DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Docket No. FDA-2015-N-2713

SENT VIA EMAIL

Dear Cyclosporine Ophthalmic Emulsion ANDA Applicant:

We are writing to solicit comments on a 180-day generic drug exclusivity matter that affects abbreviated new drug applications (ANDAs) for Cyclosporine Ophthalmic Emulsion, 0.05%. More than one ANDA applicant has submitted paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to patents listed for the relevant reference listed drug (RLD). The particular issues that are the subject of this letter are: (1) whether one or more applicants that submitted a paragraph IV certification to patent number 5,474,979 (the '979 patent) before January 14, 2014 but was not received for review until after that patent had expired is a "first applicant;" and (2) whether a forfeiture event under section 505(j)(5)(D)(i)(VI) of the FD&C Act already has occurred.

I. STATUTORY BACKGROUND

Under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. Law No. 98-417, 98 Stat. 1585 (1984) (Hatch-Waxman Amendments), a new drug application (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 (the listed drug) 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."[1] FDA publishes this patent information in FDA's *Approved Drug Products with Therapeutic Equivalence Ratings* (the "Orange Book"). The statute also provides that if a relevant patent is issued after NDA approval, the NDA sponsor must file the patent information with FDA not later than 30 days after the date the patent is issued.[2]

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

(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

[1] Sections 505(b)(1) and (c)(2) of the FD&C Act.

[2] Section 505(c)(2) of the FD&C Act.

(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) of the FD&C Act.[3] See also 21 CFR 314.94(a)(12)(i)(A).

Once an application containing a paragraph IV certification to a listed patent receives an acknowledgment that FDA has determined the application is sufficiently complete to permit substantive review (referred to as an "Acknowledgment Letter"), the applicant must provide the NDA holder and the patent owner notice of its patent certification, including a description of the legal and factual basis for the ANDA holder's assertion that the patent is invalid or not infringed.[4] The statute prohibits an applicant from providing such notice prior to FDA's formal receipt of the application for substantive review.[5]

If a patent is listed at the time an ANDA is submitted and, in response to a paragraph IV certification 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 the notice or such shorter or longer time as the court might order.[6] If a patent is listed in the Orange Book after an ANDA is submitted but before it is approved, the applicant for the pending ANDA generally must amend its application and provide an appropriate certification to the newly listed patent and the attendant notice; however, a patent listed after the ANDA is submitted will not trigger a 30-month stay for that application.[7]

The exclusivity provisions as revised by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (MMA) (Dec. 8, 2003), like the original Hatch-Waxman Amendments, provide the "first applicant(s)" to submit a substantially complete application that contains a paragraph IV certification challenging a patent — and thus to undertake the risk of litigation — an incentive in the form of the opportunity to be the only generic drug manufacturer to compete with the innovator for a 180-day period. Under these provisions, subsequently submitted ANDAs for the same product that contain a paragraph IV certification cannot be approved until after the 180-day exclusivity period has run, unless it has been forfeited.[8] "First applicant" is defined in section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act as "an applicant that, on the first day on which a substantially complete application containing a

[3] The FD&C Act provides only one circumstance in which an applicant with a pending ANDA 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) of the FD&C Act; see also 21 CFR 314.94(a)(12)(iv)).

[4] Section 505(j)(2)(B) of the FD&C Act.

[5] Section 505(j)(2)(B)(ii) of the FD&C Act.

[6] Section 505(j)(5)(B)(iii) of the FD&C Act.

[7] Id.

[8] The requirements for obtaining and retaining this 180-day exclusivity period are described at sections 505(j)(5)(B)(iv) and 505(j)(5)(D) of the FD&C Act.

[paragraph IV certification] is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a [paragraph IV certification] for the drug."

Section 505(j)(5)(D) of the FD&C Act describes a significant feature of 180-day exclusivity under the MMA in the form of a set of conditions under which an ANDA applicant loses — or forfeits — eligibility for 180-day exclusivity. There are six different forfeiture provisions, one of which is at issue in this discussion. The provision at issue regards patent expiration. Under this provision, a forfeiture event occurs if:

> EXPIRATION OF ALL PATENTS. – All of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.

