



November 15, 2002

WARNING LETTER
SJN-03-05

3695d
• FOOD & DRUG ADMINISTRATION
466 FERNANDEZ JUNCOS AVENUE
SAN JUAN, P.R. 00901-3223

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Robert C. Felder, President
ChemSource Corporation
P.O. Box 10010
Guayama, Puerto Rico 00785

Dear Mr. Felder:

From March 4, 2002, to April 11, 2002, an inspection was conducted at your Active Pharmaceutical Ingredient (API) manufacturing facility located at Rd #3 Km 143.0 Guayama, PR 00785 which resulted in the issuance of a 27 item form FDA-483 at the completion of the inspection. The Inspection found significant violations of current good manufacturing practice (CGMP) in the manufacture of active pharmaceutical ingredients (APIs). The deviations reported cause these APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Food, Drug and Cosmetic Act ("the Act"). This same section of the Act requires that all drugs be manufactured, processed, packed, and held in accordance with current good manufacturing practice. No distinction is made in this section between active pharmaceutical ingredients and finished pharmaceuticals.

Examples of your firm's failure to follow CGMPs in API production include, but are not limited to, the following:

1. Failure to have an analytical method capable of detecting the presence of impurities found in Metformin HCl batches. Your analytical method used for determination of impurities fails to detect all five (5) of the impurities listed in the product's specifications. Therefore, there is no assurance that the batches currently in distribution are in compliance.

The response in your letter of May 15, 2002 is inadequate in that it provides no information regarding the suitability of the Metformin analytical method for the detection of the five impurities. It is your responsibility to assure that the method (European/USP/ or equivalent method), as used by your firm, is capable of detecting the impurities that may be present in your products. In reference to your response, repeating a test with a fresh standard does not by itself justify the invalidation of previous results. Your response also lacks information supporting your contention (regarding the stability of the standard B preparation), that the change in retention time resulted from a degradation of the solution.

2. Failure to ensure that each lot of API released is in conformance with its quality specifications. The presence of yellow coloration and orange spots were reported through complaints received relative to released Metformin HCl batches # [REDACTED], # [REDACTED],

and # [REDACTED]. Because you have not adequately investigated the cause of the discoloration and the effect it has on the product, there is no assurance that the identity, strength, quality and purity of the API have not been affected. Furthermore, there is no assurance that the presence of the yellow coloration and orange spots would not affect the lots throughout their expiration dating period.

We consider your response inadequate in that you claim that the lots evaluated are in conformance to the "white crystal specification", but also indicate that yellow/orange colored spots were found in a few drums. In addition, there is no indication if the drums found with the spots pertained to the same lots distributed and the subject of complaints. You also reprocessed all lots present in the warehouse found with the yellow/orange material. However, there is no indication that any corrective action was taken concerning the distributed lots. Your response fails to include an acceptable justification for only testing lot [REDACTED]. You indicate that insufficient samples for testing were retained from the other batches. It is your firm's responsibility to retain sufficient samples from each batch produced and released. In addition, it is not clear from your response if any of the lots involved were placed or will be included in a stability testing program or if you plan to take any other appropriate actions. Your response also fails to fully address the presence of chromium, iron and nickel in the product, as stated in the records reviewed, indicative of "contamination by stainless steel".

3. Failure to have adequate process controls. Examples are as follows:
 - a. Metformin HCl batches are dried at temperatures higher than the temperature used during your process validation. The process requires that the product be dried at Not More Than (NMT) [REDACTED]. Examples of batches exceeding the approved parameters are: # [REDACTED] (dried at [REDACTED]), # [REDACTED] (dried at [REDACTED]), [REDACTED] (dried at [REDACTED]) and [REDACTED] (dried at [REDACTED]). Furthermore, no investigations relating to these processing deviations were performed.

We consider your response inadequate in that you provide no information relating to the impact that increasing the process temperature would have on the product.

