DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Central Region

New Jersey District
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6010

July 11, 2006

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. N.K. Rao Ramanadham, R.Ph.
President
Concord Laboratories, Inc.
140 New Dutch Lane
Fairfield, New Jersey 07004

06-NWJ-14

Dear Mr. Ramanadham:

An inspection of your manufacturing facility located at 140 New Dutch Lane, Fairfield, NJ, was conducted from February 23 through March 22, 2006. During the inspection our investigator documented deviations from the Current Good Manufacturing Practice (CGMP) Regulations, Title 21 Code of Federal Regulations, Parts 210 and 211 (21 CFR 210 and 211) for drug products manufactured and tested at this site. 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) (21 U.S.C. § 351(a)(2)(B)).

1) Written records are not always made of investigations into unexplained discrepancies, nor did investigations of unexplained discrepancies extend to other batches of the same drug product or other drug products that may have been associated with the specific failure or discrepancy [21 CFR § 211.192]. Specifically:

   a) Product samples tested in conjunction with a complaint regarding loose caps on Nitroglycerin tablets, lot 201105, produced out-of-specification results for assay and content uniformity. There was no examination of product retains or a review of the batch record. The sample results were invalidated due to product damage from environmental exposure although there was no provision for this in your firm's written procedures.
   b) Product samples tested in conjunction with complaints regarding tablets not dissolving for Nitroglycerin tablets, lots 201105 and 214605, were tested for all release specifications except assay. There was no justification for omission of this test, nor was there any evidence of an examination of stability lots, retained samples, or a review of the batch records.
   c) The reference standard injection following assay and content uniformity testing of Hyoscyamine Sulfate Tablets, lot P3274, failed to show any peaks due to a leaking column. There was no documented investigation of this deviation, there was no assessment of the impact of the leaking column on the Hyoscyamine Sulfate analysis or any other analysis conducted with the same column, and the Hyoscyamine samples were not reinjected. This same

observation was made during the previous inspection, yet no investigation was conducted.

d) There was no documented investigation regarding HPLC malfunctions requiring external repair. Both HPLC [redacted] and [redacted] required repair in June 2005; however there is no documentation regarding whether the malfunctions impacted any analyses, and if so, what the corrective actions were regarding those analyses.

e) The investigation into an out-of-specification assay result for Diphenhydramine Tablets concluded the cause to be a dilution error as a result of the use of incorrect glassware. This conclusion could not be supported as the actual glassware used was not documented and laboratory procedures do not require that glassware be maintained until the analysis is complete.

f) Power failures occurred during analyses of Nitroglycerin, lot 101005, and Senna S, lot 204103. Investigations did not document the impact on the analyses, any re-testing or resampling, or if the power outage impacted any other analyses.

2) Laboratory records fail to include the initials or signature of the person who performs each laboratory test [21 CFR § 211.194(a)(7)]. Specifically, laboratory analysis records for analyses performed on HPLCs [redacted] and [redacted] do not indicate which analyst performed the injections.

3) Failure to maintain complete records of any modification of an established method employed in testing [21 CFR § 211.194(b)]. Specifically, the records of laboratory methods stored in the [redacted] computer system do not include the identity of the person initiating method changes.

4) Appropriate controls are not exercised over computers or related systems to assure that changes in analytical methods or other control records are instituted only by authorized personnel [21 CFR § 211.68(b)]. Specifically:

   a) Laboratory managers (QC and R&D) gained access to the [redacted] computer system through a common password. Analysts were not required to use individual passwords; they operated the system following the login by the laboratory managers.

   b) Due to the common password and lack of varying security levels, any analyst or manager has access to, and can modify any HPLC analytical method or record. Furthermore, review of audit trails is not required.

5) Failure to follow written procedures applicable to the quality control unit [21CFR § 211.22(d)]. Specifically, the contracted laboratories responsible for performing analyses on Active Pharmaceutical Ingredients and other drug components, used in the finished drug products, such as LOD, nitrogen content, microbial limits, and specific rotation, have not been qualified by the quality unit as per your firm's written procedures.

6) Failure to maintain separate or defined areas or other such control systems as are necessary to prevent contamination and mix-ups in the course of manufacturing and processing operations [21 CFR § 211.42(c)(5)]. Specifically, no monitoring of the

system is conducted to demonstrate that the volume of air supplied is sufficient to maintain appropriate air pressure differentials between manufacturing rooms, corridors, and pharmacy rooms.

