

566320



Food and Drug Administration
555 Winderley Pl., Ste. 200
Maitland, FL 32751

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

FLA-08-05

January 4, 2008

Robert C. Strauss
President, CEO, and Chairman
Noven Pharmaceuticals, Inc.
11960 SW 144th Street
Miami, Florida 33186

Dear Mr. Strauss:

An inspection of your facility located at the above address which manufactures prescription transdermal drug products for human use was conducted on June 11-14, 19-22, 25-26, 28-29, and July 2, 2007 by the U.S. Food and Drug Administration (FDA). The inspection revealed that your DaytranaTM methylphenidate TD patches are adulterated within the meaning of Section 501 (a)(2)(B)) [21 U.S.C. § 351(a)(2)(B)] of the Federal Food, Drug, and Cosmetic Act (Act) in that it is a drug product and the methods used in, or the facilities or controls used for, its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with Current Good Manufacturing Practices (cGMP) regulations for drugs specified in Title 21, Code of Federal Regulations (CFR), Part 211.

The violations observed during our inspection include, but are not limited to, the following:

1. Failure to establish scientifically sound and appropriate specifications, standards and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity, as required by 21 CFR § 211.160(b). For example: A liner release force specification had not been established for DaytranaTM methylphenidate TD patches at the time of the inspection.
2. Failure to assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use by establishing an expiration date required by 21 CFR § 211.137(a) as determined by appropriate stability testing. Specifically, you have no data to assure that the new release liner [REDACTED] used to manufacture your DaytranaTM patches will have acceptable release characteristics throughout the labeled 24 month expiry period.

We acknowledge your written response dated July 23, 2007, and update response dated October 16, 2007. More information about your actions is necessary before we can consider your response adequate. Also, we remain concerned that the underlying system problems resulting in the violations have not been fully addressed.

- A. **Item 1**- Failure to establish scientifically sound and appropriate specifications, standards and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity, as required by 21 CFR § 211.160(b). [FDA483 Observation 2a] The inspection determined that you obtained liner peel force data during early stability testing of the Daytrana™ patches, e.g., protocols 00-04, 00-09, 00-10, 00-16, 02-02, 03-19, and 04-13. For example, the results of protocols 00-04 revealed that the liner peel force values varied from [REDACTED] to [REDACTED] grams. Despite such results, there was no documentation of the evaluation of the recorded liner release values and no justification for not establishing a liner release specification for commercial product.

The lower the peel force necessary to remove the liner lowers the likelihood of adhesive transfer. Liner release without adhesive transfer is a significant quality attribute of the Daytrana™ patch. The patient must be able to apply the product with the drug/adhesive matrix intact in order to receive the therapeutic effect. Your company had information and data from the development and clinical study phase of this product, i.e., the stability studies referenced above, which showed variance in the liner release peel forces exhibited by the Daytrana™ patch. More focused study of this issue and follow up at the time that the results of the early stability test results were obtained may have allowed you to establish a measurable, meaningful liner release force specification and acceptable release force profile over the product expiry period.

Your first response dated July 23, 2007 described mechanical problems during stability testing in 2002. You stated that the [REDACTED] (stability report dated May 2002) included the following statement:

"It is noted that the stability protocol called for evaluation of Peel from Release Liner. During this stability, revision to the sample preparation was required due to failure of the test leader strip (detached from sample) preventing the completion of the test (no value obtained). As such, evaluation of the data will not be performed until such time that an adequate database generated by the modified procedure is available."

Please explain why your firm has not, since the time of the [REDACTED], developed an "adequate database" using a "modified procedure." Please provide the peel force data obtained during the execution of stability protocols 00-04, 00-09, 00-10, 00-16, 02-02, 03-19, and 04-13, and your evaluation of that data. In light of the lack of evaluation of the Daytrana™ patch liner release values, we are concerned about your firm's global system(s) for gathering and analyzing data from clinical lot manufacturing which may impact critical quality attributes of other transdermal patch and transoral products you manufacture. Failure to evaluate important data from clinical lots is significant; the

results can provide key inputs to the product design and contribute to establishing the quality attributes of the future commercial product. Please address measures you have taken or will take to prevent such an omission with other transdermal patch and transoral products you manufacture.

