DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office
60 8th Street, N.E.
Atlanta, Georgia 30309

January 24, 2001

VIA FEDERAL EXPRESS

Peter A.W.F. Everding
Chairman
DSM N.V.
Het Overloon 1, Heerlen
P.O. Box 6500
6401 JH Heerlen, The Netherlands

WARNING LETTER
(01-ATL-25)

Dear Mr. Everding:

An inspection of your drug manufacturing facility, Catalytica Pharmaceuticals, Inc., located at US Hwy 264/Hwy 11 in Greenville, North Carolina, was conducted between September 19 and December 15, 2000, by Investigators Vicky C. Stoakes and Penny H. McCarver. The inspection revealed several significant deviations from the Current Good Manufacturing Practice for Finished Pharmaceuticals (CGMPs), as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 211. These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

You have failed to assure that each batch of drug product had appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. The work performed by one of your analysts over a two-year period was found to have generated questionable data effecting [redacted] lots of product. [redacted] of these lots had data quality issues and the remaining lots had documentation issues associated with the analyses performed. Documentation issues included falsified data, discarding of data, failure to report original data, data substitution, and data manipulation. This analyst generated data to support finished product release and stability testing of finished dosage forms. Testing included dissolution, content uniformity, assay, and identity. These data quality issues were attributable predominantly to one analyst, however similar issues were noted in work performed by other analysts. The investigation into the extent of these problems continues at Catalytica.

The quality control unit failed to fulfill their responsibilities to approve or reject all components, in-process materials, and drug products, and to review production records to assure that no errors have occurred or, if errors had occurred, that they had been fully investigated. The unit had failed to establish and implement appropriate laboratory controls to assure that components, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity. Drug product production, control, and test records were not reviewed to the extent necessary to ensure that products complied with all established, approved specifications before a batch was released. Numerous instances where the failure of a batch, or one of its components, to meet product specifications were noted above which were not detected and investigated as required.

Laboratory records were not maintained as required to include complete data derived from all tests necessary to assure compliance with established specifications and standards. This would have included a complete record of all data secured in the course of each test including all graphs, charts, and spectra from laboratory instrumentation. Your firm failed to enable available safeguards to prevent the substitution of data and ensure the integrity of analytical results. Laboratory equipment in use allowed for the partial saving of data and loss of traceability. No periodic verification was conducted to determine if all original data was being reported. Chromatographic data was being obtained which was not always being integrated and reported into the system. The procedure in use for HPLC Data Generation allowed for the discarding of system suitability injections in response to unexplainable variations within the HPLC system. This process was called "flagging". The discarding of these system suitability injections resulted in the performance of analytical testing using chromatographic systems that did not meet suitable standards.

Your firm failed to have a second person review all original laboratory records for accuracy, completeness, and compliance with established standards. Your firm failed to ensure that data entered into your [redacted] system, which was used for finished product review and release, could not be self verified. Our inspection identified seventeen analysts as having self verified data in this system between October 1998 and August 2000. Although this was a known problem with this system, your firm initiated no corrective action. No periodic reviews or audits were being conducted by the quality unit to confirm that data was being properly verified and reported.

You have failed to appropriately investigate and respond to out of specification (OOS) analytical results. Numerous inconsistencies were noted in the handling of data and the decisions made in response to these OOS results. You have failed to maintain adequate documentation to substantiate the invalidation of OOS results. This was noted during content uniformity, assay, and dissolution testing. The inspection noted instances of the failure to follow procedure, substitution of standards, discarding of OOS results without an investigation, and reporting of only passing results. Your procedure for the Handling of Out of Specification Results allowed for the improper discarding of OOS results without an investigation. The procedure allowed for the discarding of results without sufficient documentation of the failures and any corrective actions taken to prevent reoccurrence.

Your firm has failed to properly investigate and document OOS results obtained from malfunctioning laboratory equipment. High and missing dissolution results were noted reportedly due to problems in the operation of the [redacted] Workstations. Similarly high atypical values were generated in the dissolution and content uniformity testing due to problems with the operation of the [redacted] Workstation. This data was invalidated without any review by a supervisor or other responsible official. The lack of an investigation or appropriate documentation of these instrument failures makes the trending of these problems impossible. This allows recurring and persistent instrument failures to go uncorrected.

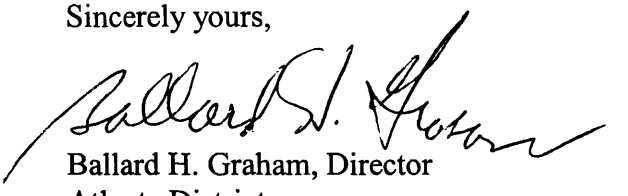
This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The above deviations were included on the Inspectional Observations (FDA 483) which was issued to and discussed with Kenneth S. Manning, Vice President Quality Operations, at the conclusion of the inspection. A copy of the FDA 483 is enclosed for your review. The specific violations noted in this letter and in the FDA 483 could be symptomatic of underlying problems in your firm's quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

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. Additionally, pending New Drug Applications, Abbreviated New Drug Applications, or export approval requests may not be approved until the above violations are corrected. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory actions being initiated by the FDA without further notice. These actions include, but are not limited to seizure and/or injunction.

I am in receipt of a formal response to the FDA 483 that was sent to me from Michael Thomas, President of Catalytica, on January 3, 2001. The response described your firm's efforts to address the issues raised during the inspection. These corrective actions were again discussed during a meeting with your corporate officials in Atlanta on January 18, 2001. We are encouraged by the corrective actions promised during this meeting and those initiated prior, and subsequent, to our inspection. We request that your response to this Warning Letter include documentation of the corrections alluded to in the January 3 response, such as investigation reports and revised procedures. Your corrective actions include ongoing investigations into data integrity and product quality issues that must be completed prior to any meaningful conclusions as to the extent of these problems at your firm. We are particularly concerned about the quality control, systems, and procedural failures that allowed these data integrity issues to go undetected and unresolved for so long. These "contributing factors" are noted in your response.

Please notify this office in writing within fifteen (15) days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. You may reference the above December 3 response if you feel it adequately addresses the observations noted. Your response should be sent to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely yours,



Ballard H. Graham, Director
Atlanta District

Enclosure

cc: Michael H. Thomas, President
Catalytica Pharmaceuticals, Inc.
P.O. Box 1887
Greenville, North Carolina 27835-1887