noven
PHARMACEUTICALS, INC.

December 23, 2013

2013 DEC 24 P 12:01

BY FedEx®

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061 (HFA-305)
Rockville, Maryland 20852

Re: Requirement for a Usability Study Before Approving ANDAs for Generic Daytrana® (Methylphenidate) Transdermal System

Dear Sir or Madam:

CITIZEN PETITION

Noven Pharmaceuticals, Inc. ("Noven") submits this Citizen Petition pursuant to section 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), among other provisions of law, and the Food and Drug Administration's ("FDA's") regulations set forth at 21 C.F.R. § 10.30. For the reasons discussed below, Noven respectfully requests that the Commissioner of Food and Drugs refuse to approve any Abbreviated New Drug Application ("ANDA") for a generic version of Noven's Daytrana® (methylphenidate transdermal system), 10 mg/9hr, 15 mg/9hr, 20 mg/9hr, 30 mg/9hr ("Daytrana® TDS"), approved under New Drug Application ("NDA") No. 021514, unless and until the conditions specified in this Citizen Petition are satisfied.

Noven is a specialty pharmaceutical company engaged in the research, development, manufacturing, marketing, and sale of prescription pharmaceutical products. Noven specializes in transdermal drug delivery and related manufacturing. Noven is the sponsor of several approved NDAs and ANDAs and has partnered with companies on a number of other NDAs, including the market leading estrogen therapy patch, Vivelle-Dot® (estradiol transdermal system). Noven's experience in developing and marketing transdermal products, including Daytrana® TDS, enables the company to understand uniquely the considerations and challenges involved in developing complex dosage forms such as transdermal products.

2013-10551
CP

FDA-2013-P-1710

I. ACTION REQUESTED

Based on recent statements from FDA regarding the importance of testing the adhesion of a Methylphenidate TDS under "real world" conditions, Noven requests that FDA refuse to approve any ANDA that cites as its Reference Listed Drug ("RLD") Daytrana® TDS unless and until the sponsor of such ANDA demonstrates in a usability study conducted in adults, adolescents, and children under "real world" conditions that its proposed generic drug product is not inferior to Daytrana® TDS with respect to patch adhesion performance.

II. STATEMENT OF GROUNDS

A. Daytrana® TDS – Background & Regulatory History

Daytrana® TDS is an adhesive-based matrix transdermal system that FDA approved on April 6, 2006 under NDA No. 021514, and that is currently approved for the treatment of Attention Deficit Hyperactivity Disorder ("ADHD"), a psychiatric disorder that is most prevalent in children. The efficacy of Daytrana® TDS in patients diagnosed with ADHD was established in two 7-week controlled clinical trials in children (ages 6-12 years) and one 7-week, controlled clinical trial in adolescents (ages 13-17 years).

Daytrana® TDS is currently available in four different dosage strengths – 10 mg/9hr, 15 mg/9hr, 20 mg/9hr, and 30 mg/9hr – providing for a nominal in vivo delivery rate of 1.1 mg/hr, 1.6 mg/hr, 2.2 mg/hr, and 3.3 mg/hr, respectively. Daytrana® TDS should be applied to the hip area 2 hours before an effect is needed and should be removed 9 hours after application; however, Daytrana® TDS may be removed earlier than 9 hours if a shorter duration of effect is desired or to mitigate late day side effects.

Methylphenidate, the active ingredient in Daytrana® TDS is a Schedule II controlled substance.

Daytrana® TDS labeling includes, among other things, specific instructions for patch application, removal, disposal, and storage important to the safe and effective use of the drug product.

FDA has recently communicated[1] to Noven approvability concerns the Agency has with respect to patch adhesion performance of an investigational Methylphenidate TDS in a usability study. Specifically, FDA has commented in one communication to Noven that:

> The lack of patch adhesion poses multiple safety risks. . . . .
>
> Efficacy: A transdermal patch is only capable of delivering drug if it is adhered to the skin. Once a patch has detached, drug delivery ends and efficacy wanes rapidly. . . . It is possible that a patch could detach at any time following application . . . . Thus, a patient would derive abbreviated benefit from the patch, and possibly no benefit if the patch detached during the initial two hours of use.
>
> Safety: The primary safety concern related to patch detachment is the potential for other children to be exposed to the drug. In treating [ADHD], the risks associated with Daytrana are carefully weighed against the potential clinical benefit by the prescribing physician. If another child finds the detached patch, that child could apply the patch (accidentally or on purpose), thus exposing the child to all the risks associated with stimulant treatment.

Moreover, FDA has specifically advised Noven that Methylphenidate TDSs "that detach cannot deliver the medication and, thus, are not efficacious. In addition, if a detached patch adheres to another child, that is a **major safety concern** (emphasis added). Even if a patch partially detaches, the patient may not receive an adequate dose."