- B. Your October 16, 2007 response provided a mechanical peel force release specification and indicated that all lots packaged since August 28, 2007 would be tested and released to distribution according to this new specification.

We have reviewed your specification, Test Method [REDACTED], *Determination of the Force to remove Methylphenidate Transdermal Systems from Release Liners*, dated October 12, 2007, and the Validation Report [REDACTED] dated October 12, 2007. Please respond to the following questions.

1. Please provide the rationale and summary data set upon which this specification is based.
 - Clarify the units of measure for this specification.
 - Identify the age of the lots included in the evaluation.
 - Discuss why the specification is established as a difference between two values as opposed to an absolute value.
 - Discuss the relevance of this specification to the commercially distributed product.
2. Your response does not indicate that this specification has been incorporated into your stability protocol. Please explain how you have assured proper performance through the expiry period. If you have not developed an acceptable peel force profile over the expiry period of the product, please provide your rationale.
3. We understand that accelerated conditions and testing may not be predictive of this quality problem. Please explain the rationale for using test values from a 1 month accelerated sample in this test method.
4. The test method [REDACTED] *Determination of the Force to remove Methylphenidate Transdermal Systems from Release Liners*, dated October 12, 2007, requires that sample preparation includes conditioning the samples at [REDACTED] and [REDACTED] for [REDACTED] hours prior to testing. Please explain the purpose of this conditioning.
5. The validation report for test method [REDACTED] shows that only the largest patch size, 37.5 cm², was used in the validation. Please address its relevance to the other size patches.
6. You stated that all lots packaged since August 28, 2007, will be tested and released for distribution according to this new specification. Please explain the significance of August 28, 2007.
7. Please address how you will handle product if this specification is not met.

Item 2- Failure to assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use by establishing an expiration date required by 21 CFR § 211.137(a).

- A. Your firm has identified and confirmed a significant quality problem, i.e., tight release and/or adhesive transfer, with your Daytrana™ patches. Although your firm has investigated and continues to investigate the exact root cause(s) of this quality problem, you have determined, at least, that the phenomenon is age related. Regarding liner release characteristics, you have also determined that accelerated stability conditions and subsequent testing may not be predictive of real time performance. Nevertheless, based on accelerated stability studies, you placed a 24 month expiration date on the Daytrana™ products currently on the market, i.e., those manufactured with the [REDACTED] release liner.

The change from the [REDACTED] to the [REDACTED] release liner was intended to make the liner easier to remove by the users. Your justification for the change was based on lower initial release peel force results (as compared to the [REDACTED] results) and three months of real time stability data which show lower peel force results than those obtained from product made with [REDACTED] liners. Also, you have submitted six month real time data (September 14, 2007 Amendment to the [REDACTED] Release Liner [REDACTED] and you have deemed those peel force values to be acceptable. We understand that nine month real time data will be available shortly.

Although you have submitted the three-month and six-month real time stability data, you have not provided information or data which assures that product manufactured with the [REDACTED] release liner will continue to have acceptable liner release characteristics during the entire 24 month expiry period. Please explain scientifically why you believe that 24 month old product will exhibit acceptable liner release characteristics.

You emphasized in your response to the FDA483 that the product has met all [REDACTED] specifications. However, your product has exhibited a unique quality issue not captured in a release or stability specification. It is your responsibility to assure that appropriate stability studies, using reliable, meaningful and specific test methods are conducted to establish a meaningful expiry period. There may be factors involved which are detrimental to product quality without affecting its strength.

Also, please explain your plan to address product currently on the market if the [REDACTED] liner does not correct these problems with tight release and adhesive transfer.

Additional comments and requests regarding your July 23, 2007 and October 16, 2007 written responses to the FDA483 issued July 2, 2007

- A. You stated in your July 23, 2007 written response that the "tight release" and/or "adhesive transfer" problem has no safety or efficacy implications for the patient. However, we are not convinced this conclusion can be made at this point based on the nature of the ongoing investigation(s) and possible root causes being explored.

It is clear from the inspectional information, your written response dated July 23, 2007, as well as your [REDACTED] dated September 14, 2007 [REDACTED] that the tight release and adhesive transfer problem is still under investigation.

