GMP Trends

DISTRICT ADDRESS	DATE OF ISSUE
GMP Trends LLC P.O. Box 1111 Firestone, Colorado 80520	November 15, 2018
	C.I. ISSUE Issue #1004

NAME AND TITLE OF INDIVIDUAL 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	TYPE OF ESTABLISHMENT INSPECTED
United States of America and Worldwide	Pharmaceutical and Medical Device

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

EDITED EXCERPTS FROM ACTUAL 483 OBSERVATION REPORTS

BY FOOD AND DRUG ADMINISTRATION INVESTIGATORS

********** **SPECIAL ISSUE** **********

483 OBSERVATIONS PERTAINING TO DEFICIENCIES REGARDING MEDICAL DEVICES
21 CFR 803 SUBPART A – GENERAL PROVISIONS, 21 CFR 820 SUBPART B – QUALITY SYSTEMS REQUIREMENTS,
21 CFR 820 SUBPART E – PURCHASING CONTROLS AND 21 CFR 820 SUBPART J – CORRECTIVE AND PREVENTATIVE ACTION

21 CFR 803 SUBPART A – GENERAL PROVISIONS

1. .....Written MDR procedures have not been implemented. {21 CFR 803.17}

   Specifically, your firm conducted assessment of MDR procedures and retrospective review of an enlarged risk-based sample in order to capture deficiencies, augment training, and implement corrective actions including the reporting of complaints that met the reportability criteria but had not been reported in accordance with the procedures timeframes. SOP ....., "Regulatory Reporting Procedure," established the process the firm must follow to determine whether an event is reportable, reporting procedures, and timeframe requirements. This procedure applies to complaints related to products approved for commercial distribution for clinical use, including investigational products which have been commercialized anywhere in the world. Your firm failed to follow this procedure as evidenced by:

   a. During the last two years, your firm reported 279 MDRs beyond the ..... timeframe as required by regulations and your procedures. Furthermore, your firm opened CAPA ..... to address "complaints resulted in not reporting to regulatory agencies" and documented a verification of effectiveness with late reporting of MDRs in the months from April to December of last year to include: 15% reported late in November, 9% reported late in April, and 6% reported late in May. This CAPA was closed to corporate quality earlier this year, which documented:

      i. Complaint and MDR Procedure revision: Completed.

      ii. Approval of retrospective review plan for complaint and MDR reportability: Completed.

      iii. Utilize the retrospective review protocol: Completed.

      iv. The phase II verification of effectiveness (by management review): Documented as being completed (not including late reporting for clinical studies complaints).

   Still, your firm has documented 37 MDRs reported beyond 30 days (late) to the FDA since the start of this year.

2. .....Written MDR procedures have not been developed and implemented. {21 CFR 803.17}

   Failure to implement procedure SOP ....., "Event and Incident Reporting for Medical Devices," in that a "supplemental" or "follow-up" report was not submitted to FDA within 30 days of the day when your firm obtained additional MDR reportable information that was not provided because it was not known, or was not available, when your firm submitted the initial report. Specifically, your firm obtained relevant information regarding the event associated with the misconfiguration of instrument ..... that prompted the issuance of a CAPA, Field Action (Recall), and design change, as well as information regarding the potential extent of the reporting of erroneous results for ..... patients and did not submit a supplemental report to update the initial report. Several months later, your firm had obtained concrete information indicating the ....., instrument ....., was incorrectly configured. The misconfiguration was traced back to last fall. A supplemental report was eventually submitted at the end of this inspection.

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

21 CFR 820 SUBPART B – QUALITY SYSTEMS REQUIREMENTS

1. …..Procedures for conducting quality audits were not established. {21 CFR 820.22}

   Specifically, you stated that your firm conducts on-site audits on a ….. basis at the contract manufacturers to ensure that the ….. devices are manufactured according to specifications. There is no written procedure regarding the quality audits your firm conducted, and no records to document that a quality audit has been conducted between your firm and the contract manufacturers over the last 10 years.

