98-028279

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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Warning Letter

FEDERAL EXPRESS
SEP 24 1999

No. 320-99-07

Mr. Henri Schiller
President and Director General
Specialties Septodont
58. rue du Pont de Creteil
94100 Saint Maur Des Fosses, France

Dear Mr. Schiller:

This is regarding an inspection of your sterile pharmaceutical manufacturing facility in St. Maur Des Fosses, France, by Investigator Richard Friedman, and Microbiologist Raymond T. Oji, of the Food and Drug Administration, during the period of April 26-30, 1999. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations in the manufacture of [ ] sterilized pharmaceutical finished products. The deviations were presented to you, on an Inspectional Observations form FDA-483 at the close of the inspection. These CGMP deviations cause your sterile pharmaceutical products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act.

We have completed our review of your company's response letters to the FDA-483 observations dated, May 21, 1999, June 30, 1999 and July 30,1999. We note that many corrections were implemented or will soon be implemented. However, we still have the following concerns regarding the most significant observations:

Failure Investigations

1. Investigations of the failure of components and drug products to meet specifications were deficient in that failures are not thoroughly investigated, documented and corrected within appropriate time frames. For example:

   a. There were 10 endotoxin failures at the WFI compounding point-of-use which occurred during a 25 month period. Actions to determine the root cause of repeated failures and corrective measures to preclude contamination were not implemented.
   b. Autoclave charts included temperatures below those required by the approved application (ANDA) and master batch records for much of the cycle. There was no investigation of this deviation.
   c. Failure to investigate excessive rejections for visual attributes during production runs.

The previous inspection on February 17-21, 1997 disclosed similar WFI endotoxin failures for parenteral compounding water. Your current response fails to indicate the cause of the endotoxin contamination, and no corrective action was taken to avoid recurrence. Your correction plan is to conduct water endotoxin testing before each usage rather than to find and correct the cause of contamination, then validate the

process. Continuing to use WFI from an unvalidated system and from a system which produces periodic failures is unacceptable.

Your response and corrective action for items 1.b and 1.c appear adequate. However, conducting investigations, evaluating product quality, and implementing corrective actions after distribution of a product is not appropriate. Corrections must be implemented prior to release. Please provide documentation that batches imported into the U.S. were not affected by the practice described above in 1.b.

Production Water Systems

2. The plumbing system included defects that could contribute contamination to the drug product. For example:

   a. There were multiple significant design deficiencies such as dead legs of various lengths, throughout the WFI system.
   b. There were no piping and instrumental diagrams for the WFI or purified water system.
   c. WFI frequently fails conductivity due to system shut down.
   d. No written procedures governing change frequency and sanitization of lengthy disposable tubing, which provided WFI for compounding ,were available.

The design deficiencies identified in this observation were addressed in your 5/21/99 and June 6, 1999 responses. Your corrections consisted of remedial actions to a poorly designed water system. This response is deficient in that it did not include the corrective action plan for the water system, or a monitoring (microbial/chemical) program along with the test results. Further, no documentation was provided demonstrating effectiveness of the corrections or system validation.

Your 7/30/99 response mentions redesign and improvement to the water and clean steam systems. However, this response did not provide details of your plans for monitoring the water and clean steam system while the systems are being validated. Please provide the water system diagrams (P&ID), further details regarding the corrections planned, the current validation status of the systems, the microbial and chemical monitoring plans and procedures, along with their results. Furthermore, continuing to produce batches for the U.S. market with a water system that is not validated, is not acceptable.

Batch Production and Control Records

3. Batch production and control records were deficient in that they did not include complete information relating the production and control of each batch.

   a. Batch records lacked specificity necessary to ensure that the process is performed in the same manner for each batch produced. Batch records lacked the order of ingredient addition, whether each ingredient is dissolved, fill weight, pH adjustment, quantities of loss from defects.
   b. Batch records lacked a requirement to record and reconcile the number of defects during final (visual) inspection.

Our previous inspection on February 17-20, 1997 disclosed a similar lack of specificity in batch records. The current written responses and discussions regarding these deficiencies indicate your firm is initiating satisfactory corrective action. However, the response failed to include copies of batch production records showing correction of the items mentioned on the FDA-483. Please provide copies of batch records with the modifications, which correct these deficiencies.

