GMP Trends

DISTRICT ADDRESS	DATE OF ISSUE
GMP Trends LLC P.O. Box 1111 Firestone, Colorado 80520	Introductory
	C.I. ISSUE Category Sample

NAME AND TITLE OF INDIVIDUALS TO WHOM REPORT IS ISSUED
To: Responsible Person, Director of Quality Assurance

FIRM NAME	STREET ADDRESS
Pharmaceutical and Related Industries	5600 Regulation Lane
CITY, STATE AND COUNTRY United States of America and Worldwide	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical and Medical Device

DURING A REVIEW OF INSPECTION REPORTS OF FIRMS (I) (WE) OBSERVED:

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

QUALITY SYSTEMS

1. .....The responsibilities and procedures applicable to the quality control unit are not fully followed.

   Specifically, your Quality Assurance Unit is ineffective. Some current examples include:

   a. **Your laboratory equipment calibration and use logbooks have not been updated in 18 months, except for one laboratory scale. This includes the HPLC used to perform assay analysis for finished drug product release.**
   b. **Your drug product retains have not been monitored or tracked for the past year. The last logbook entry for the placement of a retain sample was ten months ago. The last logbook entry for monitoring the temperature and humidity in your retain room was recorded nine months ago.**
   c. **You do not have major equipment cleaning and maintenance logs.**
   d. **None of your manufacturing procedures have been updated in the last five years.**
   e. **There is no written procedure for documenting and investigating manufacturing deviations. There were no recorded manufacturing deviations in the last two and a half years.**
   f. **Your quality assurance procedures have not been updated since before the previous FDA inspection two years ago.**

2. .....The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

   Specifically, your Quality Control Unit does not perform adequate investigations.

   a. **Your Quality Control Unit did not fully follow Work Instruction ....., "Out of Specification Procedure." This required the QC Unit to "undertake an investigation in a timely manner", however, OOS Investigation ....., was opened 68 days after the initial OOS test and subsequent release of Lot ....., for ..... Furthermore, that same Work Instruction requires that "operations are ..... within the regulatory frameworks," and that "Regulatory bodies require that: A valid reason must be determined to invalidate the OOS result." Your reason for invalidating the above OOS was that the solvent level on the autotitrator, 68 days prior, was low. There is no documentation of solvent levels on the autotitrator, therefore this conclusion cannot be considered valid.**
   b. **Your Quality Control Unit failed to fully follow Work Instruction ....., "Customer Complaint Procedure," for complaint ....., regarding a "number of skin irritations at the school" because the Work Instruction requires that the complaint investigator "Contact the complainant for additional information." There is no indication that any attempt was made to contact the customer to obtain additional information.**

3. .....The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

   Specifically, the Quality Unit is deficient. Decisions and deviations relating to testing are made without quality unit input, approval or documentation. Your firm's management stated that laboratory management may communicate with customers through a Technical Services Representative, outside of the Quality Unit, to discuss issues with laboratory testing and obtain customer approval for planned deviations. For example, an email was sent to a customer regarding Lot ..... from a laboratory personnel to Marketing Technical Services stating ..... A Technical Services Representative replied, "Customer has approved the sample. Please result and close out." The Quality Unit was not involved in the communication and your firm's management stated that there is no documented procedure for this type of communication.

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DURING A REVIEW OF INSPECTION REPORTS OF FIRMS (I) (WE) OBSERVED:

MANUFACTURING CONTROLS

1. .....There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

   Specifically, deviation investigations into the dissolution test failures for ….. lots on stability studies did not include a review and evaluation of complaints and adverse events received in this time frame. Sixty-two (62) of the 63 complaints received over the last year for ….. has been for adverse events. No lot numbers were associated with the adverse event reports, and there was no indication that additional information has been requested for these adverse event reports.

2. .....The plumbing system contains defects that could contribute to the contamination of drug products.

   Specifically, the plumbing of your ….. system is deficient in such that there is a dead leg of approximately 20 feet long located in the Utensil washroom. You connected ….. of your ….. to a water distribution line in the Utensil washroom. This distribution line consists of two sinks and a water heater. The water from ..... provides cold and hot water for utensil washings through a pair of taps fitted on the two sinks in the Utensil cleaning room. The total length of the piping that connects to ….. is about 20 feet long. You use this water to clean the utensils that are used in the manufacturing of sterile drug products. You sample the water for quality testing from the ….. that is directly situated on the ….., and this sampling does not represent the quality of water that is used directly from the tap for cleaning purpose.

