ANDA 209831

ANDA TENTATIVE APPROVAL

Teva Pharmaceuticals USA
577 Chipeta Way
Salt Lake City, UT 84108
Attention: Cherri Petrie
Executive Director, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on November 23, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Buprenorphine and Naloxone Buccal Film, 2.1 mg/0.3 mg and 4.2 mg/0.7 mg.

Reference is also made to the complete response letter issued by this office on September 20, 2017, and to any amendments thereafter.

We have completed the review of this ANDA, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. The Office of Bioequivalence has determined your Buprenorphine and Naloxone Buccal Film, 2.1 mg/0.3 mg and 4.2 mg/0.7 mg to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Bunavail Buccal Film, 2.1 mg/0.3 mg and 4.2 mg/0.7 mg, of BioDelivery Sciences International, Inc. (BioDelivery).

However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the Agency at this time (e.g., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the FD&C Act.

The RLD upon which you have based your ANDA, BioDelivery's Bunavail Buccal Film, 2.1 mg/0.3 mg and 4.2 mg/0.7 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
7,579,019 (the '019 patent)	January 22, 2020
8,147,866 (the '866 patent)	July 23, 2027
8,703,177 (the '177 patent)	August 20, 2032

9,522,188 (the '188 patent)	April 24, 2035
9,655,843 (the '843 patent)	July 23, 2027

With respect to the '019, '866, '177, and '188 patents,[1] your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Buprenorphine and Naloxone Buccal Film, 2.1 mg/0.3 mg and 4.2 mg/0.7 mg, under this ANDA. You have notified the Agency that Teva Pharmaceuticals USA (Teva) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that litigation was initiated within the statutory 45-day period against Teva for infringement of the '019, '866, '177, and '188 patents in the United States District Court for the District of Delaware [Biodelivery Sciences International, Inc. and Arius Two, Inc. v. Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd, Civil Action No. 17-cv-00282]. You have also notified the Agency that this case was dismissed.

With respect to the '843 patent, your ANDA contains a paragraph III certification to the patent under section 505(j)(2)(A)(vii)(III) of the FD&C Act stating that Teva will not market Buprenorphine and Naloxone Buccal Film, 2.1 mg/0.3 mg and 4.2 mg/0.7 mg, prior to the expiration of the patent. Therefore, final approval of your ANDA may not be granted pursuant to section 505(j)(5)(B)(ii) of the FD&C Act until the '843 patent has expired, currently July 23, 2027.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated January 23, 2017. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your final proposed REMS, submitted on July 21, 2017, can be approved with your application.

The REMS consists of a Medication Guide, ETASU, and an implementation system.

The Buprenorphine Transmucosal products for Opioid Dependence REMS uses a waiver-granted shared system for the ETASU and the REMS assessments. This waiver-granted shared system REMS currently includes the products listed on the FDA REMS website available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Prior to the submission of your amendment, you should contact Ronald Sanwo at Amneal Pharmaceuticals, who has been identified as the current point of contact for the Buprenorphine Transmucosal products for Opioid Dependence, to obtain an updated version of the REMS and

appended materials to submit to your application, if applicable. They can be reached at rsanwo@amneal.com 631-952-0214 Extension 2359 or 631-633-2359.

RESUBMISSION

To request final approval, please submit an amendment titled "FINAL APPROVAL REQUESTED" with enough time to permit FDA review prior to the date you believe that your ANDA will be eligible for final approval. A request for final approval that contains no new data, information, or other changes to the ANDA generally requires a period of 90 days for Agency review. Accordingly, such a request for final approval should be submitted no later than 90 days prior to the date on which you seek approval. A request for final approval that contains substantive changes to this ANDA or changes in the status of the manufacturing and testing facilities' compliance with cGMPs will be classified and reviewed according to OGD policy in effect at the time of receipt. Applicants should review available agency guidance for industry related to amendments under the generic drug user fee program to determine the duration of Agency review needed to review the changes submitted. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

The amendment requesting final approval should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, e.g., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a "FINAL APPROVAL REQUESTED."

In addition to the amendment requested above, the Agency may request, at any time prior to the date of final approval, that you submit an additional amendment containing information as specified by the Agency. Failure to submit either or, if requested, both types of amendments described above may result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505(j) of the FD&C Act, and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to July 23, 2027, you should amend your ANDA accordingly.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[2] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Leanna Slarsky, Regulatory Project Manager, at (240) 402-6107.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, Pharm.D.
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] The Agency notes that the '188 and '843 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Sarah Kurtz

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