Inspections, Compliance, Enforcement, and Criminal Investigations

AVEVA Drug Delivery Systems, Inc. 5/21/10

Department of Health and Human Services

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

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

FLA-10-19

May 21, 2010

Hiroyuki Watanabe
Chief Executive Officer
AVEVA Drug Delivery Systems, Inc.
3250 Commerce Pkwy.
Miramar, FL 33025-3907

Dear Mr. Watanabe:

During our October 22, 2009 through December 4, 2009 inspection of your pharmaceutical manufacturing facility, AVEVA Drug Delivery Systems, Inc., located at 3250 Commerce Pkwy., Miramar, Florida, 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 reviewed your firm's response of December 21, 2009, 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. § 211.10(a)].

For example, your firm conducts **(b)(4)** tests at a vacuum of **(b)(4)** of **(b)(4)** in accordance with STP No.901. However, on September 30, 2009, your R&D department concluded that a vacuum of **(b)(4)** is more appropriate to determine the seal quality of the pouchstock.

We acknowledge that your firm revised STP No. 901 to indicate that **(b)(4)** testing will be conducted at a vacuum of **(b)(4).** However, you have not adequately demonstrated that a vacuum of **(b)(4)** is sufficient to assure accuracy of the seal integrity tests for your drug products. We also acknowledge that your firm is qualifying the **(b)(4)** Test System. However, the instrument test methods are under development and you have not provided a timeline for implementation.

2. Your firm has not thoroughly investigated 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 failed to conduct an Out-of-Specification (OOS) investigation in accordance with your SOP 2.040, Investigation of OOS Test Results for Pharmaceutical Products. Potency results for PC160 Clonidine Adhesive Laminate, Material No. 4000253, Batch
No. 0000037305 ranged from **(b)(4)** (spec: 90.0 - 110.0% **(b)(4)**). Your quality unit released the batch on December 12, 2008 for the next stage of manufacturing with instructions to reject the affected areas during the "finishing" of the adhesive laminate. Your firm did not determine a root-cause for the OOS results, and did not investigate other batches that may have been associated with potency nonconformance.

Your response states that you opened Investigation T-181 and you provided a January 12, 2010 completion date.

However, you have not provided the results of your investigation into the root-cause for the OOS test results for batch No. 0000037305, or the T-181 investigation. Your firm should not rely on intervention to reject appropriate sections of the adhesive roll. Acceptable assurance of quality can not be inspected into a batch or replace the need for a robust process. Your investigation needs to explain the correlation between excessive potency failure and adhesive roll laminate properties. For example, appropriate limits need to be established to assure the rejection of defective adhesive laminate rolls.

b) Your firm failed to conduct an investigation into the cause(s) of 3 to 5% voided areas (areas without adhesive) identified during the packaging process of PC160 Clonidine TDS patches, Material No. 49884-776-86, Batch No. 0000037728. Your firm did not investigate other batches that may have been associated with lack of adhesion, and did not implement any corrective action.

Your response states that the Quality Complaint Investigator(s) did not adequately follow-up on the product release summary. These internal oversights notwithstanding, your firm's response does not address the root-cause of the product nonconformance. Accordingly, your firm received 570 complaints for the period August 2009 through October 2009 documented as "Adhesion (won't stick or lifts)" for the PC160 Clonidine TDS products. You have not provided results of any investigation, or any corrective and/or preventive action for this serious nonconformance.

3. Your firm failed to retest or reexamine components, as appropriate, for identity, strength, quality, and purity and your quality control unit failed to approve or reject components. [21 C.F.R. § 211.87].

For example, your firm assigns **(b)(4)** expiration dates to pouchstock material including Material No. 3001230, and Material No. 4001082, used in the manufacture of OTC Nicotine TDS. Stability data does not support the **(b)(4)** expiration date. Moreover, the manufacturer/supplier established an expiration date of **(b)(4)**.

Your response states that you opened Investigation T-154 and you provided a January 15, 2010 completion date. However, you have not provided the results of your investigation and corrective actions. This information, and potential impact on any marketed lots should be included in your response to this letter.

4. Your firm has not followed written procedures describing the handling of all written and oral complaints regarding a drug product [21 C.F.R. § 211.198(a)].

For example, your firm failed to follow your SOP 1.128, Product Complaints, and Adverse Events Administration, in that:

a) Your firm received 45 complaints including Product Complaint Nos. 20092260, 20092265, and 20092902 for OTC Nicotine TDS 21mg/24 Hrs, Batch No. 0000038112 involving adhesion failures. As required by your Sop, your firm failed to conduct a variance investigation when the number of complaints exceeded the alert limit of "**(b)(4)** to determine the root cause for the high rate of non-adhesion complaints. Your firm also failed to investigate other batches that may have been associated with adhesion failures.

Your response states that you opened investigation T-186 and you provided a January 12, 2010 completion date. You have not provided the results your investigation of the non-adhesion complaints, or the scientific justification of your **(b)(4)** limit.

b) Your firm failed to complete the investigations and close complaint files including Product Complaint Nos. 20092126 and 20092130 for OTC Nicotine TDS 21mg/24 Hrs, Batch No. 0000037648 involving adhesion failures. These complaints remained opened for over 30 business days without justification for the delay, and investigation were completed only after discrepancies were discovered during the inspection.

Your response states that you opened Investigation T-165 and you provided a January 29, 2010 completion date. You have not provided the results of the investigation and this is a repeat observation from the July 2008 inspection.

This is a repeat observation from the July 2008 inspection.

5. Your firm failed to reject any lot of components that did not meet the appropriate written specification for identity, strength, quality, and purity [21 CFR § 211.84(e)].

For example, your firm failed to quarantine, or reject pouchstock (Material No. 3001230), Batch No. 133892 which was used in the manufacture of OTC Nicotine TDS after encountering multiple occurrences of pouchstock delamination that resulted in the issuance of 15 Substandard Material Reports between June and August 2009. Multiple rolls of this batch of pouchstock material remained available for use in production while the investigation (T-064) was ongoing.

Your response indicated that your firm closed Investigation T-064 as of January 15, 2010. However, you have not provided the results of Investigation T-064, and your response does not address actions taken by your firm to remove pouchstock from use and ensure that delaminated material under investigation is withheld from use.

6. Your firm failed to check the accuracy of the input to and output from the computer or related systems of formulas or other records or data and establish the degree and frequency of input/output verifications [21 CFR § 211.68(b)].

For example, the performance qualification of your **(b)(4)** system software (Validation No. 4000-03-PQ-0002) failed to include verification of the expiration date calculations in the **(b)(4)** system. In addition, there is no established degree and frequency of performing the verification. Discrepancy reports have documented that product labeling with incorrect expiration dates have been created and issued for use.

Your response states that you opened Investigation T-139 and you provide a January 29, 2010 through February 26, 2010 completion timeline. You have not provided a response to correct this violation and establish a corrective action

plan to assure that computer systems are properly qualified.

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 or distribute OTC Nicotine TDS, Fentanyl TDS, or Clonidine TDS, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the attention of Salvatore N. Randazzo, Compliance Officer at the following address:

U.S. Food and Drug Administration
Florida District Office
555 Winderley Place, Suite 200
Maitland, Florida 32751

Sincerely,

/s/

Emma R. Singleton
Florida District Director

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