DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 202577

**TENTATIVE APPROVAL**

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 17, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fentanyl Buccal Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg.

Reference is made to your amendments dated September 28, 2011; May 10, and August 8, 2012; June 11, October 7, November 20, and December 30, 2013; January 17, April 30, May 21, November 26, and December 11, 2014. In addition, we acknowledge receipt of your correspondence dated January 11, February 2, February 24, March 8, October 26, November 17, and December 9, 2011; October 4, 2012; and January 10, August 14, and October 3, 2013 and May 1, 2014; and February 26, 2015. The February 26, 2015 submission addressed the patent issues associated with this ANDA.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. 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**.[1] This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacturing and testing of the drug product) and is therefore 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 Act.

[1] We note that the 300 mcg strength of the reference listed drug (RLD) upon which you have based your ANDA, Fentora Buccal Tablets of Cephalon, Inc., is no longer being marketed in the United States, and is currently listed in the discontinued section of the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). The agency announced its determination that Fentora Buccal Tablets, 300 mcg, was not withdrawn from sale for reasons of safety or effectiveness. 76 FR 19997; April 11, 2011. This determination allows the agency to approve ANDAs for the discontinued drug product.

The RLD upon which you have based your ANDA, Cephalon's Fentora Buccal Tablets, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Orange Book:

| U.S. Patent Number | Expiration Date |
|---|---|
| 6,200,604 (the '604 patent) | March 26, 2019 |
| 6,974,590 (the '590 patent) | March 26, 2019 |
| 7,862,832 (the '62,832 patent) | June 15, 2028 |
| 7,862,833 (the '833 patent) | June 15, 2028 |
| 8,092,832 (the '92,832 patent) | December 30, 2024 |
| 8,119,158 (the '158 patent) | December 30, 2024 |
| 8,728,441 (the '441 patent) | March 26, 2019 |
| 8,753,611 (the '611 patent) | March 26, 2019 |
| 8,765,100 (the '100 patent) | March 26, 2019 |

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Fentanyl Citrate Buccal Tablets 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg, under this ANDA. You have notified the agency that Mylan Pharmaceuticals Inc. (Mylan) complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '604, '590, '62,832, '833, '92,832, and '158 patents was brought against Mylan within the statutory 45-day period in the United States District Court for the District of Delaware [Cephalon Inc., and Cima Labs, Inc., v. Mylan Pharmaceuticals Inc. and Mylan Inc., Civil Action No. 11-164-SLR]. You also have notified the agency that the Court has entered judgment pursuant to 271(e)(4)(A) and that Mylan has appealed this decision. The district court's order of August 8, 2013 states that the effective date of approval of Mylan's ANDA shall be a date not earlier than the expiration of the '604, '590, '92,832 and '158 patents applicable to the associated strengths.[2] The agency, therefore, may not approve your ANDA at this time.

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA 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 FDCA, an ANDA is required to have a REMS if the applicable listed drug has an approved REMS.

The details of the REMS requirements were outlined in your REMS notification letter dated August 18, 2011. Transmucosal immediate-release fentanyl products use a single, shared system for the elements to assure safe use and the REMS assessments. This single, shared system is known as the Transmucosal Immediate Release Fentanyl (TIRF) REMS.

[2] With respect to the 100 mcg strength, the '158 patent is not listed in the Orange Book. With respect to the 300 mcg strength, only the '604 and '590 patents are listed in the Orange Book.

Your proposed REMS, submitted on December 11, 2014, and appended to this letter, can be approved with your ANDA. The REMS consists of a Medication Guide, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS. We will review your proposed REMS to assure that it matches the approved single, shared system REMS before final approval of your ANDA.

If your ANDA is ultimately approved, your REMS must be fully operational before you introduce Fentanyl Citrate Buccal Tablets into interstate commerce.

Because Fentanyl Citrate Buccal Tablets, if it is ultimately approved, will be a member of the TIRF REMS, the assessment plan will be the same assessment plan required for the other products covered by this single, shared system. If your ANDA is ultimately approved, the approval letter will provide the details of the assessment plan for Fentanyl Citrate Buccal Tablets.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., 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 MINOR AMENDMENT – 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 the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMPs are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also 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 of the 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 Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions 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 1 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 prior to submitting additional amendments, please contact Kevin Herkenham, Project Manager, at (240) 402-8964.

Sincerely yours,

William P. Rickman -S

Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300043242, cn=William P. Rickman -S
Date: 2015.03.04 13:53:01 -05'00'

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachments: REMS
Medication Guide