Manufacturing Process Control

4. Inadequate validation/qualification of production processes and controls:

a. There was no written program for validation of manufacturing processes or any validation studies for several products manufactured for the U.S. market.
b. Failure to validate the extended re-use period of the [ ] filters used for many different injectable product formulations and batches. Validation rinse data was inadequate to support that ingredient residue from the previous batch are removed.
c. The tank sterilization procedure failed to establish time limitations on how long the compounding/storage tank can be held following [ ] cleaning, washing, and the start of filtration. Tanks are not dried and are left open for an unrestricted time following sterilization.
d. Failure to establish the microbial quality of purified water re-cycled repeatedly within a given production day for moist heat sterilization and cooling of cartridges following the cycle. The autoclave's door remains open between cycles exposing stagnant water to possible contamination.
e. Inadequate container closure integrity qualification using fluorescent dye. There was no validation of the method performed to determine whether the dye in the concentration used would be detectable in the container using UV light.
f. No specification, beyond which investigation is mandated, was established for total defect level or critical defects regarding visual quality attributes.
g. There was no manufacturing specification established for uniformity of fill volume for any of the injectable products.

Our previous inspection on February 17-20,1997 disclosed a similar lack of validation of the washing step to demonstrate removal of endotoxin from plungers. Your current written response regarding your comprehensive validation program is encouraging, however, it is not completed. While your products have been manufactured for several years, no studies have been performed to evaluate critical process steps for reproducibility. Continuing to manufacture drug products for the U.S. market with processes that have not been validated is not acceptable. Please provide the current status of validation for those processes producing drug products for the U.S. market.

Your response to 4.b. failed to ensure that products shipped to the U.S. market do not contain unacceptable residues from prior batches of different products that used the same filters. The inspection found inadequate validation rinse data to support that drug residue from the previous batch was removed. We are concerned of the possibility of cross contamination.

Quality Control Unit

5. Lack of oversight by the Quality Control (QC) Unit to ensure that controls are implemented during the manufacturing operations. For example:

   a. Written procedures or specifications impacting on identity, strength, quality, or purity of drug products were not reviewed and approved by the QC Unit.
   b. The QC Unit inadequately monitors deviations, deviations were not maintained centrally by QC exhibiting the ability to determine trends, and deviation or investigation documentation was not mandatory when an out-of-specification raw material, in-process, or finished product result is found.

Your response describing corrective actions regarding this observation appear adequate. However, it failed to include documentation of the reported corrections. The U.S. CGMP assigns the responsibility for critical functions such as: setting performance specification, monitoring and assessing the performance of production, equipment, personnel, systems, and processes, as well as ensuring that established controls are implemented, to the QC Unit. The collection of this data by those same individuals whose actions are being assessed (production employees) without routine monitoring may not provide a true picture of your firm's state of control. Having the Quality Control and Quality Assurance units reporting to the production department rather than to top management may also diminish the authority of these units to perform their function.

The CGMP deviations identified above or on the FD-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. We recommend that you evaluate your facility on an overall basis for CGMP compliance. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practices.

Failure to correct these deficiencies may result in FDA denying entry of articles manufactured by your firm into the United States. The articles could be subject to refusal of admission pursuant to Section 801(a)(3) of the Act in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practices within the meaning of Section 501 (a)(2)(b) of the Act.

Please respond to this letter within 30 days of receipt. Your response should include copies of procedures generated as well as data collected in your correction to the deficiencies cited. Specific time frames for correction and commitments with follow up documentation should also be supplied or reported as forthcoming. Attach English translations of supporting documents. Please identify your response with CFN 9610964. Until FDA can confirm compliance with CGMP's and correction to the inspection deficiencies, this office will recommend disapproval of any new applications listing your firm as a manufacturer of terminally sterilized small volume parenteral drug products.

Please contact Edwin Melendez, Compliance Officer, at the address and telephone numbers shown above, if you have any questions, written response or concerns regarding these decisions.

Sincerely,

Joseph C. Famulare
Director,
Division of Manufacturing and Product Quality