We understand that you are investigating possible changes within the adhesive matrix over time and/or migration of the methylphenidate toward the liner surface. Other possibilities you are examining include some type of interaction between the liner and the adhesive drug matrix. We are concerned that such changes, if occurring, could change the diffusion characteristics of the drug. Sub-optimal therapeutic action, control of symptoms or atypical adverse reactions could be possible consequences to the patients. Unless and until all the factors causing or contributing to the problem of tight release and adhesive transfer are understood, we do not agree with your assertion that there are no safety or efficacy implications secondary to this quality problem.

Please comment and submit any risk analysis or evaluation as they relate to the potential root causes. Please update us regarding the status of your investigation into the root cause(s) of the tight release and adhesive transfer problem.

- B. Your October 16, 2007, response indicates that SOPs have been revised or created to address FDA483 Observations 1, 2b, 3, 4, 6a, and 8. With regard to the [REDACTED] component of the Daytrana™ patch (FDA483 Observation 2b), please provide the revised [REDACTED] specification. You state that a historical review of [REDACTED] received was conducted to justify the current viscosity range. We understand that some lots of [REDACTED] were implicated in finished product tight release problems and complaints. Please explain why the viscosity of past receipts (lots) of [REDACTED] should be the basis for establishing an in-house specification for this component. We ask this in light of your investigation which was (or is still) evaluating the contribution of the various properties of [REDACTED] (viscosity, percent solids, and residual monomers) finished product tight release and adhesive transfer problems. Please provide your rationale, the lots of [REDACTED] used in the historical review, summary data, and your conclusions.
- C. Regarding your response to FDA483 Observation 3, we will take this opportunity to point out an important connection between FDA's application review and the cGMP program, particularly as it relates to the cGMP requirements under 21 CFR § 211.192, and 21 CFR § 211.180(e). You have indicated that your Daytrana™ patches met specifications when tested. The problems and issues experienced by Daytrana™ users demonstrates how the investigation of and follow-up to complaints can lead to a specification change under 21 CFR § 211.180(e). Under 211.180(e),

Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

(1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.

(2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under 211.192 for each drug product."

(emphasis added). This requirement establishes the necessity of deliberate, systemic monitoring of product experience and the appropriate timely response to the information gathered. It is an essential element of an effective quality management system.

- D. Your responses and corrective actions regarding the remaining observations appear to be adequate and will be verified during the next inspection.

As an advisory note, we are including a comment about your company's responsibilities regarding customer complaints and follow-up. Since the inspection concluded, the agency has become aware that [REDACTED] distributor of Daytrana™, has provided a mechanism via a website for patients to obtain replacement patches if they experience a problem with Daytrana™. Although FDA is not familiar with the details of this program, we understand that patients can download a coupon or card that they can present to their pharmacists to obtain replacement patches. Please be advised that when product is dispensed through this program because the consumer had a problem with Daytrana™ [REDACTED] is required to investigate the failure of Daytrana™. 21 CFR 211.198 [REDACTED] should inform your company of the complaints received so that they can be properly investigated. Your company is then obligated under 21 CFR § 211.198, Complaint Files, to evaluate the report for a possible failure of the drug to meet any of its specifications and determine the need for an investigation.

The issues and violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to conduct a comprehensive audit of your facility and operations and assure compliance with all requirements of federal law and FDA regulations.

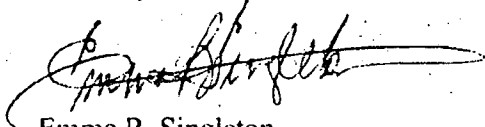
You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including seizure and/or injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A reinspection may be necessary.

Please notify this office in writing within fifteen (15) working days of receipt of this letter of the specific steps you have taken to correct these violations and to prevent the recurrence of similar violations in the future. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If corrective action cannot be completed within fifteen working days, state the reason for the delay and the time within which corrections will be completed. If you no longer manufacture or market any products, your

response should so indicate, including the reasons for, and the date on which, you ceased production.

Your reply should be directed to Brant M. Schroeder, Compliance Officer, U.S. Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, Florida 32751. If you have any questions regarding any issue in this letter, please contact Mr. Schroeder at (407) 475-4763.

Sincerely,



Emma R. Singleton
Director, Florida District

cc:

