U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Noven Pharmaceuticals, Inc. 8/25/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Los Angeles District

19701 Fairchild
Irvine, California 92612-2506
Telephone (949) 608-2900
Fax (949) 608-4415

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

August 25, 2011 W/L 54-11

Maurice J. Miller
Executive Director of the Carlsbad Operations
Noven Pharmaceuticals, Inc.
2732 Loker Avenue West
Carlsbad, CA 92010-6603

Dear Mr. Miller:

During our January 31, 2011 to February 14, 2011 inspection of your pharmaceutical manufacturing facility, Noven Pharmaceuticals, Inc., located at 2732 Loker Avenue West, Carlsbad, California, investigator(s) from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response of February 28, 2011, and note that it lacks sufficient corrective actions.

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

1. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and/or purity they purport or are represented to possess [21 C.F.R. § 211.100(a)]. For example:

a. The process validation conducted for Fentanyl Transdermal System is inadequate in that your final process validation report failed to include and evaluate the impact of all the combined deviations that occurred during process validation. The report failed to include such deviations as (1) the discovery of brown particles in a laboratory sample of Fentanyl Adhesive Mass Solution (FAMS), (2) aborting the cutting/packaging operations during the first process validation lot due to a broken cutting and packing machine, and (3) setting of the IR gauge value below specification during the coating process for the first validation lot.

In your response, your firm states that the deviations were not considered to have an impact on validation at the time the validation report was prepared. Your response, however, is inadequate because you fail to provide any supporting evidence to substantiate this claim. Your firm's "Technical Review of Process Validation for Fentanyl Transdermal System" is inadequate because the contents are broad, lacks any supporting raw data, and is unclear as to what specific elements, lot numbers, and records were reviewed.

b. Your firm failed to adequately validate the Fentanyl Adhesive Mass Solution (FAMS) mixing process to assure blend uniformity after a modification was made to raw material **(b)(4)** specification. Your firm conducted a revalidation of the FAMS mixing process, but failed to include the Fentanyl active pharmaceutical ingredient (API) in the validation.

In your response, your firm states that the API is substituted with a placebo to conduct feasibility or investigative studies for troubleshooting purposes, and that you believed the process (without Fentanyl) would be appropriate in this instance. Your response, however, is not adequate because you have yet to provide any evidence to support your claims that the studies, including the use of a placebo, demonstrate robustness of the actual mixing process. We acknowledge that your firm will revalidate FAMS manufacturing process. However, your firm has not provided a completion date or sufficient details of your revalidation plan.

2. Your firm failed to ensure that the automatic, mechanical, or electronic equipment, or other types of equipment including computers or related systems, will perform a function satisfactorily [21 C.F.R. § 211.68(a)]. For example:

a. The initial qualification for the **(b)(4)** Cutting and Packing Machine, Model **(b)(4)** was completed on June 7, 2007. Approximately 25 major and minor changes were implemented between June 14, 2007, and July 15, 2010, before your approval of the re-qualification report for equipment **(b)(4).**

In your response, your firm states that **(b)(4)** Cutting and Packing Machine is a custom-made unit. The unit consists of subunits that perform functions

independently of one another and that modification to one subunit does not necessarily adversely impact other subunits or the equipment as a whole. You added that the requalification requirement was documented in each approved Change Control. Your response, however, is inadequate because you have neither provided documentation to demonstrate your claims of independently functioning subunits, nor have you provided your rationale why each equipment change did not necessitate a re-qualification and/or a re-validation of the **(b)(4)** Cutting and Packing machine.

In addition, your firm states that further system enhancement will be made to validation procedures. However, it is not clear as to your estimated completion date because the content of your proposal entitled, "**(b)(4)**," is so broad. Furthermore, we are not able to evaluate the adequacy of your corrective actions without sufficient details of your proposed enhancement.

b. You failed to adequately qualify the **(b)(4)**, to detect missing patches.

For each product size of 25/50/75/100 mcg/hr dosage strengths, only forty (**(b)(4)**) samples were tested through the checkweigher to qualifying the equipment as a subsystem. There is no statistical basis for the selected sampling size. Furthermore, checkweigher **(b)(4)** was not validated in conjunction with the **(b)(4)** equipment using appropriate samples that represented the approximate batch sizes of **(b)(4)** units (25 mcg/hr), **(b)(4)** units (50 mcg/hr), **(b)(4)** units (75 mcg/hr), and **(b)(4)** units (100mcg/hr).

In your response, your firm states that the function to reject under-weight and over-weight sample is tested every month per SOP **(b)(4)** and that this procedure will be revised to include a functionality test at the beginning, after each break (if applicable), and end of the commercial production run to verify further control over the system. Your response, however, is inadequate because although you may have enhanced the Quality Control verification aspect of the checkweighing equipment, you did not address how you will correct the qualification deficiency as addressed above.

