

Quality Program, CAPA and Audits

3rd Annual FDA and the Changing
Paradigm for HCT/P Regulation

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Summary

- CGTP CGMP QS Regulation
 - “Quality” comparison
 - CAPA comparison
 - Audit comparison

Quality

- Quality Program – 1271.160
 - You must establish and maintain a quality program intended to prevent the introduction, transmission, or spread of communicable diseases through the manufacture and use of HCT/Ps. The quality program must be appropriate for the specific HCT/Ps manufactured and the manufacturing steps performed. The quality program must address all core CGTP requirements listed in Sec. 1271.150(b).

Quality Program

- (b) Functions. Functions of the quality program must include:
 - (1) Establishing and maintaining appropriate procedures relating to core CGTP requirements, and ensuring compliance with the requirements of Sec. 1271.180 with respect to such procedures, including review, approval, and revision;
 - (2) Ensuring that procedures exist for receiving, investigating, evaluating, and documenting information relating to core CGTP requirements, including complaints, and for sharing any information pertaining to the possible contamination of the HCT/P or the potential for transmission of a communicable disease by the HCT/P with the following: (i) Other establishments that are known to have recovered HCT/Ps from the same donor;

Quality Program (cont)

- (ii) Other establishments that are known to have performed manufacturing steps with respect to the same HCT/P; and (iii) Relating to consignees, in the case of such information received after the HCT/P is made available for distribution, shipped to the consignee, or administered to the recipient, procedures must include provisions for assessing risk and appropriate followup, and evaluating the effect this information has on the HCT/P and for the notification of all entities to whom the affected HCT/P was distributed, the quarantine and recall of the HCT/P, and/or reporting to FDA, as necessary.

Quality Program (cont)

- (3) Ensuring that appropriate corrective actions relating to core CGTP requirements, including reaudits of deficiencies, are taken and documented, as necessary. You must verify corrective actions to ensure that such actions are effective and are in compliance with CGTP. Where appropriate, corrective actions must include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence. Documentation of corrective actions must include, where appropriate: (i) Identification of the HCT/P affected and a description of its disposition; (ii) The nature of the problem requiring corrective action; (iii) A description of the corrective action taken; and (iv) The date(s) of the corrective action.

Quality Program (cont)

- (4) Ensuring the proper training and education of personnel involved in activities related to core CGTP requirements;
- (5) Establishing and maintaining appropriate monitoring systems as necessary to comply with the requirements of this subpart (e.g., environmental monitoring);
- (6) Investigating and documenting HCT/P deviations and trends of HCT/P deviations relating to core CGTP requirements and making reports if required under Sec. 1271.350(b) or other applicable regulations. Each investigation must include a review and evaluation of the HCT/P deviation, the efforts made to determine the cause, and the implementation of corrective action(s) to address the HCT/P deviation and prevent recurrence.
- (c) Audits. You must periodically perform for management review a quality audit, as defined in Sec. 1271.3(gg), of activities related to core CGTP requirements.

Definitions 1271.3

- t) Responsible person means a person who is authorized to perform designated functions for which he or she is trained and qualified.
- hh) Quality program means an organization's comprehensive system for manufacturing and tracking HCT/Ps in accordance with this part. A quality program is designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.

From the Preamble

- “..we use the term “quality program” to refer to the set of activities, including management review, training, audits, and corrective and preventive actions, that represent a commitment on the part of an establishment's management to the quality of its products. Whether this set of activities is regarded as a part of manufacture or as a separate system for overseeing manufacture, as preferred by the comment, is not material.”

From the Preamble (cont)

- “We note that the regulation does not require an establishment to hire a separate quality control employee; moreover, we have removed the requirement for the designation of an individual with authority over the program (proposed Sec. 1271.160(c)).”
- “The quality program required under Sec. 1271.160 is a system that each establishment sets up to ensure its compliance with core CGTP requirements. These regulations do not contain generalized quality requirements. “

Quality Control Unit

21 CFR 211.22

- Responsibility and authority to approve/reject all components, in-process materials, packaging, labeling and drug products and authority to review records to assure no errors have occurred and if occur; fully investigated; including contract operations.
- Responsibility to approve/reject procedures/specifications impacting on identity, strength, quality, and purity of the drug product
- Adequate laboratory facilities for testing
- Responsibilities and procedures in writing

Additionally

- 21 CFR 211.100
 - Production and process controls procedures (process validation), including changes ..reviewed and approved by the QCU.
- 21 CFR 211.160
 - Establishment of specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including changes to any...reviewed and approved by the QCU

Additionally

- 21 CFR 211.192 – Production Record Review
 - All drug product production and control records...shall be reviewed by the QCU to determine compliance with all established, approved, written procedures before a batch is released or distributed. Any discrepancies must be thoroughly investigated .

