September 2, 2022

Jeremy R. Jessen
General Counsel, Vice President, Consumer Health
Bayer U.S. LLC
Law, Patents & Compliance
100 Bayer Boulevard
Whippany, NJ 07981

Re: Docket No. FDA-2022-P-0536

Dear Mr. Jessen:

This letter responds to your citizen petition submitted on behalf of Bayer HealthCare LLC (Bayer) and received on April 5, 2022 (Petition). Your Petition requests that the Food and Drug Administration (FDA, Agency, or we) confirm that the Agency will stay the final approval of abbreviated new drug application (ANDA) 216421, which the Petition states was submitted by Apotex Inc. or Apotex Corp. (collectively Apotex), until the expiration of the 30-month period beginning on the date when Bayer, the new drug application (NDA) holder for Astepro Allergy and Children's Astepro Allergy (azelastine hydrochloride nasal spray), received Apotex's notice of paragraph IV certification to U.S. Patent Nos. 8,071,073 ('073 patent), 8,518,919 ('919 patent), and 9,919,050 ('050 patent), absent any event specified in section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)(5)(B)(iii)) that would cause the stay to be shortened, lengthened, or terminated.

We have carefully considered the information submitted in the Petition. For the reasons set forth below, your Petition is denied without comment on whether we will take the action you request.

I. BACKGROUND

A. Overview of Statutory and Regulatory Requirements

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(b)(2) and (j) of the FD&C Act. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[1] Section 505(j) of the FD&C Act established a pathway for submission of an ANDA for a drug product that is the same as a previously approved drug (the reference listed drug (RLD)) with respect to active ingredient, dosage form, route of

[1] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

administration, strength, labeling (with certain permissible labeling differences), and conditions of use, among other characteristics. An ANDA applicant also must demonstrate that its proposed generic drug product is bioequivalent to the RLD. An applicant that meets the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the RLD, and need not submit full reports of investigations that demonstrate the safety and effectiveness of the product as required for approval of an NDA submitted under section 505(b)(1) of the FD&C Act.

An NDA applicant must submit information to FDA for each patent that claims the drug or a 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 of the patent engaged in the manufacture, use, or sale of the drug."[2] For each drug product approved for safety and effectiveness in an NDA under subsection (c) of section 505 of the FD&C Act, FDA publishes in FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book)[3] the patent information submitted under subsection (c) of section 505 of the FD&C Act.[4]

The timing of ANDA approval depends on, among other things, relevant patent information listed in the Orange Book for the RLD and on whether the ANDA applicant challenges a patent listed in the Orange Book for the RLD (listed patent) or seeks approval for a use covered by a listed method-of-use patent.[5] For each patent that claims the RLD or a method of using the RLD that the ANDA references and for which the NDA applicant is required to submit information, an ANDA applicant must submit a certification:

> (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, unenforceable, 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).[6,7]

An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner with notice of its patent certification, including a description of the legal and factual basis for the ANDA applicant's assertion that the patent is invalid,

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

[3] See, e.g., section 505(j)(7)(A) of the FD&C Act.

[4] Section 505(j)(7)(A)(iii) of the FD&C Act.

[5] See 21 CFR 314.107

[6] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).

[7] The FD&C 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 [section 505(j)(2)(A)(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)(iii)(A)).

unenforceable, or not infringed.[8] If the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant before the expiration of 45 days after 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.[9]

On December 8, 2003, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (Public Law 108-173) was enacted. Section 1101 of the MMA amended the FD&C Act to provide, among other things, that a 30-month stay of approval of an ANDA is available only if a patent infringement action against the ANDA applicant was initiated within the 45-day period after receipt of notice of a paragraph IV certification for a patent "for which information was submitted to [FDA] under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted."[10]

FDA regulations require that "[i]f the holder of the approved NDA for the listed drug submits patent information required under 21 CFR 314.53 after the date on which the . . . ANDA was submitted to FDA, the . . . ANDA applicant must comply with the requirements of . . . 314.94(a)(12)(vi) and (viii) regarding submission of an appropriate patent certification or statement."[11] If the ANDA applicant submits a paragraph IV certification and complies with the requirements of 21 CFR 314.95, "[t]he 45-day period provided for in section . . . 505(j)(5)(B)(iii) of the [FD&C Act] does not apply."[12]

B. Astepro Allergy and Children's Astepro Allergy

On August 20, 2020, Bayer submitted NDA 213872 for azelastine hydrochloride nasal spray, 0.15%, and requested approval for an over-the-counter (OTC) use.[13] Bayer submitted information on the '073, '919, and '050 patents on Forms FDA 3542a as part of its NDA (Petition at 6 and Exhibit 3). On June 17, 2021, FDA approved NDA 213872 for Astepro Allergy (azelastine hydrochloride) nasal spray, 205.5 mcg per spray, and Children's Astepro Allergy (azelastine hydrochloride) nasal spray, 205.5 mcg per spray, for the temporary relief of these symptoms due to hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, and itchy nose. On July 8, 2021, Bayer submitted information on the '073, '919, and '050 patents on Forms FDA 3542 for listing in FDA's Orange Book (Petition at 6 and Exhibit 4).