FDA has also commented to Noven that adequate patch performance in *in vitro* adhesive studies does not negate the need to conduct usability studies, because the Agency has observed performance issues with patches in real world settings. As such, according to FDA, "usability studies conducted under 'real world' conditions are important in assessing Daytrana patch adhesion, especially considering the Daytrana pediatric patient population."[1]

---

[1] Due to the confidential nature of the documents in which these FDA statements are contained, Noven will submit them under separate cover as confidential attachments to this Citizen Petition once FDA has assigned a docket number.

B. FDA's Draft Bioequivalence Guidance and Prior Citizen Petition Response

In July 2010, FDA's Office of Generic Drugs ("OGD") issued a Draft Guidance on Methylphenidate (Docket No. FDA-2007-D-0369) providing guidance to generic drug manufacturers interested in seeking approval of an ANDA for a generic version of Daytrana® TDS. FDA recommends in the draft guidance that prospective ANDA sponsors conduct only two studies to obtain approval: (1) a standard single-dose, fasting, two-treatment, two-period crossover in vivo pharmacokinetic study; and (2) a randomized, evaluator-blinded, in vivo within-subject repeat test skin irritation, sensitization and adhesion study using the 10 mg/9hr strength of Daytrana® TDS. See Draft Guidance on Methylphenidate (July 2010), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf.

Noven submitted a Citizen Petition to FDA in August 2012 requesting that FDA revise its bioequivalence recommendations for generic Daytrana® TDS and refuse to approve any ANDA for a generic version of the RLD unless the applicant, among other things, conducts a usability study "showing that caregivers and patients of all ages are able to appropriately store, apply, wear, and dispose of the drug product under conditions of typical use" as stated in Daytrana® TDS labeling. Noven Citizen Petition, Docket No. FDA-2012-P-0932 (Aug. 24, 2012). FDA denied this aspect of Noven's petition, stating in relevant part:

> We are aware that there have been problems with Daytrana where caregivers and patients are not able to appropriately store, apply, wear, and dispose of the product under the conditions of typical use as stated in the product labeling. These problems include the inability to remove (or difficulty in removing) the release liner from the patch, adhesive transfer to the release liner, accidental exposure of caregivers or parents to methylphenidate when applying the patch to their patients or children, and the application of heat to the patches. Although the scope of the usability issues is wide, the adverse outcomes observed are mainly nonserious in nature or relate to lack of effect, and we disagree with the proposition that a usability study is necessary for ANDAs referencing the Daytrana product.
>
> The labeling for Daytrana already contains considerable information on how to store, apply, wear, and dispose of this transdermal product and because generic products are required to have the same labeling as the RLD (see

> background section above), it is not necessary for ANDA applicants to conduct usability studies. Patients would use a generic version of the methylphenidate transdermal drug product the same way they use Daytrana. You mention that requiring a usability study would be consistent with the feedback that Noven received from FDA related to Daytrana (Petition at 11); we note that our feedback pertained specifically to Daytrana, an NDA product, and is not applicable to ANDAs referencing Daytrana as the RLD. . . . [T]he requirements for an NDA differ from the requirements for an ANDA in that an NDA sponsor must demonstrate safety and efficacy and an ANDA applicant relies on the previous finding of safety and efficacy of the reference product, but must demonstrate that its product is bioequivalent to the RLD. Therefore, we are denying your request to require a usability study for applicants referencing Daytrana.

FDA Citizen Petition Response, Docket No. FDA-2012-P-0932, at 6-7 (Jan. 23, 2013).

C. FDA Should Require ANDA Applicants to Demonstrate Non-inferiority to Daytrana® TDS with Respect to Patch Adhesion Performance

Notably, FDA did not consider the safety and efficacy concerns of patch adhesion performance in their previous denial of Noven's request that ANDA sponsors conduct a usability study and, in contrast, FDA has recently communicated to Noven that new safety and efficacy concerns pertaining to adhesion can emerge in a usability study in a "real world" setting. If the adhesion performance of a Methylphenidate TDS in the intended population in a "real world" setting is different than the RLD, it cannot be assumed that the previous safety and efficacy findings of the RLD would apply, even if bioequivalence is demonstrated in a pharmacokinetic study.

Noven believes that the new concerns conveyed by FDA support, at the very least, the need for FDA to require generic applicants to demonstrate that their proposed Methylphenidate TDS drug product is not inferior to Daytrana® TDS with respect to patch adhesion performance in a usability study. Such a request is entirely consistent with the statutory requirement that a generic applicant demonstrate that its proposed drug product is bioequivalent to the RLD, see 21 U.S.C. § 355(j)(2)(A)(4), and with precedent FDA decisions. See, e.g., FDA Citizen Petition Response, FDA Docket No. 1998P-0434, at 16 (Mar. 17, 2000) ("The Agency's position is that equivalent skin adhesion is a criterion for approval of a generic transdermal product, and FDA will not approve a generic transdermal product that fails this comparison."). As such, FDA should refuse to

approve any ANDA for a generic version of Daytrana® TDS unless and until the sponsor of such application also demonstrates in a usability study conducted in adults, adolescents, and children under "real world" conditions that its proposed generic drug product is not inferior to Daytrana® TDS with respect to patch adhesion performance. This study should be in addition to the bioequivalence with pharmacokinetic endpoints and skin irritation, sensitization and adhesion studies FDA recommends that ANDA sponsors seeking approval for a Methylphenidate TDS should otherwise conduct to obtain approval.