Additionally

- 21 CFR 211.198 - Complaint Files
 - Written procedures established and followed, including provisions for review by the QCU of any complaint related to drug product failures; need for investigation; need to evaluate whether represents and adverse drug experience and, if so, reported properly

Definition – 210.3(b)

- (15) Quality Control Unit means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

Quality System Requirements

- 820.20 Management Responsibility – establish and maintain:
 - Quality policy
 - Organization
 - Responsibility and authority
 - Resources
 - Management representative
 - Management review
 - Quality planning
 - Quality system procedures
 - Quality Audits

Definitions - 820.3

- (s) Quality means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance.
- (u) Quality policy means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility.
- (v) Quality system means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

Differences: CGTP vs. CGMP and QS Regulation; include:

- Organizational
 - Designated individual(s) or unit or structure (CGMP and QS Regulation)
- Responsibility/Authority
 - Review and approval by QCU (CGMP)
 - Management representative (QS Regulation)
- Scope
 - Fitness for use; safety and effectiveness or performance (CGMP and QS Regulation)
 - Communicable Disease Transmission – Core CGTPs

CAPA 1271.160

- (3) Ensuring that appropriate corrective actions relating to core CGTP requirements, including reaudits of deficiencies, are taken and documented, as necessary. You must verify corrective actions to ensure that such actions are effective and are in compliance with CGTP. Where appropriate, corrective actions must include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence. Documentation of corrective actions must include, where appropriate: (i) Identification of the HCT/P affected and a description of its disposition; (ii) The nature of the problem requiring corrective action; (iii) A description of the corrective action taken; and (iv) The date(s) of the corrective action.

CAPA 211.192

- Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup.

CAPA 820.100

- (a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:
 - (1) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;
 - (2) Investigating the cause of nonconformities relating to product, processes, and the quality system;
 - (3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;

820.100 (cont)

- (4) Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;
 - (5) Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;
 - (6) Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; and
 - (7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.
- (b) All activities required under this section, and their results, shall be documented.

Audits 1271.160(c)

- (c) Audits. You must periodically perform for management review a quality audit, as defined in Sec. 1271.3(gg), of activities related to core CGTP requirements.

Definition 1271.3(gg)

- (gg) Quality audit means a documented, independent inspection and review of an establishment's activities related to core CGTP requirements. The purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

Audits 211?

- No specific requirement for internal audits
- Common industry practice to conduct such audits
- Requirement for annual product review

211.180 (e)

- Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:
 - (1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.
 - (2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under Sec. 211.192 for each drug product.

Audits 820.22

- Each manufacturer shall establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system. Quality audits shall be conducted by individuals who do not have direct responsibility for the matters being audited. Corrective action(s), including a reaudit of deficient matters, shall be taken when necessary. A report of the results of each quality audit, and reaudit(s) where taken, shall be made and such reports shall be reviewed by management having responsibility for the matters audited. The dates and results of quality audits and reaudits shall be documented.

Definition 820.3

- (t) Quality audit means a systematic, independent examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to determine whether both quality system activities and the results of such activities comply with quality system procedures, that these procedures are implemented effectively, and that these procedures are suitable to achieve quality system objectives.

For all internal audits:

- Compliance Policy Guide 130.300
- FDA's policy is .."not to review or copy a firm's records and reports that result from... audits"
- FDA may seek written certification that such audits and inspections have been implemented, performed, and documented and that any required corrective action has been taken
- The intent of the policy is to encourage firms to conductaudits and inspections that are candid and meaningful.
- Limited exceptions – e.g. inspections by warrant