are triggered for that applicant.⁴ This includes a “failure to market” provision that causes forfeiture of the 180-day exclusivity period when commercial marketing has not begun within 75 days after an appellate court – not a district court – rules on the patent challenge.⁵ Because of its overarching significance, the discussion below will focus only on the “failure to market” forfeiture event.

In general, the “failure to market” forfeiture is designed to afford a 30-month period to begin marketing after a patent challenge is made before the forfeiture can take effect. However, in some cases a longer period may apply depending on actions taken with respect to each of the patents that are the subject of Paragraph IV certifications qualifying the first applicant for its “first applicant” status, i.e., the Paragraph IV certifications that are contained in its application on the first applicant date and that are lawfully maintained thereafter.

Circumstances Extending the “Failure to Market” Forfeiture Beyond 30 Months

For each Paragraph IV certification originally made on the first applicant date and lawfully maintained thereafter, the “failure to market” forfeiture can take place beyond 30 months after the patent challenge only if one of the following three triggering events takes place after that 30-month period:

- (1) A final appellate court decision of invalidity or non-infringement of the patent is entered,
- (2) A court judgment of invalidity or non-infringement of the patent is entered pursuant to a settlement order or consent decree, or
- (3) The patent is withdrawn from the Orange Book.

For the court decision or court judgment, the triggering event can be the result of a court action involving either the first applicant or involving any other applicant (whether or not a first applicant) as long as the other applicant has tentative approval. Thus, any applicant that has tentative approval and obtains a court judgment of invalidity or non-infringement will cause the 75-day grace period to begin (which precedes a “failure to market” forfeiture) with respect to the particular patent that is the subject of the court decision. Consistent with FDA rules requiring separate certifications for separate patents, the “failure to market” forfeiture provisions are administered on a patent-by-patent basis.

In summary, after one of the three triggering events takes place with respect to a “contained and lawfully maintained” Paragraph IV patent, the 75-day “grace period” begins to run. At the expiration of the last of the 75-day grace periods for any of the Paragraph IV patents meeting the “contains and lawfully maintains” criteria, any first applicant that has not yet begun commercial marketing forfeits the 180-day exclusivity period.

Court Decision Trigger to Begin Running of the 180-Day Period

Under previous law, a district court decision of invalidity or non-infringement could start the running of the 180-day generic exclusivity period. Under Section 1102, the start of the 180-day period is no longer triggered by a court decision, but rather by the first commercial marketing of the generic drug.⁶ However, the new “failure to market” forfeiture provisions described above provide, in effect, a surrogate trigger for a first applicant, whereby the 180-day period must normally start within 75 days after a final appellate court decision or be forfeited.

⁴ 21 U.S.C. § 355(j)(5)(D)(ii)

⁵ 21 U.S.C. § 355(j)(5)(D)(i)(I)

⁶ 21 U.S.C. § 355(j)(5)(B)(iv)(I)

Action Needed by FDA

Appropriate implementation of Title XI of the MMA depends on FDA taking appropriate action to implement the letter and spirit of the 180-day provisions as set forth above. This requires FDA to continue to enforce existing FDA rules for separate certifications of each listed patent⁷ and requirements for amending certifications.⁸ It also means that FDA will need to completely re-write its existing regulations on the 180-day exclusivity for ANDAs.⁹ Finally, it will be critical that FDA interpret and apply the new principles such as “first applicant day certifications,” “contain and lawfully maintain,” and “failure to market forfeiture” as directed by Title XI.

Again, Lilly very much appreciates FDA’s willingness to take these comments into account as it implements the MMA.

Sincerely,



Robert A. Armitage
Senior Vice President and General Counsel
ELI LILLY AND COMPANY

⁷ 21 C.F.R. § 314.94(a)(12)(i)(A)(1)-(4); 21 C.F.R. § 314.107(b)(4)

⁸ 21 C.F.R. § 314.94(a)(12)(viii)

⁹ 21 C.F.R. § 314.107(c)