DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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CERTIFIED MAIL
RETURN RECEIPT REQUESTED

JA 17 1997

Roquette Freres
62136 Lestrem, France

Dear

FDA has completed its review of the inspection of your bulk pharmaceutical chemical manufacturing firm in Lestrem, France by CSO Terri L. Dodds during the period of November 4 - 7, 1996. To date, we have not received a formal written response from your firm regarding the deviations discussed at the conclusion of the inspection.

The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of bulk pharmaceutical chemicals. The deviations were presented on an FDA-483 List of Observations issued to at the close of the inspection. These CGMP deviations cause your active pharmaceutical ingredient (API) to be unacceptable for use by pharmaceutical dosage form manufacturers in the United States, since, under United States law, those CGMP deviations make your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Our comments regarding the most significant observations are shown below:

1. Your firm was cited (FDA-483 Item # 1) for not having validated the manufacturing process nor having an approved validation plan for production of

   At present, FDA expects that all active pharmaceutical ingredient (API) manufacturers be actively engaged in a validation program for all of their products. The agency will seek legal or administrative actions if (1) an API manufacturer has not established or is not following an adequate plan to validate all API's; or (2) there is evidence that an API process is not validated as demonstrated by repeated batch failures due to manufacturing process variability.

Based on discussions during the inspection, it appears that your firm intends to perform retrospective validation for the manufacturing process. Retrospective validation has been found to be an acceptable practice when the following situations have been meet: (1) there is documented evidence that there have been no significant process changes; (2) there is documented evidence that the critical parameters of the manufacturing process have been controlled; (3) there is documented evidence that manufactured lots have remained within acceptance release specifications over time for in process and finished product testing; and (4) there is adequate evidence that process and change controls exist and are being followed.

If retrospective validation is not possible, the Agency would expect firms to conduct prospective validations as if they were implementing new or revised manufacturing processes. This prospective validation would involve obtaining and evaluating documented processing and analytical control histories for multiple batches manufactured, sampled, and tested according to an adequate validation protocol. The protocol should include a description of the critical steps of the manufacturing process; identify process equipment, critical process parameters and operating ranges, API characteristics, sampling and testing data to be collected; the number of process runs needed to show consistency of the processes, and specify what constitutes acceptable results.

We have enclosed a copy of the FDA guideline, Guideline on General Principles of Process Validation which you may use for your reference.

Please advise FDA of your firm's intentions regarding validation of the manufacturing process for Please also include copies of validation protocols.

2. Your firm was also cited for not having adequate control and maintenance of your batch record system (FDA-483 Item # 2). The foreman of your firm completes the handwritten batch records and maintains ultimate control over the process with no additional review to assure the batch has been manufactured correctly and in accordance with written procedures. Additionally, a quality unit does not review your batch records for assurance that in-process tests were completed, critical steps within your manufacturing process were performed correctly, and expected results were achieved.

Without a second review of the batch record, your firm lacks assurance that the manufacturing process has not deviated from or changed in any significant manner which could result in a lower quality or different substance than expected.

Lastly, your firm does not maintain any Master control records for products. Master control records are those from which copies are made and completed for each batch manufactured. Master control records should be updated when significant changes are made and should follow proper change control procedures with authorized approval.

Please explain how your firm intends to correct these batch record system deficiencies to assure a documented high degree of control in your manufacturing process. In addition, please include in your response the length of time in which your firm will maintain any batch records.

3. Your firm was cited for using unapproved operating ranges in the manufacturing processes (FDA-483 Item # 2D). Operating ranges should be selected based upon historical data and or data supported by a validated manufacturing process. FDA would expect your firm to have data which supports the rationale behind any selected operating ranges. Additionally, from a quality standpoint, these operating ranges should have been reviewed and approved by a quality unit prior to implementation. Please explain how your firm intends to correct this deficiency. Further, please include what assurance your firm has that these unapproved operating ranges are not being implemented in other products. Please include whether or not these ranges are included in your current, or will be included in future batch records.

4. Your firm was cited for failing to conduct investigations of out of specification results, specifically for testing (FDA-483 Item # 4). The inspection disclosed that your firm has rejected of lots manufactured at various times in 1996. FDA would not consider this to be indicative of a well controlled, and validated manufacturing process nor one acceptable for retrospective validation.

During the inspection, our investigator discussed with your personnel the practice of – This is not an acceptable practice for a product intended for parenteral use; and labeled as

We are concerned with the use of to remove from your product. Please submit data to support your firm's use of to successfully remove from your product on a consistent basis, for the anticipated levels of involved. Based upon your number of rejects for testing in 1996, the step does not appear to be effective in removing from your product.

We recognize that your firm may be rejecting batches intended for parenteral grade, and diverting these for food grade material. Although this may resolve the immediate problem with specific batches, from a quality standpoint this is not an acceptable practice nor does it correct the control issue. This practice also indicates there is not a reproducible, validated manufacturing process ongoing at your facility, which will consistently yield a product meeting specifications.

Please identify how your firm intends to assure that product failures will be investigated to assure will not adversely affect the quality of your product. Additionally, include how your firm will provide assurance that any corrective actions you take will confirm that the manufacturing process renders your product and within its pre-determined specifications.

5. Your firm was cited for using an E.U. monograph test method instead of an U.S.P. test method in testing of (FDA-483 Item # 6E). If your firm intends to label the product as U.S.P., than the product must be tested in conformance with the U.S.P.. Should your firm decide to use another test method, as was the case with the method; a comparison study must be performed and documented which shows that any method different from the U.S.P. is equal to or better than the U.S.P. method. The Certificate of Analysis you issue should cite which test method was actually used. The material you manufacture is used in New Drug Applications in the United States and Certificate of Analysis you issue citing U.S.P. must conform to such.

   Please identify what actions your firm will be taking to assure that the testing performed by your firm is reflective on your Certificates of Analysis. Additionally, please explain what studies your firm has performed or intends to perform to certify that any test methods you utilize for U.S.P. requirements are equal or superior to the required U.S.P. testing.

The CGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your firm. 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 firm on an overall basis for CGMP compliance. If you wish to ship your products to the United States, it is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers.

Until FDA has confirmed that your firm is in CGMP compliance, we will not recommend approval of any applications listing your firm as a supplier of the drug substance. A reinspection of your firm may be warranted to confirm corrective actions taken subsequent to the inspection and receipt of this letter.

Please contact Patricia L. Alcock, Compliance Officer at the address and telephone numbers listed below, if you have any questions regarding the information requested or wish to submit additional information detailing corrective actions that you plan to take or have taken to bring your operations into compliance.

U.S. Food & Drug Administration
Center for Drug Evaluation & Research
Foreign Inspection Team, HFD-322
7520 Standish Place
Rockville, Maryland USA 20855-2737

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Within your written response to this letter, detail corrective actions you plan to take or have taken to bring your operations into compliance. Please include a timetable of when each of the corrections will be completed and attach English translations of any supporting documents.

Please reference within your written response, and any supporting documentation.

Sincerely,

Patricia L. Alcock

Patricia L. Alcock
Compliance Officer

Encl: Guideline on General Principles of Process Validation