[8] Section 505(j)(2)(B) of the FD&C Act; see also 21 CFR 314.95(c).

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

[10] Section 505(j)(5)(B)(iii) of the FD&C Act; see also section 505(c)(3)(C) of the FD&C Act.

[11] 21 CFR 314.107(b)(2).

[12] 21 CFR 314.107(b)(2).

[13] Azelastine hydrochloride nasal spray, 0.1% (137 micrograms (mcg) per spray) and 0.15% (205.5 mcg per spray) had previously been approved for prescription use and was marketed under the tradename Astepro. See approvals for NDA 022203 and 022371, available at Drugs@FDA. Both of these products are currently listed in the Discontinued Drug Products List of the Orange Book.

In your Petition, you state:

> By letters dated August 25 and 26, 2021, Apotex notified Bayer that Apotex had submitted ANDA 216421 referencing NDA 213872 and had submitted a paragraph IV certification as to each of the Patents. On October 7, 2021—within 45 days after receiving Apotex's paragraph IV notices—Bayer and a co-plaintiff filed a complaint against Apotex in the United States District Court for the District of Delaware alleging infringement of the Patents in connection with ANDA 216421.

(Petition at 6, internal citations omitted).

C. Section 505(q) of the FD&C Act

Section 505(q) of the FD&C Act was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) and was amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144). Section 505(q), as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on such a petition no later than 150 days after the date on which the petition is submitted.

II. DISCUSSION

In your Petition, you request that FDA "confirm that FDA will stay the final approval of ANDA 216421 until the expiration of the 30-month period beginning on the date when Bayer received the notice described in [FD&C Act] § 505(j)(2)(B) (i.e., the paragraph IV notice)" (Petition at 1). You assert that "FDA should apply a 30-month stay of approval to ANDA 216421 because the statutory prerequisites for a stay are met regardless of whether Apotex submitted [its] ANDA before or after Bayer submitted the Forms 3542 for the Patents" (Petition at 7). You contend that "[b]ecause Bayer submitted the Forms 3542a with the original NDA 213872, they necessarily preceded Apotex's submission of an ANDA referencing this NDA, and thus fulfilled this statutory requirement for eligibility for a 30-month stay" (Petition at 8).

As described above, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific request in the Petition regarding whether a 30-month stay of approval of ANDA 216421 would apply at such time as the ANDA otherwise meets the requirements for approval under section 505(j) of the FD&C Act.

FDA has not made a final determination on whether to approve or not approve ANDA 216421.[14] FDA's decision to approve or not approve a specific application will be based on the particular

[14] Under applicable statutory and regulatory provisions, we are generally prohibited from disclosing information regarding any applications that have not been approved.

facts that are applicable to that application at the time of the decision. The action requested in your Petition may have different implications depending on the particulars of the ANDA and/or the timing of its eligibility for approval.

Therefore, we must determine whether it would be appropriate for us to take final Agency action on the action requested in your Petition before taking final action on the approvability of the application as a whole. As described above, the decision whether to approve an ANDA, and the timing of its eligibility for approval, may have implications for the action requested in your Petition. For example, the question of whether FDA will stay the final approval of an ANDA for 30 months from when Bayer received the notice of paragraph IV certification may become moot if that ANDA is not otherwise eligible for approval within that timeframe.

The FD&C Act and FDA regulations establish review processes and protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA regulations in part 314 (21 CFR part 314) describe certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved (section 505(c) and (j) of the FD&C Act; 21 CFR 314.105) or may not be approved (section 505(c), (d), and (j) of the FD&C Act; 21 CFR 314.125 and 314.127), or identifies the deficiencies in the application or other bars to final approval and the steps an applicant may take to respond to the deficiencies (21 CFR 314.110 and 314.105(d)).

There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of pending applications outside of the process established under the FD&C Act and FDA regulations. Therefore, we do not interpret section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the 150-day statutory deadline in circumstances such as these, where a petition requests action pertaining to a particular application for which FDA has not made a final decision regarding eligibility for approval, and where the request in the petition (e.g., the availability of a 30-month stay) may become moot depending on when such application otherwise might become eligible for approval. Accordingly, we deny without comment the specific request in the Petition regarding the timing of the final approvability of ANDA 216421.[15]

[15] We will continue to evaluate each citizen petition on a case-by-case basis on the appropriateness of responding to requests regarding any pending application.

III. CONCLUSION

For the reasons stated above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2022.09.02 11:27:18 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research