



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Public Health Service
Food and Drug Administration

Dallas District
3310 Live Oak Street
Dallas, Texas 75204-6191

March 12, 1998

Ref: 98-DAL-WL-25

WARNING LETTER

VIA FEDERAL EXPRESS

Mr. Lawrence E. Boos, Jr.
President
Sovereign Pharmaceuticals, Inc.
7590 Sand Street
Fort Worth, TX 76118

Dear Mr. Boos:

During an inspection of your facility located at the above address on February 3/17, 1998, a Food and Drug Administration (FDA) investigator documented deviations from the Current Good Manufacturing Practice Regulations (21 C.F.R. 210 and 211). The deviations cause your drug products to be adulterated with the meaning of Section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

Examples of significant deviations from Current Good Manufacturing Practice's (CGMP's) observed in your firm include:

- Failure to validate the manufacturing processes for tablet, liquid, and capsule dosage form drugs (21 C.F.R. 211.100). The Validation Protocols prepared during the dates of the inspection and provided to the investigator at the completion of the inspection lack the necessary information required to ensure that process and production procedures will consistently result in the purported or expected qualities for the various drugs.
- Failure to have an established production record review procedure to assure a thorough investigation of any unexplained discrepancy in product specifications (21 C.F.R. 211.192). For example, the results of the nine month stability ambient analysis for [REDACTED] show the active ingredients [REDACTED] and [REDACTED] increased from the initial assay by 9.6% and 8.3% respectively. No record of investigation is on file.

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- Failure to have an established sampling and testing procedure for in-process materials and drug products to ensure that drug products meet established specifications (21 C.F.R. 211.110). For example, [REDACTED] failed in-process specifications for hardness. No record of investigation is on file.

This letter is not intended to be an all inclusive list of the products and violations which may exist at your drug production facility. Your firm's inspectional history has shown a pattern of your immediate attempt to initiate corrections to CGMP's only when cited on an FDA-483 presented by our investigators. It is your responsibility to review your entire production and control processes for CGMP compliance and to take the initiative to assure that all drugs are in compliance with the Act and related regulations. 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.

I have reviewed your February 17, 1998, written response to the current FDA-483. Additionally, the Validation Protocols #528894-00 for encapsulated [REDACTED], and #519764-00 for liquid [REDACTED] provided at the completion of the inspection were also reviewed.

The Validation Protocols are not complete and do not provide all the required information. For example, descriptions of manufacturing processes, equipment performance qualifications and range of operating parameters, processing water quality and source, mixing times, and number or replicate processing runs to be made are not included in the protocols. There is no information provided on manufacturing equipment, including critical and ancillary equipment, or necessary support utilities. You have indicated product is to be encapsulated using qualified equipment and personnel, however, no clarification or other documentation is provided. You have listed a number of different methods of analysis and SOPs to substantiate product potency and content uniformity, however, no documentation of assurance of validation of these methods and procedures has been provided.

You should review the original product developmental reports on the drugs being manufactured during your further review and evaluation of the Validation Protocols.

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Our investigator provided you with a copy of FDA's Guide to Process Validation which should be of assistance.

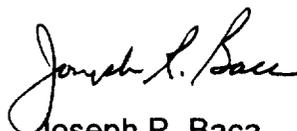
Your response to Item 2 of the FDA-483 includes a SOP - Guideline for Unexpected Results. This SOP is designed to determine if laboratory error may have occurred causing the unexpected results. You have not considered other possibilities, such as deviations in ingredient and component controls, in-process controls, and the need to review batch production records, as well as all other documentation maintained in an effort to ensure all critical aspects of production and inspection are met. You have not provided a satisfactory evaluation of the specific batch of product and the root cause of unexplained increases in active ingredient levels.

You should also assure that the corrections indicated to be made in batch production records, as noted in your response to Item 3 of the FDA-483, are also incorporated into Master Production and Control Records for your products to assure uniformity from batch to batch.

Please notify this office in writing within fifteen (15) working days of the receipt of this letter as to the specific steps you will take to correct the noted violations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include seizure of drug products and/or injunction.

Please direct your response to James R. Lahar, Compliance Officer at the above address.

Sincerely,



Joseph R. Baca
Dallas District Director

JRB:JRL:jab