2. …..Quality audits were not performed at defined intervals to determine whether the quality system activities and results comply with quality system procedures. {21 CFR 820.22}

   Specifically, your procedure requires an Internal Audit schedule for each calendar year, and the schedule must be approved within the first quarter of the calendar year. A schedule was not created for the last two years, nor were any audits conducted during this time. This year's audit schedule was signed on the starting day of this inspection.

3. …..Quality audits were not performed at defined intervals to determine whether the quality system activities and results comply with quality system procedures. {21 CFR 820.22}

   Specifically, quality audits that were scheduled to be completed in ….., according to your firm's audit schedule, as per SOP….., "Internal Audits," were not completed. Your firm did not complete quality audits, including but not limited to the following areas: Labeling and Packaging, Post Market Surveillance, Control of Non-Conformities, Corrective and Preventative Action and Device History Record. Your firm was actively manufacturing and selling medical devices, yet senior management officials were unable to assess the effectiveness of their quality system during the same time period.

4. …..Personnel do not have the necessary training to perform their jobs. {21 CFR 820.25(a)}

   Specifically, during my inspection, I interviewed two personnel in Quality Assurance who are responsible for complaint processing. These personnel lacked the understanding of the regulatory requirement to report to FDA within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device has malfunctioned and would likely cause or contribute to a death or serious injury if the malfunction were to recur.

5. …..Procedures for training and identifying training needs have not been adequately established. {21 CFR 820.25(b)}

   Specifically, the last two revisions of the Site SOP for training does not ensure that employees are adequately trained and that their training is documented. For example,

   a. Manufacturing employee ….. did not have a training record documenting that he was trained to manufacture the ….. product line. He was observed manufacturing lot number .....

   b. Manufacturing supervisor ….. trained manufacturing employees on procedure ….. "To Assemble ….." in January of this year. There is no documentation that the supervisor was trained on the procedure prior to training the employees.

6. …..Procedures for training and identifying training needs have not been established. {21 CFR 820.25(b)}

   Specifically, there are no established procedures for defining how third-party sales personnel will be trained in complaint handling responsibilities so they recognize a reportable complaint event, including documentation of any adverse events and how this information is to be conveyed to the complaint handling unit.

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

21 CFR 820 SUBPART E – PURCHASING CONTROLS

1. …..Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established. {21 CFR 820.50}

   Specifically, your firm's procedure, SOP ….., "Supplier Management Program," documents potential suppliers will be reviewed to identify if they meet or have the ability to meet your requirements. The procedure documents that Level 3 suppliers are those that provide finished product assemblies or accessories, which are unique to the design or manufacture of your products, and that this level includes Contract Manufacturers and Significant Suppliers. The procedure defined Significant Suppliers as a Contract Manufacturer where the activities performed are considered to have a higher level of risk with respect to the quality of the device. Your firm required facility audits and supplier questionnaires for Level 3 suppliers and facility audits, supplier questionnaires, contract manufacturing agreements and quality agreements for Level 3 Significant Suppliers. This procedure and the controls it requires have not been adequately defined, documented or implemented as demonstrated by the following:

   a. **Your firm's form Supplier Facility Audit documents areas to be audited during a supplier facility audit. Additionally, the Suppler Management Program required that upon completion of the audit the auditors shall issue an audit report which must contain all pertinent information (i.e. Audit date, auditor, auditees, findings) and informs the supplier as to the correctives measure that are required. However, there is no definition of what would be considered an acceptable audit, and the supplier's ability to meet specified requirements.**

   b. **Your firm's Medium and High Risk Supplier Questionnaire documents yes/no questions for the supplier to answer. However, there is no definition of what answers are considered acceptable or what documentation is required from suppliers to support the answers in order to ensure the suppliers conforms to specified requirements.**

   c. **Your firm identified the contract manufacturer of the ….. as a Level 3 supplier. However, your firm does not have a Supplier Questionnaire for this contract manufacturer.**

2. …..Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established. {21 CFR 820.50}

   Specifically, your Purchasing procedure requires process validation requirements to be outlined in a detailed statement of work and to communicate the requirements with the supplier. This was not completed for several validations.

