DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

SENT VIA FACSIMILE

Dear Applicant:

We are writing to you as a sponsor of an abbreviated new drug application (ANDA) referencing Novartis Pharmaceuticals' Starlix (nateglinide) Tablets, 60 and 120 mg, (NDA 21-204). This letter addresses 180-day exclusivity for these products.

The ANDAs were submitted after December 8, 2003, and thus 180-day exclusivity is governed by section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA). *See* section 1102(b) of the MMA.[1]

This matter raises, for the first time, the issue of the effect of a forfeiture of 180-day exclusivity by one or more ANDA applicants when at least one other applicant remains eligible for 180-day exclusivity. Because this is a question of first impression for the agency, we sought and received comment from the immediately affected parties on the effect of such forfeiture on the timing of approval of the applications at issue.

After consideration of the facts this matter, the applicable statutory provisions, and submitted comments, we have determined that a first applicant that forfeits exclusivity may obtain approval as described in section 505(j)(5)(B)(iii), and that first commercial marketing by any first applicant (including a first applicant that forfeits exclusivity) will begin the 180-day exclusivity period.[2] The statutory basis for this determination is described below.

Abbreviated New Drug Applications and 180-Day Exclusivity

Under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments), an NDA applicant must submit information for each patent that claims the drug or method of using the drug that is the subject of the NDA and for 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." Sections 505(b)(1) and (c)(2) of the Act. FDA publishes this patent information in the Orange Book.

An applicant must include in its ANDA one of the following certifications with respect to each patent for the listed drug it references:

[1] FDA has not yet promulgated regulations implementing these new statutory provisions; until we do so, we are regulating directly from the statute as needed to resolve regulatory matters.

[2] We note that this decision does not apply in the case when exclusivity is forfeited by all first applicants. As described in section 505(j)(5)(D)(iii), if all first applicants forfeit exclusivity, approval of any ANDA containing a paragraph IV certification will be governed by section 505(j)(5)(B)(iii), and no applicant will be eligible for a 180-day exclusivity period.

(I) that such patent information has not been filed (a paragraph I certification),
(II) that such patent has expired (a paragraph II certification),
(III) of the date on which such patent will expire (a paragraph III certification), or
(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).

Section 505(j)(2)(A)(vii).[3] An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and the patent owner notice of its patent certification, including a description of the legal and factual basis for its assertion that the patent is invalid or not infringed. Section 505(j)(2)(B). If the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the date of receipt of the notice or such shorter or longer time as the court might order. Section 505(j)(5)(B)(iii).[4]

The MMA exclusivity provisions provide the first applicant(s) to submit a paragraph IV certification challenging a patent — and thus undertake the risk of litigation — an incentive in the form of the opportunity to be the only generic drug manufacturer(s) to compete with the innovator for a 180-day period. Section 505(j)(5)(B)(iv) provides, in a subsection entitled "180-Day Exclusivity Period," that

> (I) Effectiveness of Application. - Subject to [the forfeiture provisions], if the application contains a [paragraph IV certification] and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

The 180-day exclusivity period is defined as "the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause." Section 505(j)(5)(B)(iv)(II)(aa). First applicant is defined as "an applicant that, on the first day on which a substantially complete application containing a [paragraph IV certification] is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug." Section 505(j)(5)(B)(iv)(II)(bb).

Section 505(j)(5)(D) describes a set of conditions under which an ANDA applicant loses — or forfeits — eligibility for 180-day exclusivity. The Act provides that the 180-day exclusivity period described in section 505(j)(5)(B)(iv) "shall be forfeited by a first applicant if a forfeiture

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[3] The Act provides only one circumstance in which an ANDA applicant need not certify to a listed patent: "if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection," the applicant can submit "a statement that the method of use patent does not claim such a use" (referred to as a "section viii statement"). Section 505(j)(2)(A)(viii); see also 21 CFR 314.94(a)(12)(iv).

[4] If the listed drug is protected by new chemical entity exclusivity under section 505(j)(5)(F)(ii) of the Act, an ANDA that contains a paragraph IV certification to a listed patent will be subject to a stay of seven and one-half years from the date of approval of the listed drug if the paragraph IV certification and notice give rise to timely patent litigation.

event occurs with respect to that first applicant." Section 505(j)(5)(D)(ii). The Act further provides, in a subsection entitled "Subsequent Applicant," that "[i]f all first applicants forfeit the 180-day exclusivity period … approval of any application containing a [paragraph IV certification] shall be made effective in accordance with [505(j)(5)(B)(iii)]," and "no applicant shall be eligible for a 180-day exclusivity period." Section 505(j)(5)(D)(iii).