3. .....Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

   Specifically, your firm failed to perform hold-time studies in support of holding ANDA ….. drug products in an uncovered bulk storage/mixing tank greater than ….. hours prior to the packaging into smaller containers and closure systems to ensure the delay does not alter the quality of the drug product. Your firm's Director of Technical Operations reported no hold-time studies were performed for ANDA …..

4. .....Equipment for adequate control over micro-organisms and dust is not provided when appropriate for the manufacture, processing, packing or holding of a drug product.

   Specifically, during a review of your firm's Cleanroom Certification Report, three out of ….. HEPA filters located in Manufacturing Room ….., along with one out of ….. HEPA filters located in Manufacturing Rooms ....., were found to be leaking, as documented within CAPA ….. The leaking HEPA filters were not replaced and re-qualified until six months after they started leaking. A total of ….. drug product batches were manufactured in Manufacturing Room ….., and ….. batches in Manufacturing Room ….., between the date the leaking HEPA filters were identified to replacement date. Your firm's Director of Quality Assurance reported no deviation was initiated to document the HEPA filter failure.

5. .....Buildings used in the manufacture, processing, packing or holding of drug products are not free of infestation by rodents, birds insects, and other vermin.

   Specifically, during my walk-through, accumulations of dead beetle-like and fly-like insects were present within the weighing and batching rooms of the ….. manufacturing area. The firm's ….. and ….. products were being filled in the firm's filling room on this day.

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DURING A REVIEW OF INSPECTION REPORTS OF FIRMS (I) (WE) OBSERVED:

MANUFACTURING-ACTIVE PHARMACEUTICAL INGREDIENTS (API)

1. .....The water system used to generate water for processing of APIs is not suitable.

   Specifically,

   a. Your firm has not qualified and calibrated ….. water system since its installation over 15 years ago.
   b. Your firm's Production Manager stated that the water system is regenerated after ….. hours of its usage. However, we observed the water system was regenerated after 93:30 hours. Additionally, your firm's water system regeneration procedure is not validated and approved for its intended use. Your firm's QC/QA Manager provided no scientific justification for setting the regeneration frequency after ..... hours.
   c. We observed the water system was in shut-down mode. Your firm's Production Manager stated that in the event of no manufacturing, the water system is turned off. There is a potential for microbial growth inside the water system that if not running may hold water inside units, connecting pipes and other units.
   d. Your firm's QC/QA Manager stated that the firm has no microbiological laboratory, and no microbiological tests are conducted on ….. water that is used in the API manufacturing.
   e. Your firm's QC laboratory has not identified a sampling location for hardness of water.

2. .....Failure of your quality unit to ensure that critical deviations are investigated and resolved.

   Specifically, you did not initiate an investigation for a returned shipment of mislabeled ..... You initiated Reject/Return Number ..... to allow ..... drums of mislabeled ….. to return to this facility. You documented the reason for the shipment reject/return as "Material was mislabeled." You did not initiate an investigation for this discrepancy, as required by SOP ….., "System for Rejected and/or Returned Materials," SOP ....., "Returned and Quarantined Products Handling," and SOP ....., "Reprocessing." Four months later you reprocessed this mislabeled lot into ….., lot ….., and then distributed it.

3. .....Failure to ensure that materials are handled and stored in a manner to prevent degradation or contamination.

   Specifically, I observed several uncapped unused hoses and hose adapters, used to transfer raw materials ..... and ….. from the railcar tankers to the raw material storage silos, stored directly on the ground outside the facility (in the tanker railcar area), exposed to environmental elements.

4. .....Failure of your quality unit to prepare, review, and approve documents related to the manufacturing of intermediates and API in accordance with written procedures.

   SOP ….., "Equipment Cleaning Use and Maintenance Log," were not observed to be followed. Specifically, section 6.11 of your SOP requires every complete page of the log to be reviewed and signed by the Operations Supervisor and checked by the Quality unit. This practice was not observed to be followed for the following production equipment, including but not limited to: equipment log ..... Classifier and equipment log ..... Dryer. For example, nine completed pages of the equipment log ..... Classifier does not include the signatures of the operations or the quality unit, in addition, two completed pages of the equipment log ..... Dryer does not include the signatures of the operations and the quality unit.

