DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993

MAY 20 2014

Joel S. Lippman, M.D., MPH
Executive Vice President and Chief Medical Officer
Noven Pharmaceuticals, Inc.
11960 SW 144th Street
Miami, FL 33186

Re: Docket No. FDA-2013-P-1710

Dear Dr. Lippman:

This responds to your citizen petition received on December 24, 2013 (Petition), requesting that the Food and Drug Administration (FDA or the Agency) take certain actions with respect to any abbreviated new drug application (ANDA) that references Daytrana (methylphenidate) Transdermal System, 10 milligrams (mg)/9 hours (hr), 15 mg/9 hr, 20 mg/9 hr, and 30 mg/9 hr, held by Noven Pharmaceuticals, Inc. (Noven), under new drug application (NDA) 021514. Specifically, you request that FDA refuse to approve any ANDAs for generic[1] versions of Daytrana unless the ANDA applicant demonstrates in a usability study conducted in adults, adolescents, and children under real-world conditions that the proposed generic is not inferior to Daytrana with respect to patch adhesion performance.

We have carefully considered the issues raised in your Petition. For the reasons stated below, your Petition is denied.

I. BACKGROUND

A. Daytrana

FDA approved Noven's NDA for Daytrana on April 6, 2006 (NDA 021514). Daytrana is an adhesive-based transdermal system indicated for the treatment of attention-deficit hyperactivity disorder (ADHD). Daytrana's active ingredient, methylphenidate, is available in four dosage strengths: 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr, and 30 mg/9 hr. The Daytrana transdermal system should be applied 2 hours before an effect is needed and removed no more than 9 hours after application. The Daytrana patch consists of three layers: (1) a polyester/ethylene vinyl acetate laminate film backing, (2) a proprietary adhesive formulation, and (3) a fluoropolymercoated polyester protective liner, which is attached to the adhesive surface and must be removed before the patch can be used. The Daytrana labeling includes specific instructions for patch application,

[1] *Generic* is not defined in the Federal Food, Drug, and Cosmetic Act (FD&C Act) or in FDA regulations. As used in this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act (21 U.S.C. 355(j)).

removal, disposal, and storage and a warning with respect to exposing the application site to external heat sources.

On August 27, 2012, we received a petition from Noven requesting that FDA take certain actions, including a request regarding usability studies for ANDAs that reference Daytrana.[2] On January 23, 2013, we issued our response (2013 Daytrana Petition Response) and denied Noven's request to require usability studies as a condition for approval for ANDAs that reference Daytrana because the current Daytrana labeling already contains considerable information on usability, and we would expect the labeling for generic products referencing Daytrana to contain the same information regarding usability.

B. Legal and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD)[3] is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act).

In addition, an ANDA must contain (with certain exceptions not relevant here) information to show that the proposed drug has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD (section 505(j)(2)(A) of the FD&C Act). FDA must approve an ANDA unless the information submitted in the ANDA is insufficient to meet the requirements delineated in section 505(j)(2)(A), including a demonstration of bioequivalence (section 505(j)(4) of the FD&C Act). The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet certain criteria are therapeutically equivalent and

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[2] Docket No. FDA-2012-P-0932.

[3] A reference listed drug is defined in 21 CFR 314.3 as "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." Section 314.3 further defines a "listed drug" as "a new drug product that has an effective approval under section 505(c) of the [FD&C] act for safety and effectiveness or under section 505(j) of the [FD&C] act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the [FD&C] act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as "the Orange Book."

may be substituted for each other.[4] The general criteria for therapeutic equivalence include the following: the products (1) contain identical amounts of the same active ingredient(s) in the same route of administration and dosage form; (2) meet applicable standards of strength, quality, purity, and identity; (3) are manufactured in compliance with current good manufacturing practices regulations; and (4) are adequately labeled.[5]

FDA regulations at 21 CFR part 320 list acceptable methodologies for determining the bioequivalence of drug products. These methodologies include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies. The selection of the method used depends on the purpose of the study, the analytical methods available, and the characteristics of the drug product under consideration (§ 320.24). The courts have expressly upheld FDA's regulatory implementation of the FD&C Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995); *Sanofi-Aventis v. FDA*, 842 F. Supp.2d 195, 214 (D.D.C. 2012); and *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994)).

FDA's general recommendation for bioequivalence testing of systemically acting transdermal products is a single-dose fasting study. FDA recommends administering single doses of the test and reference drug products to subjects using a crossover design, with measurement of the concentrations of the test and reference drugs in blood, plasma, or serum over time. In addition to the fasting study, FDA recommends a skin irritation, sensitization, and adhesion study for systemically acting transdermal products.

C. FDA's Bioequivalence Recommendations for Methylphenidate (Film for Extended-Release for Transdermal Administration)

FDA's *Draft Guidance on Methylphenidate*[6] for film, extended-release/transdermal, (Methylphenidate Guidance) provides recommendations on how to design bioequivalence and related studies to support ANDAs for such methylphenidate products. It recommends the following:

- Single-dose, fasting, two-treatment, two-period crossover in vivo bioequivalence studies comparing the 30 mg/9 hr strength test product to the RLD (in this case, Daytrana).