7) Failure to provide adequate measures to control air contamination and recirculation of dust from production areas where air is recirculated [21 CFR § 211. 46(c)]. Specifically:

   a) No studies have been conducted to assure that the system removes contaminants from the production area and that cross-contamination does not occur.
   b) Modifications made to the air handling systems of production rooms 6 and 8, to add exhaust ventilation, were not qualified to show their effectiveness at the time of installation.

8) Failure to establish master production and control records for each drug product including a statement of the maximum and minimum percentages of theoretical yield beyond which investigation is required [21 CFR § 211.186(b)(7)]. Specifically, actual and theoretical yields are calculated after tablet compression but your firm has not established appropriate specifications for acceptable yields.

9) Test devices are deficient in that apparatus not meeting established specifications are used [21 CFR § 211.160(b)(4)]. Qualification studies for the [redacted] room temperature stability chamber were deficient in that they did not always include specifications, acceptance criteria, or raw data. Specifically:

   a) There was no data to demonstrate that the chamber alarm would perform as required in the event of a humidity excursion.
   b) There were no specifications or acceptance criteria for the water pressure or water quality to the chamber. There are specific requirements for these outlined in the operating manual for the chamber.

10) Failure to maintain equipment at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product [21 CFR § 211. 67(a)]. Specifically, the [redacted] Packaging Hopper was found to be cracked. Cracked equipment cannot be easily cleaned to prevent cross-contamination between products.

In addition, the inspection revealed that certain drug products manufactured by your firm are in violation of sections 505(a) and 502(f)(1) [21 U.S.C. § 355(a) and § 352(f)(1)]of the Act, for the following reasons:

You manufacture the following prescription products:

- Colchicine Tablets
- Hyoscyamine Sulfate Tablets
- Nitroglycerin Sublingual Tablets

These products are drugs within the meaning of section 201(g) of the Act [21 U.S.C. § 321(g)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. FDA is unaware of substantial scientific evidence that any of these products as manufactured by your firm are generally recognized by qualified experts as safe

and effective for their labeled indications. Therefore, they are "new drugs" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)].

Section 505(a) of the Act [21 U.S.C. § 355(a)] requires that any new drug be the subject of an FDA-approved new drug application before it is introduced into interstate commerce. There are no approved applications on file for the above products and their continued marketing violates section 505(a) [21 U.S.C. § 355(a)].

In addition, these drugs are misbranded. As prescription drugs, adequate directions cannot be written for them so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for use as required under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)] and, lacking required approved applications, they are not exempt from this requirement under 21 CFR § 201.115.

We have received your written response to the FDA-483, dated May 3, 2006. This response will be added to our official files. For the reasons below, we do not find this response to be sufficient. Please note that the comments below pertain only to the CGMP observations; the exclusion of a discussion of the responses to the observations made about the drug products subject to ANDAs does not mean that the responses were adequate. An assessment of the responses to the ANDA-related observations will be sent under separate cover.

The response does not include documentation to show that the corrective actions have been implemented (see FDA-483 items 3, 4, 6, 8, 9, 11, and 12). For example you did not submit the revised calibration procedures referenced in your response to FDA-483 item # 4. In addition, some of the responses to the FDA-483 items (1 and 6) do not include timeframes for completion of the corrective action. For example, your response to item #1 states that a new password system will be implemented but does not specify a completion date. Also, some of the responses fail to address the underlying issues inherent in the noted deficiencies. For example, the response to item # 2 states that the in-specification test results obtained for products tested before and after various failures of the analytical instruments show that the reliability of the analyses was not impacted by the failures. However, obtaining in-specification test results from a product analysis does not, by itself, indicate the suitability of the analytical system used or the reliability of the results.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It does not include observations of deficiencies related to ANDA products which have not yet been approved and marketed. It is your responsibility to ensure that drug products your firm manufactures are in compliance with the Act and the regulations promulgated under it. Federal agencies are advised of the issuance of all warning letters about drug products so that they may take this information into account when considering the award of contracts. Until FDA can confirm correction of the deficiencies observed during the most recent inspection, this office can recommend disapproval of any new applications listing this site as a manufacturer of drugs.

You should take prompt action to correct deficiencies at your facility. Failure to do so may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

You should notify this office within 15 working days of receipt of this letter of the additional corrective actions you plan to implement to address the deficiencies at your firm. If

corrective actions cannot be completed within 15 working days, please state the reason for the delay and the time frame within which corrective actions will be completed.

Your response should be addressed to: U.S. Food & Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attn: Sarah A. Della Fave, Compliance Officer.

Sincerely,

Douglas I. Ellsworth

Douglas I. Ellsworth
District Director
New Jersey District