5. .....Failure of production operations to quarantine and identify API intermediates.

   Specifically, I observed five sacks of API intermediates for ….. held without any in-process holding tags. All five sacks were held on the second floor of building ….., by ….. Dryer ....., and were marked with ..... You provided five in-process holding tags to demonstrate that these sacks were for API intermediate lot ..... However, none of these tags were observed to be affixed to the five API intermediates during the walkthrough.

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DURING A REVIEW OF INSPECTION REPORTS OF FIRMS (I) (WE) OBSERVED:

DATA INTEGRITY

1. .....Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

   Specifically, the firm's high performance liquid chromatography (HPLC) data acquisition system did not have sufficient controls to prevent deletion or alteration of raw data files. During the inspection, three analysts were observed to have administrative privileges giving them access to the electronic storage system for the HPLC data, and the potential to delete or change directories and files leading to data integrity vulnerabilities. In addition, the firm has had eleven (11) aborted HPLC runs between January to July. The firm was unable to provide any documentation to explain the aborted runs, and the Quality Unit failed to review or evaluate the aborted runs. Furthermore, the Quality Unit has failed to enable the audit trail feature and therefore have not reviewed any of the audit trails to ensure that the analytical methods are being followed or that the analytical raw data is accurate.

2. .....Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

   Specifically, electronic records are used, but they do not meet systems audit trail requirements to ensure that they are trustworthy, reliable, and generally equivalent to paper records. Equipment includes, but may not be limited to: HPLC, GC, and BioLumix. Your BioLumix computer allowed the quality control analysts the ability to change the date and time of the computer and, in turn, the BioLumix system. Your QC Laboratory Manager, who also runs sample tests in the HPLC equipment, did not have access controls that would prevent the deletion or altering of raw data files in the HPLC equipment.

3. .....Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

   Specifically, the warehouse management systems used for the receiving and distribution of raw materials, components and finished drug products is not validated for its intended use. The system is also used to generate batch records used during the manufacture of drug products. There is no assurance that information inputted into the systems are reliable or prevented from deletion or alteration.

4. .....Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, sampling plans and test procedures designed to assure that components and drug products conform to appropriate standards of identity, strength, quality and purity.

   Specifically, according to your Director of Quality Assurance and Analytical Services, you do not perform a complete review of all system audit trails to assure the integrity of the data.

5. .....Test devices are deficient in that instruments and recording devices not meeting established specifications are used.

   Specifically, the Quality Control Supervisor was observed and capable of changing the HPLC testing parameters, such as, but not limited to, delete saved testing method folder and renaming saved files containing testing results.

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DURING A REVIEW OF INSPECTION REPORTS OF FIRMS (I) (WE) OBSERVED:

LABORATORY CONTROLS

1. …..Laboratory controls do not include the establishment of scientifically sound and appropriate standards designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

   Specifically,

   a. **You have not performed method validation and suitability testing on your finished drug products to establish that client test methods for both analytical and microbial analysis are appropriate for determining concentration and detecting microbial limits. Per your VP of Quality and Regulatory, your contract laboratories use USP monographs to analyze these products for microbial analysis and non-compendial methods for all analytical testing, with the exception of the ….., which follows a USP method.**

   b. **You implemented in-house microbial water testing for your ….. water system. Per your Microbiologist, you have not performed growth promotion testing on purchased media used for this analysis to determine if the media is capable of growth.**

2. …..Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity.

   Specifically, laboratory documents are not always fully completed in a contemporaneous manner. I observed that the Drug Product Stability Study Data Record fields for microbiological test results were pre-filled in by the Analyst ….. before ….. received these test results. ….. stated that he filled out this information by accident, and your Quality Assurance Manager instructed ….. to correct this documentation by crossing out the pre-filled values with ….. initials and date. Additional non-contemporaneous data entries include, but are not limited to, the stability sample data records for the ..… drug products that have multiple worksheets that show white-out was used to cover original entries, that are missing dates, and/or that show dates of test completion were pre-filled on the sheets by typing.

3. …..There is no written testing program designed to assess the stability characteristics of drug products.

   Specifically, the firm claims that both their ….. have a 5-year expiry period. However, specifically,

   a. **The firm has no written stability protocol and no documentation of any stability studies for their ….. drug products that they manufacture.**

   b. **The firm ships out samples of the their ..... drug product to a contract laboratory for testing, however, only .... .assay testing is conducted. No testing for the presence of impurities or degradants is conducted.**

4. …..Testing and release of drug product for distribution does not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release.