The specific forfeiture event at issue in this matter is section 505(j)(5)(D)(i)(IV)(Failure to Obtain Tentative Approval). Under this provision, a first applicant will forfeit exclusivity if it "fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed."

Factual Background

On December 22, 2004, the Office of Generic Drugs received ANDAs for nateglinide tablets. Each of these ANDAs cited Starlix as its reference listed drug. Because of the new chemical entity exclusivity and listed patents for Starlix, December 22, 2004, represents the earliest possible date that the Office of Generic Drugs could receive an ANDA for review for this product (provided that the generic applicant submitted a paragraph IV certification to at least one listed patent for Starlix). *See* 21 CFR 314.108.

According to information on file with the FDA, the following patents were listed when the ANDAs were submitted on December 22, 2004: U.S. Patent Numbers RE34878 ('878 patent); 5,463,116 ('116 patent); 5,488,150 ('150 patent); 6,559,188 ('188 patent); 6,641,841 ('841 patent). All ANDA applicants provided paragraph III certifications to the ‘878 patent and paragraph IV certifications to the ‘116, ‘150, ‘188, and ‘841 patents. On or about February 10, 2005, the FDA listed U.S. Patent Number 6,844,008 ('008 patent) at the request of Novartis and all pending applicants responded by filing paragraph IV certifications to this timely filed patent as well. Each of the applicants provided notice to the required parties after receiving a filing letter, and none of the applicants was sued within 45 days on the ‘116, ‘150, ‘188, ‘841 or ‘008 patents.

On or about October 12, 2005, Novartis submitted U.S. Patent Number 6,878,749 ('749 patent) for listing in the Orange Book. ANDA applicants responded to this patent listing.

Certain first applicants received tentative approvals for their applications within 30 months of the date the applications were filed. At least one other applicant did not receive tentative approval within that time period.

Eligibility for 180-Day Exclusivity

All of the applicants that submitted ANDAs on December 22, 2004, are "first applicants" within the meaning of section 505(j)(5)(B)(iv)(II)(bb) of the Act. The MMA 180-day exclusivity provisions clearly contemplate that there can be multiple first applicants. Under these provisions, first applicant status is determined by, along other things, the day on which an application is submitted. Section 505(j)(5)(B)(iv)(II)(bb). Long experience with ANDA submissions has established that often multiple ANDAs will be submitted to the agency on a single day. *See* Guidance for Industry: 180-day Exclusivity When Multiple ANDAs are

Submitted on the Same Day (July 2003). The MMA exclusivity provisions further recognize the possibility of multiple first applicants in, for example, references to "any" first applicant in section 505(j)(5)(B)(iv)(I); to "a" first applicant in section 505(j)(5)(B)(iv)(II)(aa); and, in particular, to "all first applicants" in section 505(j)(5)(D)(iii).

The applications submitted on December 22, 2004, were substantially complete[5] and were all submitted on the same "first" day on which any ANDA referencing Starlix was (and, in this case, could be) submitted. These applications have lawfully maintained the paragraph IV certifications that qualified them for exclusivity.[6]

Forfeiture of Exclusivity by Some First Applicants

After considering the ANDAs for nateglinide tablets, 60 and 120 mg, in light of the MMA forfeiture provisions, we have determined that certain applicants remain eligible for 180-day exclusivity, while at least one applicant has forfeited 180-day exclusivity under section 505(j)(5)(D)(i)(IV) because it has failed to obtain tentative approval for its ANDA within 30 months of submission and there has been no change in or review of the approval requirements for these applications.