In addition, you firm states that "[a]s is industry standard with checkweigher qualification studies, the purpose is to seed the run with a known number of rejects and recover 100% of said rejects at the end of the study." We disagree with your assessment because you did not provide a sound scientific rationale for selecting a sample size of **(b)(4)**. Your manufacturing process has variability that affects your outputs. The number of samples chosen for the Performance Qualification needs to reflect the variability in your manufacturing process. Also, your multiple customer complaints of missing patches serve as evidence that your checkweigher may not be adequately qualified to ensure your missing patches can be identified consistently and reliably.

3. Your firm has not thoroughly investigated any unexplained discrepancy or the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192]. For example:

a. Your firm has failed to conduct thorough investigations into the defects found in pouches for Fentanyl Transdermal System batches during the cutting and packaging operations with the **(b)(4)** Cutting and Packing Machine, Model **(b)(4)**. Your firm failed to determine the root cause(s) even though you installed a Primary Packaged Product Inspection Camera and implemented a 100% batch visual inspection.

In your response, your firm states that you will improve the investigation process by assessing all closed investigations within the last six months as well as enhancing site procedures. Your response, however, is inadequate because you fail to provide any details of your proposed enhancements. Additionally, your firm has not provided any steps and/or corrective actions to resolve the deviation described above.

b. Your firm has failed to conduct thorough investigations of customer complaints resulting from the missing patches from pouches of the Fentanyl Transdermal System. Your firm failed to determine the root cause(s) and/or initiate corrective and preventive actions as required by your Standard Operating Procedure, , titled, "," Revision **(b)(4)**.

In your response, your firm states that the various complaints (i.e., **(b)(4)**) are pending and still under investigation. Your response is inadequate because you received some of the complaints as early as September, 21, 2010, and there is no evidence to demonstrate that your firm has attempted to conduct a root cause analysis or tried to obtain the investigational report from your distribution partner. Additionally, you stated that your SOP, **(b)(4)**, will be enhanced, but you have not provided a revised SOP for our evaluation.

4. Your firm has failed to exercise appropriate controls over computer or related systems to assure that changes in master production and control records, or other records, are instituted only by authorized personnel [21 C.F.R § 211.68(b)].

For example, your firm has failed to periodically conduct back-up procedures for the **(b)(4)** Server, Equipment **(b)(4)** (Building **(b)(4)**, Room **(b)(4)**) since August 2010. This server was used to store, back-up, and/or archive raw test data from computer systems (Software: **(b)(4)**) controlling and monitoring **(b)(4)** High-performance liquid chromatography (HPLC) systems in accordance to SOP, **(b)(4)**, titled, "**(b)(4)**." During the inspection, the **(b)(4)** server was observed as being tagged out-of-service since February 2009.

In your response, your firm states that you have revised your procedure to include the implementation and installation of qualified **(b)(4)** backup software on **(b)(4)** server to allow for remote backup. Your response, however, is inadequate because you fail to adequately address whether you were able to recover the critical data not backed-up between August 2010 and when you first implemented the daily backup process. Your firm has yet to indicate whether HPLC raw data records could be retrieved for the duration of time that the **(b)(4)** server was not backing-up the HPLC system data.

5. Your firm has failed to determine actual yield and percentages of theoretical yield at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product [21 C.F.R § 211.103].

For example, your firm has failed to determine theoretical yields at appropriate phases of manufacturing based on statistical rationale and/or historical data. For Fentanyl Transdermal System (25/50/75/100 mcg/hr dosage strengths) Change Control #**(b)(4)**, your firm changed the theoretical yield from **(b)(4)** to **(b)(4)** for the cutting and packaging operation using only developmental process validation and engineering lots instead of historical data of batches manufactured during the 2009 – 2010 period.

In your response, your firm states that you will establish a plan to revisit the current yield specifications while continuing to collect data over the next six months to ensure adequate data for establishing statistically relevant yield specifications throughout the appropriate phases of manufacturing. Your response is inadequate because you have not provided sufficient details of your plan including the specified types of data to be collected, dosage type, and "appropriate phases" of manufacturing. In addition, your firm has not provided a rationale for collecting only six additional months of data and how that will be statistically relevant to your product/process.

The violations cited in this letter are not intended to be an all-inclusive statement 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 and the occurrence of other violations. It is your responsibility to 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, without limitation, seizure and 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 drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture of distribute any of the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address:

Blake Bevill
Director, Compliance Branch
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2506

If you have questions regarding this letter, please contact Ms. Mei-Chen (Jessica) Mu, Compliance Officer at 949-608-4477.

Sincerely,
/S/
Alonza E. Cruse
District Director

Cc: Ingeborg Small, Branch Chief
California Department of Public Health
Food and Drug Branch
1500 Capitol Avenue, MS-7602
P.O. Box 997413
Sacramento, CA 95899-7413

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