EDITED EXCERPTS FROM ACTUAL 483 OBSERVATION REPORTS
BY FOOD AND DRUG ADMINISTRATION INVESTIGATORS

MANUFACTURING CONTROLS

1. .....Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically, the QCU approved document titled “Process Validation Protocol” to evaluate the accuracy of scale readings for the sustained release coating process as the difference in the ..... readings was identified as the cause for the shift in dissolution performance at the 8th hour. Five commercial batches of ..... were manufactured under this validation protocol, which resulted in three batches that failed dissolution specifications at the 8th hour and a batch that deviated from the target capsule fill weight specified in the manufacturing batch record, in order to meet dissolution specification at the 8th hour. The remaining six finished product batches of ..... capsules that had acceptable dissolution results were released by the Quality Control Unit and distributed despite the demonstrated variability and significant inconsistencies of the manufacturing process documented in interim reports ..... and the final validation report approved on ..... 

2. .....Written procedures for cleaning and maintenance fail to include a description in sufficient detail of the methods, equipment and materials used. Specifically, eight out of ten cleaning SOPs reviewed are not specific regarding the washing method (scrub, sponge, cloth, rinse) the number of rinses, or rinsing time or volume of the rinsing agent to be used for the rinsing step:
   a. Section ..... of SOP ..... indicates: “If necessary, brush the interiors and exteriors and walls with ..... detergent.” When asked when brushing is necessary, one operator said that he “thinks” it is always necessary to brush while another operator said that it should be done for every major cleaning.
   b. Several sections of SOP ..... indicate spraying or rinsing parts with ..... Operator ..... said that he can either spray the part with ..... and wipe it with a cloth a “little bit” damp with ..... or just wipe it with the ..... damp cloth.
   c. Several sections of SOP ..... (version 4) is missing a rinse step. After washing parts with the detergent solution, step ..... indicates wiping with ..... According to the firm’s officials, this step was inadvertently left out when the current version was written.

3. .....Written records of investigations into unexplained discrepancies do not include the conclusions and follow-up. Specifically, the cleaning swab failure investigations reported ..... disclosed that the root cause was the failure to thoroughly rinse or clean equipment or that the cleaning procedures were not specific enough. The QC Unit failed to follow up on these findings and none of the SOPs involved in these investigations have been revised to make the rinsing and/or cleaning instructions more specific.

4. .....Written procedures are not followed for evaluation conducted at least annually to review records associated with a representative number of batches, whether approved or rejected. Specifically, Drug Product Annual Reviews for ..... Tablets reporting periods ..... were not completed, approved, or signed by management. The Drug Product Annual Review’s stability summary, regulatory review, quality summary report, conclusions and recommendations and signatures were not performed.
MANUFACTURING-STERILE PRODUCT CONTROLS

1. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process. Specifically, the firm’s documentation of the deviation observed during the examination of vials from media fill and the written investigation which covered this media fill performed are inadequate in that:
   a. There is no documented assurance that all trays were examined and no explanation for the fact that two positive vials were subsequently found during the random selection of vials for post-incubation growth promotion testing of the media.
   b. The two organisms Staphylococcus epidermidis and Micrococcus sp., were isolated from the positive vials. There is no documented explanation which would explain the failure of the positive vials to have been identified and in fact, the following statement was recorded in Microbiology Investigation: “It is remotely possible, although unlikely, that growth of slow growing organisms only became visible after the 14 day inspection. Growth in these vials was clearly visible and was not typical of slow growing organisms.”
   c. On , a final tally sheet prepared to include the positive vials was signed by both the microbiology manager and a QA employee who verified the results. However, despite the fact that the sheet recorded three positive vials, the media fill was accepted as passing. Three positive vials would have exceeded the limit. On , the number of positive vials was crossed out, changed and initialed without a note to explain the correction. It is also noted that the Microbiology Investigation Log Book has a record of three positive vials “discovered in GPQ samples from lot ”.
   d. On , a correction was made on the visual inspection reject tally sheet to change the recorded “inspection number” from “1” to “3”.

2. The firm has failed to assess the need for revalidation of its “Cleaning & Sanitization of Aseptic Process Cleanrooms” procedure after making a significant revision. Specifically, on , the firm obsoleted the performance of spray fogging of all equipment, walls, windows, doors, door handles, and floors with 70% IPA.

3. A deviation from the written procedure entitled, “Sterile Filtration of Products” was not appropriately recorded and justified. Specifically, the firm inserted a fine type stainless steel mesh (micron width) into each of the nozzles used in the aseptic filling of saline solution. The firm has utilized the stainless steel mesh since with no assessment as to the impact of the change on sterile finished product.

4. The firm has failed to maintain an adequate written record of major equipment maintenance. Specifically, the firm passivates stainless steel production equipment used in the manufacture of sterile ophthalmic solutions with an acid wash to render it clean and free of metal particulates and oxides. The firm has only recorded passivation of tank on and the filling pump on .