Notably, "[i]f all first applicants forfeit the 180-day exclusivity period under [505(j)(5)(D)(ii)] … no applicant shall be eligible for a 180-day exclusivity period."[9]

II. FACTUAL BACKGROUND

Restasis Ophthalmic Emulsion, 0.05% is the RLD for Cyclosporine Ophthalmic Emulsion, 0.05%. The new drug application (NDA 050790) for Restasis is held by Allergan, Inc. FDA approved Restasis on December 23, 2002.[10] The first patents for Restasis were listed in the Orange Book in late 2008: U.S. Patent Nos. 4,839,342 (the '342 patent) and 5,474,979 (the '979 patent). The '342 patent expired on August 2, 2009, and the '979 patent expired on May 17, 2014. One or more ANDAs or patent amendments submitted after the '342 patent expired but before January 14, 2014 contained a paragraph IV certification to the '979 patent, potentially qualifying the ANDA sponsor(s) as a "first applicant" eligible for 180-day exclusivity.

The following patents, all expiring on August 27, 2024, were first listed in the Orange Book in 2014, and are the five unexpired patents currently listed in the Orange Book for Restasis:

U.S. Patent No.	Date of Orange Book Listing
8,629,111 (the '111 patent)	January 14, 2014
8,633,162 (the '162 patent)	January 22, 2014
8,642,556 (the '556 patent)	February 4, 2014
8,648,048 (the '048 patent)	February 11, 2014
8,685,930 (the '930 patent)	April 1, 2014

Until the '111 patent was listed on January 14, 2014, the '979 patent was the only patent listed in the Orange Book for Restasis since expiry of the '342 patent in 2009.[11]

The one or more paragraph IV certifications to the '979 patent submitted to FDA after the '342 patent expired but before January 14, 2014, were the first paragraph IV submissions made for

[9] Section 505(j)(5)(D)(iii) of the FD&C Act.

[10] Restasis was approved in NDA 021023. Shortly after its approval, the number of this NDA was changed to 050790.

[11] On January 14, 2014, the date the '111 patent was submitted to the Agency and listed in the Orange Book, one or more applicants submitted a paragraph IV certification to the '111 patent.

Restasis. But the '979 patent expired before FDA issued an Acknowledgement Letter to any applicant with a pending ANDA for this drug product, and before any sponsor had the opportunity to provide notice of the paragraph IV certification to that patent.

III. QUESTIONS PRESENTED

The issues before the Agency are whether, in light of the foregoing facts:

(1) the one or more applicants that submitted ANDAs or patent amendments with paragraph IV certifications to the '979 patent after the '342 patent expired but before January 14, 2014, and that did not receive Acknowledgement Letters until after the '979 patent had expired, are "first applicants" under FD&C Act section 505(j)(5)(B)(iv)(II)(bb); and

(2) whether 180-day generic drug exclusivity for this product was forfeited on May 17, 2014, when the '979 patent expired, such that no ANDA applicant for Cyclosporine Ophthalmic Emulsion, 0.05%, is eligible for 180-day generic drug exclusivity.

As part of its consideration, FDA is considering whether the fact that FDA did not issue an Acknowledgement Letter for this drug product until after the patent expired impacts this analysis. FDA also seeks comment on whether there are any other factors that are material to this question. With this docket, we are soliciting any interested parties' position on this matter.

It is FDA's general policy to make exclusivity decisions at the time an application becomes eligible for approval, and not before. However, due to the unusual facts of this case, the Agency has determined that it is in the best interest of all concerned to alert affected parties to the facts of this case, and to allow the submission of comments.

This letter is addressed to applicants of ANDAs that reference Restasis, but any interested party may submit comments. We ask that interested parties submit comments to http://www.regulations.gov by August 28, 2015. Please include the proper docket number, FDA-2015-N-2713 in your correspondence. If you have any questions regarding this correspondence, please contact Maryll W. Toufanian, Acting Deputy Director, Office of Generic Drug Policy, at 240-402-7944.

Sincerely yours,

Timothy G. Jetton -S

Digitally signed by Timothy G. Jetton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000480206, cn=Timothy G. Jetton -S
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for Johnny Young, M.A.
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