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[4] See section 505(j) of the FD&C Act.
[5] See the Orange Book, 34rd ed., at vii.
[6] The draft guidance, when finalized, will represent FDA's current thinking on this topic (available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

- In vivo skin irritation, sensitization, and adhesion study using the 10 mg/9 hr strength.

Bioequivalence should be demonstrated based on a 90 percent confidence interval (pharmacokinetic study only). If the bioequivalence study utilizing the 30 mg/9 hr strength is successful, in vivo studies using the 10 mg/9 hr, 15 mg/9 hr, and 20 mg/9 hr strengths may be waived if certain criteria are met.

II. DISCUSSION

You request that FDA require ANDA applicants referencing Daytrana to conduct a usability study in adults, adolescents, and children under real-world conditions to demonstrate patch adhesion performance (Petition at 2). In support of your request, you describe your recent communications with FDA regarding patch adhesion performance and approvability concerns regarding your investigational methylphenidate transdermal system (Petition at 3). Specifically, you state that FDA is concerned that a lack of patch adhesion for this product would pose multiple safety risks, including the risk that a detached patch could adhere to another child. You also mention that FDA has efficacy concerns related to patch adhesion because a detached patch cannot deliver adequate medication to the patient (Petition at 3). You maintain that the Agency has communicated to Noven that in vitro adhesive studies do not negate the need to conduct usability studies and such studies should be conducted under real-world conditions (Petition at 3). In addition, you claim that FDA did not consider safety and efficacy concerns in the denial of Noven's request for usability studies in the 2013 Daytrana Petition Response (Petition at 5).

Our position has not changed since issuing the 2013 Daytrana Petition Response, and your suggestion that FDA did not consider safety and efficacy in that response reflects a misunderstanding of how safety and effectiveness are established for a drug approved under an ANDA. As we stated in the 2013 Daytrana Petition Response and as discussed in the legal and regulatory background section of this response, the requirements for an NDA differ from the requirements for an ANDA. An NDA applicant must demonstrate safety and efficacy. For an NDA transdermal patch drug, FDA may seek a usability study to demonstrate that the proposed product is safe and effective when used in real world conditions. Once that demonstration is made for the RLD in the NDA, an ANDA applicant relies on the previous finding of safety and efficacy of the RLD and must demonstrate that its product is bioequivalent to the RLD, has similar adhesion, skin sensitization and irritation effects, and is labeled in the same way. A usability study is not necessary to make that demonstration.

In addition to evaluating bioequivalence for ANDAs, FDA has established procedures for evaluating aspects of product performance through the review of adhesion as well as

irritation and sensitization data submitted for transdermal ANDA products, and data on each of those characteristics will be required for any generic version of Daytrana. Therefore, we are denying your request to require ANDAs that reference Daytrana to conduct usability studies.

You also support your request to require usability studies under real-world conditions with the claim that the bioequivalence and skin irritation, sensitization, and adhesion studies required by FDA for generic versions of Daytrana are inadequate to assess adhesion for this type of product, especially because it is indicated for children ages 6-17 with ADHD (Petition at 6).

We disagree with your claim that the adhesion study design described in the Methylphenidate Guidance is inadequate to assess adhesion of this product, even when considering the difference in the adult age of the population in which the adhesion study is recommended to be conducted compared with the child/adolescent age in which the product is intended to be used. The Methylphenidate Guidance recommends evaluation of adhesion on a 5-point scale, 9 hours after patch application (the normal wear time for Daytrana), followed by evaluating adhesion at the end of the study. The adhesion study is carried out as a non-inferiority study with statistical analysis. Such study designs are well-characterized and known to be sensitive to determine significant differences in adhesion between an ANDA product and the RLD.

We are not aware of a significant difference in the adhesion of Daytrana in adults compared with children or adolescents. Healthy adult volunteers[7] are typically evaluated in the adhesion studies for generic drugs because they have better tolerance for most drugs, and to avoid any unnecessary risk in children. Furthermore, we are not aware of studies relevant to this issue that demonstrate that the adhesion of a transdermal product is significantly different as a function of age. Therefore, considering the risk to children as test subjects, and in the absence of a compelling necessity to test adhesion in children as opposed to adults, adhesion studies in children currently are not recommended for any ANDA submissions. Thus, we expect that equivalence in adults would imply equivalence in children. As such, there is insufficient evidence to indicate that the

[7] Healthy volunteers are evaluated for bioequivalence, adhesion, irritation, and sensitization for other transdermal ANDA products, including fentanyl, which can be used in children aged 2 years and older.

current adhesion study design is inadequate or to warrant a requirement for adhesion studies in children. This may be in contrast to the requirements for an NDA, for which it may be appropriate to demonstrate whether relevant real-world differences exist among populations of different ages.

III. CONCLUSION

For the reasons explained above, your Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research