The bioequivalence and skin irritation, sensitization, and adhesion studies required by OGD for a generic Methylphenidate TDS are inadequate for the assessment of adhesion for this type of product: a controlled substance indicated for use in children 6-17 years of age with ADHD. Both of the OGD-recommended studies are conducted in healthy adult volunteers in the clinic, whereas a usability study would include children, adolescents and adults with ADHD in a "real world, naturalistic setting." As such, the OGD-recommended studies may not detect an adhesion issue that would occur in the "real world" with the indicated patient population. This is supported by FDA feedback to Noven regarding the Agency's concerns with patch adhesion, and where FDA identified a number of issues, such as inadequate drug delivery because of patch detachment and inadvertent drug exposure through patch detachment. Thus, concluded FDA, "usability studies conducted under 'real world' conditions are important in addressing Daytrana patch adhesion, especially considering the Daytrana pediatric population."

Given these significant concerns, FDA should require generic Methylphenidate TDS drug applicants to demonstrate in a "real world" setting, and in the indicated pediatric population, that their proposed drug product is not inferior to Daytrana® TDS with respect to patch adhesion.

D. Conclusion

FDA's position is that equivalent skin adhesion is a criterion for approval of a generic transdermal product. The OGD's current standard to assess adhesion, however, is inadequate for Daytrana® TDS, a controlled substance indicated for use in children 6-17 years of age with ADHD. As FDA has recently indicated, it is important that adhesion also be tested under "real world" conditions. In support of the need for usability studies to assess adhesion, FDA has expressed safety and efficacy concerns posed by the lack of adequate adhesion for a Methylphenidate TDS. Accordingly, FDA should refuse to approve any ANDA for this controlled substance unless and until the conditions specified in this Citizen Petition are satisfied. Approving a generic version of Daytrana® TDS

without the data and information specified in this petition showing that such generic version can be safely and effectively used as a therapeutically equivalent version of Daytrana® TDS could jeopardize public health.

III. ENVIRONMENTAL IMPACT

Noven claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

IV. ECONOMIC IMPACT

Information on the economic impact of the action requested by this Citizen Petition will be submitted if requested by FDA.

V. CERTIFICATIONS

Noven certifies that, to the best knowledge and belief of the company, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to Petitioner that are unfavorable to the Petition.

Noven makes the following certification pursuant to FDC Act § 505(q)(1)(H): I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 27, 2013 and November 14, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Noven. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Joel S. Lippman, MD

Joel S. Lippman, M.D., MPH
Executive Vice President & Chief
Medical Officer
Noven Pharmaceuticals, Inc.

From: (212) 682-4420
Marlen Gumny

350 5th Avenue 37th Floor

New York, NY 10118

Origin ID: BICA

FedEx Express

J13201306280326

Ship Date: 23DEC13
ActWgt: 1.0 LB
CAD: 105999537/INET3430

Delivery Address Bar Code

Ref #
Invoice #
PO #
Dept #

SHIP TO: (212) 229-4235 BILL SENDER

Division of Docktes Management
FDA Dep. of Health & Human Services
5630 Fishers Lane
Room 1061 (HFA-305)
ROCKVILLE, MD 20852

TUE - 24 DEC 10:30A
PRIORITY OVERNIGHT

TRK# 0201 7974 8756 1310

20852
MD-US
IAD

EP NSFA

51AG4/99D5/1A9E

After printing this label:
1. Use the 'Print' button on this page to print your label to your laser or inkjet printer.
2. Fold the printed page along the horizontal line.
3. Place label in shipping pouch and affix it to your shipment so that the barcode portion of the label can be read and scanned.

Warning: Use only the printed original label for shipping. Using a photocopy of this label for shipping purposes is fraudulent and could result in additional billing charges, along with the cancellation of your FedEx account number.
Use of this system constitutes your agreement to the service conditions in the current FedEx Service Guide, available on fedex.com.FedEx will not be responsible for any claim in excess of $100 per package, whether the result of loss, damage, delay, non-delivery,misdelivery,or misinformation, unless you declare a higher value, pay an additional charge, document your actual loss and file a timely claim.Limitations found in the current FedEx Service Guide apply. Your right to recover from FedEx for any loss, including intrinsic value of the package, loss of sales, income interest, profit, attorney's fees, costs, and other forms of damage whether direct, incidental,consequential, or special is limited to the greater of $100 or the authorized declared value. Recovery cannot exceed actual documented loss.Maximum for items of extraordinary value is $1,000, e.g. jewelry, precious metals, negotiable instruments and other items listed in our ServiceGuide. Written claims must be filed within strict time limits, see current FedEx Service Guide.