3. …..Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established. {21 CFR 820.50}

   Specifically, your firm has not implemented the purchasing control procedure SOP ….., "Supplier Qualification Procedure," in that the evaluation for the contracted company that performs calibration services of the power meters and the consultant used to perform the internal quality audit last year was not documented.

4. …..Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established. {21 CFR 820.50}

   Specifically, your firm did not adequately assess the process validation for the several suppliers. Your firm approved ….. as a supplier responsible for manufacturing ….. The process validation provided by supplier documents validation of the ….. process but does not document how a pass/fail continuity test was validated or how crimping and soldering processes were validated. Your firm identified issues with crimping and soldering during design verification. However, your firm did not require process validation of the crimping or soldering process.

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21 CFR 820 SUBPART J – CORRECTIVE AND PREVENTATIVE ACTION

1. …..Procedures for corrective and preventive action have not been adequately established. {21 CFR 820.100(a)}

   Specifically, your firm has failed to investigate the cause of nonconformities described as "drift" related to your ….. machine and identify the actions needed to prevent recurrence of the nonconformities. SOP ….., "Corrective and Preventive Actions," describes your firm's process for handling product that fails to meet your specifications. Section 6.2.6 of this procedure describes a goal of 45 days to complete a root cause investigation of the nonconformance. You opened Corrective/Preventive Action Report (CPAR) ….. to address the issue of "1-3 [inch] drift," exhibited by your ….. machines. Drift was described by your firm's management as the ….. There was no documented action on this CPAR until three months later, when a meeting was held with a consultant to discuss the potential root cause of the drift issue. A root cause was not identified during that meeting and no further work has been conducted on this CPAR as of the start of the current inspection six months after that meeting. Since the meeting with the consultant, your firm has received thirty-nine (39) additional complaints for "drifting," including at least three for machines that drifted the full distance to the base of the unit.

2. …..Procedures for corrective and preventive action have not been adequately established. {21 CFR 820.100(a)}

   Specifically, you did not implement your Corrective and Preventive Action procedure, SOP ....., "Corrective and Preventive Action," in that the increased number of complaints related to issues with "rattling" and "cracks" on the ….. devices met criticality 3 criteria, but you did not issue a CAPA or justify why a CAPA was not required to investigate the root cause and implement corrective/preventive action to resolve these two issues, as required by your procedure. Although an investigation was conducted by your contracted engineering firm and identified a root cause for both issues, you did not verify the corrective/preventive actions prior to implementation to ensure that the actions taken would be effective.

3. …..Procedures for corrective and preventative actions have not been adequately established. {21 CFR 820.100(a)}

   Specifically, your Corrective and Preventative Action Procedure does not include adequate procedures for how to analyze sources of quality data utilizing appropriate statistical methodology.

4. …..Procedures for corrective and preventative actions have not been adequately established. {21 CFR 820.100(a)}

   Specifically, SOP ....., "Quality Planning," does not clearly specify when quality issues identified from trended quality data will result in CAPA action. For example, over the last 18 months your firm received 76 complaints related to the ..... Complaint investigations identified that 30 of these complaints were attributed to a ….. leak. Further investigation to the root cause of the ….. leaks was not elevated to a CAPA.

5. …..Procedures for design change have not been adequately established. {21 CFR 820.100(b)}

   Specifically, change control ….. involved changing the ….. of ….. packaging. The design change has not been adequately verified or validated. For example, hazards associated with the design of ..... devices, in both normal and fault conditions, have not been identified. For example, 36 of 87 complaints (-41%) received for these products over the last three years pertain to difficultly opening the product packaging. The documented risk analysis does not identify this hazard or its associated risks.

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