   Specifically, your firm does not receive, review, and approve microbiological test results for ….. prior to release. Microbiological tests not being performed prior to release include: ….. and testing for objectionable microorganisms.

5. …..Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without performing at least one specific identity test on each component establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

   Specifically, your firm failed to conduct testing to the ....., which contains ….., which is used for the formulation of the solution for the ….. with ..... In addition, reliability of the supplier has not been established to ensure that the quality results of the CoA are from validated analytical methods, and the expiration date reported is based on stability studies at the supplier site. At least one batch of ….. was accepted and used without complying with the specifications.

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DURING A REVIEW OF INSPECTION REPORTS OF FIRMS (I) (WE) OBSERVED:

PACKAGING & LABELING CONTROLS

1. …..Documents were not approved by designated individual(s) prior to issuance.

   Specifically, I observed the ….. labeling procedures were not released and approved prior to issuance. The firm has not established adequate written procedures to ensure proper release of Quality System documents.

2. …..A process whose results cannot be fully verified by subsequent inspection and test has not been adequately validated according to established procedures.

   Specifically, your firm's Process Validation procedure is inadequate in that validations do not provide adequate assurance that processes will consistently produce product that meets specifications. For example, your firm's Operational Qualification (OQ) Protocol and Report for the ..... Heat Sealer protocol ....., and Process Qualification (PQ) Protocol and Report for ….. Packaging, Packaging-PQ:

   a. **Failed to include seal integrity testing to ensure the sealing process for the ….. would consistently produce seals that maintain the sterile barrier. These validations only consisted of testing for seal strength and visual inspection of gross seal defects.**
   b. **Failed to ensure measuring and test equipment was sufficiently calibrated and capable of producing valid results for the range of values expected in the validation.**

3. …..There is a lack of written procedures describing in sufficient detail the receipt, identification, handling and examination of labeling and packaging materials.

   Specifically, your firm lacks written procedures for the labeling operations of drug products. Your firm relabels ….. drug products. Your firm custom prints company logos, as well as the drug ingredient information on packaging with the lot and expiration date pre-printed. Currently, your firm has no written procedures that detail the issuance, examination, use, and destruction of labels for ….. drug products.

4. …..Results of inspection of packaging and labeling facilities are not documented in the batch production records.

   Specifically,

   a. **Examination of labeling materials for suitability and correctness before labeling operations is not documented in the batch production records. Prior to labeling operations, Quality Control compares the label proof (in the batch production record) to the physical labels, however, this check is not documented in the batch production record. Additionally, during labeling, employees inspect the labels for stickiness, which is also not documented in the batch production record.**
   b. **Inspection of the labeling facilities immediately before use to assure that all drug products have been removed from previous operations and to assure that labeling materials not suitable for subsequent operations have been removed is not documented in the batch production records. The line operators are responsible for line clearance and the lead is responsible for verifying and inspecting the line prior to labeling operations.**

5. …..Establishment of the reliability of the container and closure supplier's report of analyses is deficient in that the test results are not appropriately validated at appropriate intervals.

   Specifically, when I requested the firm's management to review the release data on the packaging containers and closures, your director stated that the jars had been accepted without COA from the vendor and no other testing had been performed.

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DURING A REVIEW OF INSPECTION REPORTS OF FIRMS (I) (WE) OBSERVED:

MANUFACTURING-STERILE PRODUCT CONTROLS

1. .....There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

   Specifically,

   a. SOP ….., "Investigations of Out of Specification Results in Microbiological Analysis," states: "If evidence of microbial growth is observed, the product does not comply with the test for sterility unless it can be demonstrated that the test was invalid," and lists the following reasons for invalidating the test:

      i. The data of the microbiological monitoring of the sterility testing facility shows a fault.

      ii. A review of the test procedure used during the test in question reveals a fault.

      iii. Microbial growth is found in the negative controls.

      iv. Identity of microorganisms isolated from the test may be ascribed unequivocally to faults with respect to the material and/or technique used in conducting the sterility test procedure. The SOP notes that unequivocally means that the exact strain match for the microorganism isolated from the sterility test positive and the organism found on the personnel monitoring or within the area or room where the sterility test was conducted.

