CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-514

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-514

Noven Pharmaceuticals, Inc.
Co-Development Partner Shire Pharmaceuticals, Inc.
Attention: Harris L. Rotman, Ph.D.
725 Chesterbrook Boulevard
Wayne, PA 19087-5637

Dear Dr. Rotman:

Please refer to your new drug application (NDA) dated and received June 27, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Daytrana (methylphenidate) Transdermal System.

We acknowledge receipt of your submissions dated:

June 28, 2005	August 2, 2005	August 25, 2005	November 18, 2005
July 14, 2005	August 5, 2005	September 7, 2005	November 21, 2005
July 25, 2005	August 19, 2005	November 14, 2005	December 15, 2005

The June 28, 2005 submission constituted a complete response to our April 25, 2003 action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies, requests, and other issues:

Specific Safety Issues

Contact Sensitization

We have added to labeling a Warning statement regarding contact sensitization, however, there are questions that remain to be addressed. One in particular is the question of what is the rate of sensitization under conditions of use in the clinic. At the PDAC meeting, you suggested that there might have been a case of sensitization in your clinical program, i.e., patient 31-002 in Study SPD485-303. In your most recent E-Mail communication (12-16-05), however, you have reconsidered this case and now appear to have concluded that this was in fact not a case, and we tend to agree. The difficulty is that patients in your clinical program were not assessed in a manner to definitively identify those who might have developed sensitization, as you did in your provocative sensitization protocol. We believe it will be important to definitively address this question, thus, we ask that you develop a protocol for estimating the risk of sensitization in a clinical setting and commit to conducting this study post-approval. You should consult with your own experts in planning this study, however, you would likely need a large cohort of patients who would be followed carefully to identify those who have developed possible sensitization. This would include patients who have erythema plus some other indication of more serious skin reaction, e.g., edema, papules, or vesicles. Once identified, we would

suggest doing additional testing on these patients to determine if they have a specific sensitivity to methylphenidate. We would be happy to work with you in the design of such a study.

A related question is what might be done to better educate clinicians most likely to be using methylphenidate transdermal system (MTS) in recognizing skin reactions that need further evaluation for possible allergic sensitization. We have proposed language for labeling, however, this issue requires more thought. It is important to have an approach with sufficient sensitivity to detect potential cases but not overly sensitive, because we believe it would not be useful for every instance of mild erythema to be required to have special testing for sensitization. Thus, we ask that you propose a program to educate prescribers in how to efficiently identify potential cases.

Erthema and Irritation Associated with the Use of Methylphenidate Transdermal System (MTS),

At the PDAC meeting, you provided detailed data on the formal assessments of dermal response and discomfort in the placebo-controlled trials, and this was helpful in quantifying the extent of irritation and discomfort associated with the use of MTS. Unfortunately, this information has not been included in your proposed labeling, except in a non-quantitative form in a Precautions subsection "Skin Irritation." We have added a Warning statement to highlight the skin sensitization concern, but we ask that you add a revised "Skin Irritation" section following the adverse events table (Table 3) in our proposed labeling. This section should provide more details of the type provided at the PDAC meeting, so that prescribers are aware that roughly 25-30 % of patients experience some degree of erythema and mild irritation. This section should also mention the possibility of sensitization and what findings would lead one to suspect sensitization (i.e., edema, papules, vesicles, etc), and then refer to the Warnings statement on sensitization.

Adverse Events Stratified by Age

We have observed substantially different exposures to d-methylphenidate in younger and older children treated with methylphenidate transdermal system (MTS), and this raises the question of whether or not adverse event incidence varies in different age groups. Thus, we ask that you provide data on adverse events stratified by age, e.g., 6 to 9 vs. 10 to 12.

Monitoring and Reporting on Abuse, Misuse or Diversion with Methylphenidate Transdermal System (MTS)

- We ask that you agree to submit all serious outcome cases of abuse, misuse, or diversion on an expedited basis (15-day).
- We ask that you agree to summarize in a section of the Periodic Report all cases of abuse, misuse, and diversion regardless of whether an adverse event occurred. Sources of such cases include, but are not limited to, the MTS toll-free line, the Internet Monitoring Program, News/Media monitoring, and your general information phone lines and direct emails to you. In addition, please provide a summary in the Periodic Report of all other surveillance monitoring data (e.g., from Federal Surveys, School/Community Monitoring, etc.).
- Please submit the School/Community Monitoring protocol and data analysis plan for FDA information.
- Please better describe the purpose for the toll-free number, how this purpose would be explained, and where the number would be found by potential users (e.g. professional labeling, patient labeling, supplemental materials, website, and or patch itself). A toll-free number for a

more generally described use, such as "for questions regarding Daytrana please call..." may be more appropriate.

- Please more clearly define the role of the risk management coordinator, a liaison position to interface with the various stakeholders, including method and frequency of reporting data to the FDA.

Proprietary Name

The Division of Medication Errors and Technical Support (DMETS) finds your proposed proprietary name, Daytrana, acceptable; however in your response to this action, the name will be re-evaluated to rule out any objections based upon approval of other proprietary or established names.

