



US/EU GMP Collection for Sterile Products including selected annexes

21 CFR Part 210

Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs; General

21 CFR Part 211

Current Good Manufacturing Practice for Finished Pharmaceuticals

21 CFR Part 11

Electronic Records; Electronic Signatures

EU Guidelines for GMP, Part I

Medicinal Products for Human and Veterinary Use

EU Guidelines for GMP, Part II

Basic Requirements for Active Substances used as Starting Materials

EU Guidelines for excipients

EU Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use

EU Guidelines for GMP, Annexes

- 1 Manufacture of Sterile Medicinal Products
 - 2 Manufacture of Biological active substances and Medicinal Products for Human Use
 - 8 Sampling of Starting and Packaging Materials
 - 11 Computerised Systems
 - 13 Manufacture of Investigational Medicinal Products
 - 15 Qualification and validation
 - 16 Certification by a Qualified person and Batch Release
 - 17 Parametric Release
 - 19 Reference and Retention Samples
- Glossary

§210.2 Applicability of current good manufacturing practice regulations

(a) The regulations in this part and in Parts 211, 225, and 226 of this chapter as they may pertain to a drug and in Parts 600 through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise.

In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in Parts 211, 225, and 226 and Parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

(c) An investigational drug for use in a phase 1 study, as described in § 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in § 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a phase 2 or phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211.

[43 FR 45076, Sept. 29, 1978, as amended at 73 FR 40463, July 15, 2008, 74 FR 65431, Dec. 12 2011]

§210.3 Definitions

(a) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in Parts 211, 225, and 226 of this chapter.

(b) The following definitions of terms apply to this part and to Parts 211, 225, and 226 of this chapter.

(1) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).

(2) *Batch* means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

(4) *Drug product* means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

- 5) *Fiber* means any particulate contaminant with a length at least three times greater than its width.
- (6) *Non-fiber-releasing filter* means any filter, which after any appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered.
- (7) *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.
- (8) *Inactive ingredient* means any component other than an "active ingredient."
- (9) *In-process material* means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.
- (10) *Lot* means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.
- (11) *Lot number, control number, or batch number* means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.
- (12) *Manufacture, processing, packing, or holding of a drug product* includes packaging and labeling operations, testing, and quality control of drug products.
- (13) The term *medicated feed* means any Type B or Type C medicated feed as defined in 558.6 of this chapter. The feed contains one or more drugs as defined in section 201(e) of the act. The manufacture of medicated feeds is subject to the requirements of Part 225 of this chapter.
- (14) The term *medicated premix* means a Type A medicated article as defined in 558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of Part 226 of this chapter.
- (15) *Quality control unit* means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.
- (16) *Strength* means:
- The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or
 - The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

- (xii) systems to ensure that any activity contracted out is subject to a written contract;
- (xiii) maintenance of an effective system whereby complaints are reviewed and excipients may be recalled;
- (xiv) change management and deviation management system;
- (xv) self-inspection program;
- (xvi) environmental control and storage conditions.

Chapter 3 - Determination of excipient manufacturer's risk profile

3.1. After determination of the appropriate GMP, a gap analysis of the required GMP against the activities and capabilities of the excipient manufacturer should be performed.

3.2. Data/evidence to support the gap analysis should be obtained through audit or from information received from the excipient manufacturer.

3.3. Certification of quality systems and/or GMP held by the excipient manufacturer and the standards against which these have been granted should be considered as such certification may fulfil the requirements.

3.4. Any gaps identified between the required GMP and the activities and capabilities of the excipient manufacturer should be documented. Furthermore, the manufacturing authorisation holder should perform a further risk assessment to determine the risk profile, e.g. low risk, medium risk or high risk, for that excipient manufacturer. EudraLex Volume 4, Part III, ICH Q9 should be used for that purpose. Quality risk management tools such as those listed there — HACCP etc. — should be used for this.

3.5. The manufacturing authorisation holder should have a series of strategies ranging from acceptance through control to unacceptable for the different risk profiles and based on these a control strategy, e.g. audit, document retrieval and testing, should be established.

Chapter 4 - Confirmation of application of appropriate GMP

4.1. Once the appropriate GMP for the excipient and the risk profile of the excipient manufacturer have been defined, ongoing risk review should be performed through mechanisms such as:

- (i) number of defects connected to batches of excipient received;
- (ii) type/severity of such defects;
- (iii) monitoring and trend analysis of excipient quality;
- (iv) loss of relevant quality system and/or GMP certification by excipient manufacturer;
- (v) observation of trends in drug product quality attributes; this will depend on the nature and role of excipient;
- (vi) observed organisational, procedural or technical/process changes at the excipient manufacturer;
- (vii) audit/re-audit of excipient manufacturer;
- (viii) questionnaires.

Based on the outcome of the risk review, the established control strategy should be reviewed and revised if needed.

© Key2Compliance AB