5. Established laboratory control mechanisms are not followed. Specifically, following an out of specification result for particulates in the 6 month, inverted CRT stability sample of , the analyst reported that the “Test Failed” on the report sheet and forwarded this to the group leader, however, no action was taken. According to the microbiology manager, the sheet must have been missed and was not discovered for more than two months.
DURING A REVIEW OF FD483 INSPECTION REPORTS WE OBSERVED:

LABORATORY CONTROLS

1. .....Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier’s test results at appropriate intervals.
   a. The reliability of the component supplier’s Certificate of Analysis for active ingredients are only based upon testing of the initial lot of active ingredient that is received. In addition, the verification of the supplier’s Certificate of Analysis for active ingredients can be accomplished every three years.
   b. The firm did not complete full testing to establish the reliability of the vendor’s Certificate of Analysis for ..... raw materials used to manufacture ..... The supplier’s Certificate of Analysis for ..... indicates the presence of sulphates, heavy metals, 2,6 dimethylaniline. In addition, melting range, acidity, clarity and color of solution, water content, and chromatographic purity have not been conducted at least once by the firm. The supplier’s Certificate of Analysis for ..... indicates that the following analyses such as volatile oil, pipirine, refractive index, optical rotation, specific gravity, scoville value, color units, residual solvents following analysis were not performed at least once by the firm.

2. .....The investigation report ..... was for the assay of ..... raw material. The sample was analyzed twice with one of the two assay results not meeting specification. A re-injection of the original vial was made which confirmed the original OOS result. A new aliquot from the original flask was taken and analyzed which gave a within specification result. The firm concluded analyst error in that the analyst did not mix the flask sufficiently or did not mix the flask at all. However, in this case, the analyst stated the flasks were properly mixed. Furthermore, in an attached memorandum, the analyst involved refused to sign an acknowledgement of analyst error. The firm could not provide scientific justification as to what sufficient mixing would be for this analysis or any documented evidence that the analyst did not follow procedure. There was no further investigation into this lot of raw material.

3. .....The investigation report ..... was for intermediate product testing of lot ..... The Phase I investigation as described on form ..... does not state why the original OOS result was invalidated, no details on how the samples were re-analyzed and there is no assignable cause mentioned, yet there was no Phase II investigation performed and the original investigation record was voided with product being released as meeting specification.

4. .....The investigation report ..... was for the assay of ..... raw material. This lot along with three other lots was tested for impurities with lot ..... failing to meet the specification for ..... impurity. The assignable cause was determined to be equipment failure (bad injection of the sample most likely due to an air bubble). During the investigation, the laboratory reviewed the online ..... logbook which did not indicate any equipment problems or malfunctions. The laboratory also reviewed the chromatograms as part of the investigation and determined that this lot had a different baseline than the other three lots. However, there is no description of how the baseline was different and how that would impact on the results. Furthermore, the firm did not perform any type of verification of the injector system before making the conclusion that the equipment did not inject properly and there was no corrective action implemented for the ..... system. Therefore, there is no specific justification for invalidating the OOS results. The other three lots tested concurrently were not re-injected. Though ..... is not a currently marketed product, the laboratory practices shown in this investigation were inadequate. This is a repeat observation from the previous FDA 483 dated .....
DURING A REVIEW OF FD483 INSPECTION REPORTS WE OBSERVED:

MEDICAL DEVICE-MANUFACTURING CONTROLS

1. .....Corrective and preventive actions have not been verified or validated to ensure that the action is effective and does not adversely affect the finished device. Specifically, the firm implemented two corrective actions in response to potential patient sample mismatches occurring with the use of ..... with ..... software. These corrective actions included: manual workaround for patient sample identification and new purging instructions. The firm failed to verify or validate these corrective actions prior to implementation in the field.

2. .....The procedures addressing documentation of corrective and preventive action activities were not implemented. Specifically:
   a. CAPA procedures require the documentation of risk assessment. There are no procedures that define or indicate how this risk assessment is/will be determined. At least ..... CAPA files reviewed only indicate the addressed non-conformance was of “minimal impact.” There is no documented explanation or rationale for this assessment. At least ..... of CAPA files reviewed lack any required risk assessment.
   b. CAPA files, ..... lack the required information to show investigation, action, closure and verification information.
   c. CAPA files that indicate they have been closed and verified as effective do not indicate how the effectiveness was determined.
   d. CAPA procedures do not provide time-frames for monitoring completion or closure of CAPAs.
   e. CAPA procedures give a time frame of ..... days after closure to verify the adequacy of the CAPA. However, ..... CAPA files reviewed show that this time frame was exceeded or that there was no review done at all. The CAPA files do not contain or refer to evidence to justify this.

3. .....Procedures to ensure that equipment is routinely maintained were not implemented. Specifically, at least ..... maintenance records maintained by firm to show routine, as well as non-routine maintenance do not reflect the specific repairs, do not indicate whether or not the issues requiring repair do/do not require re-qualification or any impact on the finished device, and the records are not signed or approved.

4. .....Procedures for addressing the evaluation and investigation of nonconforming product were not complete. Specifically, failure investigation procedure to review, evaluate, and investigate complaints involving possible failure of a device or labeling to meet any of its specifications, is incomplete. For example: In the case of ..... complaints, there are no established procedures and/or requirements including but not limited to:
   a. Collecting and documenting treatment history data when available.
   b. Collecting and documenting I/O (input and output volumes during a treatment) history including the I/O of the time period(s) in question when available.
   c. The methodology used in identifying the failure mode(s) and/or mechanisms(s) along with the associated component(s) involved.
   d. The methodology including the tools/equipment/supplies used to perform the simulated run (to verify machine functionality and accuracy).