4. Failure to demonstrate that the manufacturing process for Todosil (Etodolac) produces an API that meets the pre-determined quality specifications. Examples are as follows:
 - a. During 1998, two of the three validation batches ([REDACTED] and [REDACTED]) were redried after failing the water content specifications. You considered your process validated even though two of the three batches produced needed to be reprocessed.
 - b. Batch [REDACTED] failed for color; batch [REDACTED] failed water content; batch [REDACTED] failed the chlorine test; batch [REDACTED] failed the residual solvent test. These batches were reprocessed. However you lack data to demonstrate that reprocessing the batches results in a product that complies with all established standards, specifications and characteristics.

5. Failure to have method validation protocols describing the pre-established specifications, parameters and requirements for the method validation studies of Metformin HCL, Nabumetone, Etodolac and Lisinopril.

We consider your response to be inadequate in that it does not indicate that the current analytical methods for the above four drug products have been evaluated to assure that the validation parameters are scientifically sound.

6. Inadequate laboratory procedures and records to assure that the APIs have the appropriate quality and purity. The inspection reported significant deficiencies regarding the following laboratory procedures and records for your API products:
 - a. Inadequate analytical methods validation
 - b. Lack of scientifically sound test procedures
 - c. Failure to have complete records and or raw data related to all the products tested
 - d. Poor laboratory practices and failure to follow established procedures
 - e. Failure to identify unknown peaks during the Organic Volatile Impurities test of Nabumetone
 - f. Failure to perform analytical laboratory investigations of anomalies such as the Metformin HCL peak retention time variation.
7. Failure to have adequate laboratory controls. Examples are as follows:
 - a. Lack of adequate training for laboratory analysts and manufacturing employees
 - b. Failure to demonstrate that impurities B and C are not present in all lots of Metformin HCL
 - c. Failure to identify impurities greater than 0.1 % in Lisinopril batch # ~~XXXXXXXXXX~~ as required by the US Pharmacopoeia (USP XXV).
8. The inspection revealed that your laboratory equipment calibration program is inadequate in the following ways:
 - a. Failure to have written procedures describing specific calibration instructions, and limits.
 - b. Failure to maintain complete calibration records in that they do not include all raw data.
 - c. Failure to have a complete calibration program for the HPLCs in that the gradient accuracy and detector linearity is not being verified.
 - d. Failure to conform to the USP XXV Section <41> for weight and balance determination. The inspection revealed that erroneous values are being used to perform the minimum weight studies.

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9. Failure to have validated cleaning procedures for manufacturing equipment and transfer lines for both API facilities identified as Guayama I and Guayama II. Records reviewed and collected during the inspection indicate a lack of adequate cleaning procedures. Samples collected on March 4, 2002 by your firm showed the presence of Metformin HCl and Nabumetone in the same production area.

There are no records to demonstrate that the process line filters are being replaced after the manufacture of a product or between product campaigns to prevent cross contamination. There are also no records documenting cleaning and release of production areas prior to March 5, 2002.

We acknowledge and agree with your decision to conduct a voluntary recall of three batches of Metformin HCl. However, this action does not address the likelihood that other batches produced in the same area and manufactured under the same conditions may also be contaminated. It is your firm's responsibility to conduct a full investigation to insure that marketed products meet all of their specifications throughout their expiration dating period.

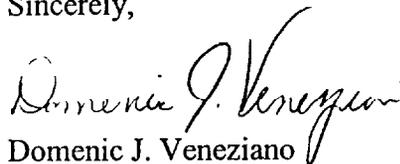
Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the awarding of contracts. In addition, pending new drug applications (NDA), abbreviated new drug applications (ANDA), or export approval requests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

You should take prompt action to correct these deviations and to prevent their future recurrence. Failure to make prompt corrections could result in regulatory action without further notice. Possible actions include seizure and/or injunction.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violation, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective actions can not be completed within 15 working days, state the reason for delay and the time within which corrections will be completed.

Your reply should be sent to the Food & Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, PR 00901-3223, Attention: Mr. Carmelo Rosa, Compliance Officer.

Sincerely,


Domenic J. Veneziano
Acting District Director