Effect of Forfeiture of 180-Day Exclusivity by Fewer than All First Applicants

The MMA 180-day exclusivity provisions expressly contemplate that an applicant previously eligible for 180-day exclusivity as a first applicant may forfeit that exclusivity. The statute provides that "the 180-day exclusivity period … shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant." Section 505(j)(5)(D)(ii). It further provides that "if all first applicants forfeit the 180-day exclusivity period … approval of any application containing a [paragraph IV certification] shall be made effective in accordance with [505(j)(5)(B)(iii)]," and "no applicant shall be eligible for a 180-day exclusivity period." Section 505(j)(5)(D)(iii). The statute does not, however, specifically address the effect of forfeiture of exclusivity by fewer than all of the first applicants. In particular, the statute does not describe the timing of approval of the ANDA held by an applicant that has forfeited exclusivity, or the effect on 180-day exclusivity of the commercial marketing of the product approved in that ANDA. Notwithstanding the absence of a specific rule for these circumstances, the statutory language can be applied to render a reasonable regulatory outcome.

The MMA exclusivity provisions contemplate that an ANDA applicant will be either a "first applicant," as defined in section 505(j)(5)(B)(iv)(II)(bb), or "an applicant other than a first applicant" (i.e., a subsequent applicant), sections 505(j)(5)(B)(iv)(II)(aa) and (D)(iii). The timing of approval of an ANDA turns on whether the sponsor is a first applicant or a subsequent

[5] A first applicant's ANDA must be a "substantially complete application." Section 505(j)(5)(B)(iv)(II)(bb). A "substantially complete application" is an application that "on its face is sufficiently complete to permit substantive review and contains all the information required by [section 505(j)(2)(A)]." Section 505(j)(5)(B)(iv)(II)(cc). The first applicant's submission of an ANDA that is determined to be sufficiently complete to permit review establishes eligibility for the benefits of 180-day exclusivity.

[6] Forfeiture of exclusivity for failure to obtain a tentative approval within 30 months does not constitute failure to lawfully maintain a paragraph IV certification. The former pertains to the ability of the ANDA applicant to meet the technical and scientific requirements for approval; the latter generally pertains to the applicant's assertions regarding the listed patent.

applicant. A first applicant will obtain approval as described in section 505(j)(5)(B)(iii); a subsequent applicant will have its approval delayed for the period of any applicable 180-day exclusivity as described at sections 505(j)(5)(B)(iv)(I) and (II).

As an initial matter, the statutory language does not provide that a first applicant that forfeits exclusivity becomes a subsequent applicant (i.e., an applicant other than a first applicant). The forfeiture provision at section 505(j)(5)(D)(ii) says only that "the 180-day exclusivity period … shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant." Neither this section, nor any other provision, states that in forfeiting exclusivity, a first applicant becomes a subsequent applicant whose ANDA can be approved only after the 180-day exclusivity period has run. Thus, a first applicant that has forfeited exclusivity need not await expiration of 180-day exclusivity to obtain approval of its ANDA.

A first applicant that has forfeited exclusivity can obtain approval as described in section 505(j)(5)(B)(iii). The same timetable governs the approval of ANDAs that remain eligible for 180-day exclusivity. Once FDA has approved one or more ANDAs under section 505(j)(5)(B)(iii), commercial marketing by any first applicant will begin the running of the 180-day exclusivity period for nateglinide tablet ANDAs. The commencement of the exclusivity period does not depend upon whether commercial marketing of the drug is begun by a first applicant that has forfeited exclusivity or a first applicant that retains eligibility for exclusivity. Section 505(j)(5)(B)(iv), which governs the running of exclusivity, does not distinguish among first applicants, providing instead that a subsequent applicant's ANDA may be approved 180 days after the date of first commercial marketing by *any* first applicant. Therefore, commercial marketing of nateglinide tablets by any first applicant will begin the running of the 180-day exclusivity period for nateglinide tablets, regardless of whether the first applicant forfeited exclusivity.

In light of the applicable statutory provisions, when fewer than all first applicants forfeit exclusivity, the practical effects of that forfeiture on the timing of approval of ANDAs will be negligible. A first applicant that forfeits exclusivity will not - in light of the forfeiture - delay the approval of subsequent ANDAs; however, approval of subsequent ANDAs will be constrained nonetheless by the 180-day exclusivity of any first applicant that has not forfeited exclusivity. Moreover, the running of exclusivity, and thus the timing of approval of subsequent ANDAs, will continue to depend upon the date of first commercial marketing by any of the first applicants, as would have been the case in the absence of a forfeiture.

If you have any question regarding this issue, please contact Martin Shimer at 240-276-8419.

Sincerely,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GARY J BUEHLER
09/11/2009