Comments on Educational Plan and Patient Package Insert

- You indicate that educational materials will be distributed at doctor's offices and will be available at pharmacies. We ask that you agree to also ensuring to include the information sheet for parents and caregivers that currently appears at the end of the professional labeling in the (10-count and 30-count) cartons or trays of the product to increase the likelihood that it would be received by the parent or caregiver.
- We also have the following suggestions regarding the information sheet:
    - Add a section about how to use the administration chart, which is part of your proposed risk management program.
    - Move the instructions for use to the end of this information sheet. The caregiver should first be informed of important safe use information before being told how to apply the patch to their child.
    - Highlight the importance of the 9-hour wear-time as a separate section or bullet and emphasize that longer wear times may increase side effects.
    - The labeling for the patient should also include clear instructions on how to ensure that the 9 hour recommended wear time for the product is accomplished, e.g., by providing instructions to write down time of application and at the same time "calculate" and write down the removal time.
    - Any other educational materials aimed at patients, parents or caregivers should be written at a 6th-8th grade reading level to enhance the understanding by lower literacy populations.

Miscellaneous Labeling Issues (Package Insert, Patch Label, Pouch Label, and Carton Label)

Trailing Zeroes

We note the use of trailing zeroes when expressing product strengths (e.g., 3.0 mg/hr) throughout the container labels, and carton and insert labeling. The use of terminal zeroes may result in error as decimals are often overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs....the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of

The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as ISMP also list terminal zeroes on their dangerous abbreviations and dose designations list. Revise the labeling so that strengths are expressed without the use of a terminal zero (e.g., 3 mg/hr rather than 3.0 mg/hr).

Patch Label

The patch backing should be revised to include both the proprietary and established name of the drug. This information, as well as the product strength, should be prominent and readable on every patch backing.

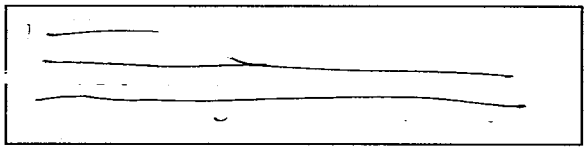
Pouch and Carton Labeling

1. The proprietary and established names should be the most prominent information on the label. Please ensure that the information is prominent and legible and meets 21 CFR 201.10(g)(2). Likewise, we recommend increasing the prominence of the established name.

2. In addition, the green font color of the established name is difficult to read against the white background, and it is difficult to read the blue and white text font against the various pouch color backgrounds. Revise accordingly so that the font is prominent and easy to read.

3. The following bullets pertain to the presentation of the strength:

a. The statement "*nominal dose delivered over 9 hours" is confusing and the term "nominal" is not defined. Additionally, the amount delivered over 9 hours should be the primary expression of strength rather than the milligram amount delivered per hour. We recommend deleting the statement "*nominal dose delivered over 9 hours" and revise the strength to read "[redacted]" and "[redacted]" should appear as the secondary expression of strength. For example,



b. The statement "Each system (patch) contains XX mg of methylphenidate" should also be increased in prominence, by increasing the size of the statement.

4. In addition, we recommend that the warning statement "Patch should not be applied longer than 9 hours" be placed on the primary display panel.

5. The four color blocks located to the left of the proprietary name distracts from what should be the most prominent information on the label (proprietary name, established name, and product strength). We recommend removing the graphic design from the principal display panel.

6. The net quantity should be revised to read "Contains: 1 patch".

7. We recommend relocating the Schedule II controlled substance symbol as the drug name may be misinterpreted as Daytrana "C".

Postmarketing Commitments

We ask that you commit to conducting a study post-approval to better estimate the risk of contact sensitization associated with the use of methylphenidate transdermal system (MTS) in a clinical setting. Important details to consider in designing such a study are provided under the heading "Specific Safety Issues, Contact Sensitization." This commitment must be fulfilled within 2 years from the date of approval of this application.

Pediatric Research Equity Act (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 2 to 5 years and deferring pediatric studies for ages 13 to 17 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of INDICATION in pediatric patients ages 13 to 17 years.
   Final Report Submission: 3 years from the date of approval of this application.

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

Labeling (Package Insert)

Accompanying this letter (Enclosure) is the Agency's proposal for the labeling of methylphenidate transdermal system. We have used, as our base labeling, the labeling provided by you on November 15, 2005.

You must submit revised, draft labeling for methylphenidate transdermal system as part of your response to this letter. If you propose revisions to the attached labeling, we ask that you provide a highlighted or marked-up copy that shows all changes and identify which version of labeling was used as the base document. This type of labeling document will facilitate the review.

In addition, we request that you provide a line-by-line comparison of your proposed labeling as compared to the approved Ritalin Tablet labeling. We suggest that this labeling comparison be a highlighted or marked-up document where Ritalin Tablet labeling is used as the base document. The goal of this comparison is to provide a document that permits us to easily identify (word for word) precisely how your methylphenidate transdermal system labeling differs from Ritalin Tablet labeling.

Lastly, if additional information relating to the safety or effectiveness of this drug becomes available, further revision of the labeling may be required.

Safety Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Richardae Araojo, Pharm.D., Regulatory Project Manager, at (301) 796-1152.

Sincerely,
{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

33 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Thomas Laughren
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