DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
Cincinnati District Office
Central Region
6751 Steger Drive
Cincinnati, OH 45237-3097
Telephone: (513) 679-2700
FAX: (513) 679-2771

November 12, 2002

WARNING LETTER
CIN-03-13127

Certified Mail
Return Receipt Requested

Cornelius L. Van Gorp, President
Celsus Laboratories, Inc.
12150 Best Place
Cinicinnati, OH 45241-1569

Dear Mr. Van Gorp:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Cincinnati, OH, by the Food and Drug Administration from January 9, 2002 to March 13, 2002. The inspection revealed significant deviations from U.S. good manufacturing practices in the manufacture of APIs, and resulted in the issuance of a form FDA- 483 to you at the completion of the inspection. These deviations cause these APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice. No distinction is made between active pharmaceutical ingredients or finished pharmaceuticals, and failure of any to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have also reviewed your written response to the FDA-483. We acknowledge the commitments to correct the deficiencies. Specific areas of concern include, but are not limited to:

1. Your stability program is insufficient in that samples are not tested at the established frequency, results are not correctly compared against specifications, stability sample container/closures are not equivalent to the containers you use for marketing, and investigations of aberrant results are not fully investigated and in consideration of already marketed products. In sum, your labeled "retest by" date is unsupported by adequate data. Some data you have collected indicate that the material in fact will not meet its specifications for the full length of the labeled shelf-life. We acknowledge your written responses committing to a reduced expiry period of six months and to including in your stability test program samples from recently manufactured batches.

2. Your cleaning procedure for product contact equipment surfaces has not been shown capable of reducing microbial and endotoxin contamination to acceptable levels. And this procedure, SOP #101, *General Sanitation Procedure*, lacks sufficient detail to ensure that cleaning is performed consistently and acceptably from batch-to-batch. Specifically, the procedure lacks minimum time limits for cleaning agent contact, method of wash and rinse, and volume of

cleaning agent(s) to be used. A sanitation cleaning procedure should include such information to ensure adequacy and reproducibility of cleaning. As an example, while your letter of March 27, 2002 (item 3B) points out that endotoxin removal can be effected with a "hard flush" of surfaces your procedure does not, in fact, specifically require a "hard flush." We acknowledge your commitment to validate the effectiveness of this procedure contained in your March 27 letter.

3. Your March 27 response indicates that you calculate dry-basis potency by using loss-on-drying (LOD) data from a previous analysis of samples from the same lot. Dry-basis potency should be calculated using LOD results from a portion of the sample used to test for potency. In this way, potency calculations will accurately reflect the material under test. You should correct all previous miscalculations and compare the results against the established specification, and follow-up as necessary on the accurate data.

4. Product complaints are to be investigated thoroughly and with respect to their relevance to related batches and material. CGMPs also require all complaints to be investigated in a timely manner. We acknowledge your April 19, 2002 letter includes a commitment to reopen several complaints cited in the FDA 483. We may cover your complaint handling procedure during our next inspection, and will expect at that time to find that you have conducted a complete investigation and taken all appropriate corrective action in response to each complaint.

5. Our recent inspection also found inadequate investigation of several LOD stability test failures. Merely re-testing material is insufficient to dismiss the original results in this case. Your March 27 letter states that you do not know why re-testing was performed. A fundamental principle of CGMPs is that manufacturers behave purposefully in ensuring product quality. Conducting tests for unknown reasons is not purposeful action. We acknowledge also that you have recalled the affected batches from the market. Our next inspection will include an evaluation of your investigation of any recent aberrant or failing test results and the outcomes.

6. Similarly, we expect that any material not meeting specifications be rejected and not released for distribution. While we acknowledge your response that a change in specification was established before the particular OOS occurred, your procedure failed to accurately reflect this change. Further, we believe your current procedure for handling OOS results is inadequate because it permits re-testing without sufficient controls on the extent and need for justifying re-tests.

7. Water used in processing your active ingredients has been found at times to have unusually high endotoxin levels in testing you have performed, but you did not properly respond to the atypical results at the time they were detected. Your written responses indicate your intent to revise your procedure for handling atypical and out-of-specification test results, which will include establishing alert and action limits for this attribute. But you do not report the alert and action limits and the data supporting the limits. We agree that setting alert and action limits based on both historical data and in consideration of established water quality specifications will help you to recognize atypical results and respond in a timely and appropriate manner. Our next inspection will also assess your written justification for the water system alert/action limits you have promised to establish, and your compliance with the procedure.

8. Our investigation also found that a change to the process (i.e., [redacted] was not evaluated as to impact on material stability and other aspects of material quality to ensure consistent, acceptable results. We acknowledge your written response to update your DMF accordingly and to validate this reprocessing step (you expect to need to use this processing step on occasion to stabilize an intermediate). When implementing process changes it is good practice to generally include one or more batches from the changed process in your stability program.

The CGMP deviations identified above are not to be considered as an all-inclusive list of deficiencies at this facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. It is the responsibility of your firm to assure compliance with all standards for current good manufacturing practices.

Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. In addition, pending new drug applications (NDA), abbreviated new drug applications (ANDA), or export approval requests may not be approved until the aforementioned deviations are corrected.

Please notify this office in writing within 15 working days of receipt of this letter of the specific steps you have taken or will take to correct the noted violations and include documentation confirming that corrections have been applied to all drug operations and have been successfully implemented. Failure to promptly correct these deficiencies may result in regulatory action without further notice, including seizure and injunction.

Please direct your written response to Compliance Officer Gina M. Brackett at the address shown in the letterhead.

Sincerely,

Carol A. Heppe

Carol A. Heppe
Acting District Director
Cincinnati District Office