

Examples of failures to follow cGMPs in the production of API by your firm include, but are not limited to the following:

1. Failure to demonstrate the validity of analytical methods used for impurity determinations for API

Our inspection revealed that you are not using USP-prescribed methods for determination of [REDACTED] and [REDACTED]. The current method used by your firm to determine release specifications for these two known impurities of [REDACTED] has not been validated to show equivalence or superiority to USP methods. Our investigation also revealed that the methods utilized by Rhodia for analysis of [REDACTED] have not been consistently applied over the past 2 years of production.

Your response dated June 2, 2000 indicates the production facility is currently using a modification of USP General Test <[REDACTED]> for the determination of [REDACTED] and [REDACTED]. The USP does not have any provision for the determination of ethylene oxide using this method. USP General Test <[REDACTED]> for Organic Volatile Impurities (OVI), under [REDACTED], specifically states "The standard solution parameters and the method for determination are described in the individual monograph" (in this case [REDACTED]). The [REDACTED] monographic method for [REDACTED] determination differs significantly from the method for Organic Volatile Impurities. We additionally find an improper use of the OVI method for detection of [REDACTED]. The [REDACTED] monograph specifies USP General Test <[REDACTED]> for the determination of [REDACTED], with a detection limit of 10 ppm. The OVI method <467> indicates a detection limit of 100 ppm. You have not demonstrated that your current, modified method is capable of detecting the 10 ppm limit for [REDACTED].

Your response indicates you are in the process of validating the test procedure currently in use, however, you failed to include a copy of the validation protocol for the method being validated. Your protocol should include specific elements in order to assess equivalence. USP 24 Chapter 1225, Validation of Compendial Methods, describes "typical analytical performance characteristics that should be considered in validation" of analytical methods. Furthermore, this new method should not be used prior to validation and evaluation to show that it is equivalent or better than the USP method(s).

2. Failure to establish a complete impurity profile.

In addition to using unvalidated methods, you have not established an impurity profile for this API. Laboratory chromatographic records for the past 2 years show several

recurring, unidentified peaks in GC chromatograms for release testing. Moreover, unidentified peaks are present on HPLC chromatograms for ██████████ assay in 3 of the 7 lots reviewed during the inspection.

Your response indicates these unidentified peaks are also found in the standard and are likely an artifact of the analytical matrix. While this statement may be true, it certainly cannot be evaluated based on the inconsistency of the method applications and standard preparations employed by your laboratory. It is your responsibility to ensure that your API meets all of the requirements in the monograph defining it."

FDA expects manufacturers to establish appropriate impurity profiles for each API as part of the process validation effort. An API manufacturing process can neither be validated nor can process changes be evaluated without an awareness of the impurity profile. USP 24 (Chapter <1086>, page 2049) describes an impurity profile as "A description of the impurities present in a typical lot of a drug substance produced by a given manufacturing process." The impurity profile includes "the identity or some qualitative analytical designation (if unidentified), the range of each impurity observed, and the classification of each identified impurity." Without an established impurity profile, you cannot adequately evaluate the quality and purity of your API.

If a firm lacks impurity profile data for their established API process, then FDA expects manufacturers to conduct retrospective validation as if they were setting up a new or modified manufacturing process. This retrospective validation would involve obtaining and evaluating documented processing and analytical control histories for multiple batches manufactured, sampled, and tested according to a pre-established and adequate validation protocol. This protocol should describe the synthesis reactions, key intermediates and purification steps. It should also identify process equipment, critical process parameters and operating ranges, API characteristics, sampling and testing data to be collected, the number of process runs needed to show consistency of the processes, and specify what are acceptable results.

Your response quotes USP General Notices (under Procedures in Tests and Assays), whereby you convey your confidence that your API product meets USP monograph specifications. Without documentation to show that your methods, when applied consistently, can accurately or reproducibly quantify these substances at or below the specification limits, the results of your analyses cannot be reliably accepted.

3. The method used by your firm to determine whether the API release specifications are met for [REDACTED] and [REDACTED] impurities is not in writing.