   b. During our review of your film's sterility testing failure investigations, the following was observed:

      i. Investigation .....: Your firm's sterility testing of ….., Batch ....., was observed to be positive for growth in a ….. canister on day 3 of incubation. Spore forming organism Lysinibacillus fusiformis was recovered from the sample. The same organism was previously recovered from environmental monitoring (EM) samples found in the microbiological laboratory; however, the DNA sequence of the sample and lab organisms did not match. Your investigation states: "Based on the laboratory investigation, no probable cause was identified for sterility positive results," and "a definite cause for the observed OOS could not be identified in laboratory and production investigation."

      ii. Batches ….. were each ….. sterilized in a different ….. load, and all passed their individual sterility tests. Your investigation concluded these ….. were sterile, and they were released for distribution; however, your firm's investigation into the sterility test sample failure in ….. did not conclusively demonstrate that the contamination in the sample test canister was unrelated to a sealing machine problem noted during filling activities.

2. .....Procedures for the cleaning and maintenance of equipment are deficient regarding the protection of equipment from contamination prior to use.

   Specifically,

   a. We observed a small test tube rack with a brownish-black, gummy substance placed in the shelf labelled as 'Clean' along with other cleaned items. In addition, a dirty spatula with what appeared to be a human hair was observed in a second shelf labeled as 'Clean.' Another spatula with numerous small dents filled with black material was also seen in the same shelf. A dirty soiled glove was found on the rack labelled as 'Clean.'

   b. The hose used to transfer ….. from the ….. tank into the compounding vessel was observed to be discolored. The Plant Manager stated that the hose is air dried by hanging in the class 100000 area and then reused.

3. .....Procedures for the cleaning and maintenance of equipment are deficient regarding maintenance and cleaning schedules, including, where appropriate, sanitizing schedules.

   Specifically, no written procedures exist for the sanitization of the ….. System, and the firm does not perform periodic sanitization of the ….. System.

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DURING A REVIEW OF INSPECTION REPORTS OF FIRMS (I) (WE) OBSERVED:

MEDICAL DEVICE-MANUFACTURING CONTROLS

1. .....Complaints involving the possible failure of a device to meet any of its specifications were not investigated where necessary.

   Specifically, your firm failed to investigate the causes of the complaints to determine the possible failure of a device. For example: Complaint ….. was reported for the ….. device with ….. for failing to function properly. The device was returned, and the firm analyzed the device on the same date. There is no documented record to demonstrate that the firm conducted any test to determine the possible failure for the device.

2. .....Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established.

   Specifically, your firm's Vendor Qualification procedure is inadequate in that:

   a. Suppliers are not consistently evaluated and monitored in accordance with established procedures. For example, review of seven (7) randomly selected suppliers revealed:

      i. Two (2) suppliers, classified as Level One, had no documented evaluation for initial selection or on-going monitoring. Section 2.2.i in Step B states the vendor evaluation for a Level One supplier is "Request for completion of ….. Vendor Evaluation Form and ….. after the initial qualification."

      ii. One (1) supplier, classified as Level Three, did not have an on-site audit completed, although they were added to the approved supplier list and your firm had purchased ….. pouches from them for use in sterile packaging devices and other products. Your firm had no documented justification for use of the components prior to the supplier audit.

   b. Suppliers are not consistently categorized in accordance with established procedures. Review of seven (7) randomly selected suppliers revealed one (1) supplier was classified as Level One when it should have been Level Two. Additional controls on Level Two suppliers include a vendor audit when necessary and vendor evaluations at least …..

3. .....Procedures for finished device acceptance have not been established.

   Specifically, your firm has not established procedures for finished device acceptance to ensure that each production lot meets acceptance criteria. The ….. measurements, specified in the DMR, are not documented in the DHR for ….., for Lot ….. The president stated that these measurements are taken using a ....., during production; however, these measurements are not documented.

4. .....Sampling plans are not based on valid statistical rationale.

   Specifically, your firm's sampling plans are not consistently based on a valid statistical rationale. For example, you firm's Operation of the Tester procedure states in section 6 "For ….., ... per sealer is tested ….. of sealing operations." This sampling plan could not be traced back to a valid statistical rationale.

5. .....Service reports are not documented and do not include the required information.

   Specifically, I observed that the service reports for the repaired ….. do not contain the required information and data. The records do not record the service performed nor the test and inspection data.

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