Our inspection disclosed that the modified analytical methods being employed to detect and quantify these impurities are not in writing. It was determined that the methods described in the latest version of your Drug Master File (DMF) 339 (12/96) have not been followed since approximately mid-1998. No amendment has been filed to record or justify these changes.

GC chromatograms for [REDACTED] and [REDACTED] varied widely from lot to lot and generally revealed poor chromatography practices. There were numerous modifications to the USP analytical methods for determining the known impurities [REDACTED] and [REDACTED]. When multiple peaks were present in the chromatogram, it was often unclear how the analyst distinguished the [REDACTED] and [REDACTED] peaks.

It is your firm's responsibility to operate under your current DMF commitments and to notify FDA of any changes in DMF procedures. As stated above (1), all methods used to determine specifications for a compendial product must be equivalent to USP methods, as demonstrated by a controlled, scientifically sound study. Documentation of the successful completion of such studies is a basic requirement for determining a method's suitability for its intended applications. Any change to an analytical method that relaxes the specification or establishes a new regulatory analytical method requires an amendment and notification of the sponsor(s) so that the application(s) referencing your DMF can be supplemented.

4. Laboratory procedures and records are incomplete, and do not include provisions for calibration of laboratory instrumentation and maintaining original laboratory data.

The laboratory procedures documented during the April 2000 inspection indicate a lack of laboratory controls to assure that test materials conform to established standards of identity, quality and purity. The inspection showed a lack of procedures for calibration of the GC and HPLC, as well as a lack of documentation and use of standard preparations.

Additionally, review of general laboratory practices and records revealed lack of documentation for:

- a. preparation of test articles and other solutions (such as standards, reagents, mobile phase);
or your analyses cannot be reliably accepted.
b. chromatographic conditions (such as instrument and

- c. lot and/or sample identification on chromatograms, identity of analyst, date and time of analysis, calculations performed, and review by a second person;
- d. original printouts for calibration runs.

You failed to maintain all original chromatograms for HPLC and GC analyses. Several API analytical packages were missing sample and standard chromatograms (printouts), and there was no explanation for non-sequential file or run numbers. HPLC files corresponding to missing data could not be recovered because the files were routinely deleted from the hard-drive and were not backed-up. Unused GC auto-integrator printouts were routinely discarded with no explanation.

Your response did not adequately address these issues and indicates an unwillingness to perform instrument calibrations. It is your responsibility to assure that equipment is properly maintained and calibrated, and that standard preparations conform to compendial requirements. System suitability on poorly maintained or calibrated equipment is meaningless. System suitability is not a substitute for calibration and/or maintenance.

You are required to have and follow written procedures corresponding to laboratory controls, and to maintain complete and properly identified records of data. This includes records of calculations performed in connection with tests; identity and signature of the person performing each test and the date performed; review by a second person; testing and/or standardization of laboratory solutions and test articles; and equipment maintenance and calibration. Please submit copies of your Standard Operating Procedures related to these procedures, as well as a schedule of calibration for instruments, apparatus, gauges and recording devices.

5. You failed to isolate, identify, and quantify potential degradants in this API through forced degradation studies. You failed to establish reliable, meaningful and specific test methods which are capable of separating degradation products from the active ingredient. The test methods used on your stability samples (pH, Acid Value, Color, and Cloud Point) are not stability indicating methods.

Your response indicates the DMF statements of stability are justified with knowledge of the product's chemistry, historical data, and specific physical property tests indicative of stability. Please provide this information so that this issue may be properly evaluated.

Neither this letter, nor the Form FDA 483, Inspectional Observations, issued at the conclusion of the inspection to Mr. Dave Hardin, Technical Manager, is intended to be an all-inclusive list of deficiencies at your facility. A copy of the Form FDA 483, Inspectional Observations, is attached. It is your responsibility to assure that all drugs are manufactured, processed, packed, and held according to 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. Until FDA confirms that these deficiencies have been corrected, we will recommend withholding approval of all applications listing your firm as a supplier of bulk API [REDACTED]

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.

You should 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 prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. Your response should be sent to Serene A. Kimel, Compliance Officer, at the address noted in the letterhead.

Sincerely yours,

for Roger E. Kline
Ballard H. Graham, Director
Atlanta District

cc: Mr. Jim Trafton
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