

7.A Official requirements

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Here you will find answers to the following questions:

- What are the purpose and the objective of process validation?
- Which legal requirements have to be followed in Europe and in USA?
- What are the expectations of the January 2011 FDA Guidance for Industry addressing Process Validation?
- Which are the general principles of process validation?
- Which requirements apply to the different types of process validation?
- How can the validated status be maintained?
- When and how should a revalidation be carried out?
- Which documents have to be established for process validation?
- How long have validation documents to be archived?

7.A.1 Regulatory aspects

Process validation is a basic factor for drug product safety and quality and thus a fundamental component of the quality assurance system used by pharmaceutical manufacturers. It should verify that the procedures and processes used in drug and drug product manufacturing are suitable for their purposes and guarantee that the processes used to produce the drugs or drug products will consistently deliver quality products that meet their pre-determined specifications and quality characteristics.

A **procedure** is an established way of carrying out an activity. A **process** is a set of methods and actions that interact to convert inputs to outputs.

7.A.1.1 Legal requirements for drug products

The holder of a manufacturing authorization or drug application must ensure that manufacturing and analysis are carried out in line with the most recent developments in science and technology. Moreover, he must also operate a **quality management system** that includes good manufacturing practice, in line with the type and scale of the activities.

Within **Europe**, the *EU Guidelines to Good Manufacturing Practice for Medicinal Products* (see chapter C.4) must be consulted whenever the foundations for good manufacturing practice are laid out. This gives the EU Guidelines to Good Manufacturing Practice a high regulatory binding character. Bear in mind that methods other than those described in the EU guidelines may also be suitable for implementing the goals of the quality assurance principles. The *EU Guidelines to Good Manufacturing Practice for Medicinal Products* do not in any way intend to restrict the development of new concepts or technologies provid-

ing that these are validated and ensure a level of quality assurance that is at least equal to that described in the EU guidelines. The EU guidelines, therefore, have the character of prefabricated expertise representing modern scientific and technological standards for drug product manufacturing and testing.

Materials produced in or for the **United States** are expected to meet the *Current Good Manufacturing Practices for Finished Pharmaceuticals* as defined in 21CFR Parts 210 and 211 (see chapter D.1). While the USA and EU have similar GMP requirements, they are not identical as some expectations may differ. However, compliance with one area's GMP will generally be found to be in reasonable compliance with the others.

In January 2011, the US FDA issued a new **Guidance for Industry** which is specifically written to address process validation (see chapter D.2). This new Guidance replaces the 1987 Guidance issued by the FDA and aligns Process Validation with a lifecycle concept and the FDA/ICH Guidances Q8(R2) *Pharmaceutical Development* (see chapter E.8), Q9 *Quality Risk Management* (see chapter E.9), and Q10 *Pharmaceutical Quality System* (see chapter E.10). FDA is interested in incorporating a **lifecycle approach** which uses modern concepts associated with development, risk management and quality.

The process validation guidance covers several categories of drugs in the USA. They include:

- Human drugs
- Veterinary drugs
- Biological and biotechnology products
- Finished products (medicinal products) and active pharmaceutical ingredients (API)

as well as:

- The drug constituent of a combination (drug and medical device) product

In accordance with article 10 §3 of Directive 2003/94/EC (see chapter C.2) and the CGMP regulations and drug laws of the USA (see chapter D.1 and chapter D.16), it is incumbent upon all European and United States manufacturers to validate new manufacturing procedures and other significant changes.

The procedures applied in manufacturing must be validated in line with modern scientific and technological standards. Critical phases in a manufacturing procedure must be revalidated on a regular basis. When test preparations are used, the manufacturing process must be validated as a whole as far as this is indicated, and the production development phase must be allowed for; critical processing steps must always be validated. All steps taken for the design and development of the manufacturing process must be documented in full.

7.A.1.2 Responsibilities

In **Europe**, the *head of production* is responsible for validation within the manufacturing area. In accordance with §2.5 and 2.7 EU GMP Guide, he must ensure that the necessary validations of manufacturing procedures are carried out. The written instructions and operating procedures (manufacturing instructions) which are compiled under his responsibility form the basis of process validation. These documents must conform to the marketing authorization/registration documents. Responsibilities should be clearly defined, if other internal areas (e.g. Engineering, Research&Development) are involved in the validation.

A written contract must be drawn up between the contract giver and the contract acceptor, if the task of process validation is transferred to **third parties** (EU GMP Guide §7.1). The contract must clearly define the responsibilities of both sides, and in particular regulate compliance with good manufacturing practice. The contract giver must ensure that the contract acceptor carries out the task in line with the instructions given. Transferring the task of process validation to external service providers does not change regulations concerning responsibility in line with EU GMP Guide in any way: the head of manufacturing can transfer the execution of, but not the responsibility for process validation. This means that he retains the legal and public responsibility for completing all validation work in line with regulations in his area.

The *holder of the manufacturing authorization* is responsible for ensuring that key personnel are able to carry out their duties in compliance with the regulations. In accordance with EU GMP Guide §2.2, he must bestow sufficient authority on staff in leading or responsible roles to enable them to meet the demands of their tasks. He must, therefore, make the necessary organizational arrangements (organizational diagrams and job descriptions) and provide the necessary utilities.

For compliance under **United States** laws and regulations, the firm holding the approvals and filings is legally responsible. The expectations and general requirements for validation are similar to the EU with the exception that the specific person responsible for performing the validation is more flexible. The head of the appropriate organizational unit is responsible for assuring that validations are conducted and properly documented with the documented review and approval of the **quality unit**. The president or most senior manager/director of the firm is ultimately held accountable for all CGMP compliance requirements. Contracts and agreements can be executed to assign defined responsibilities for activities associated with validation; however, the ultimate direct responsibility always remains with the application holder and the firm's quality unit. Under USA law, FDA expects and holds the *drug application holder* responsible for these regulatory responsibilities and they cannot be delegated to a third party.

7.A.1.3 GMP requirements

Detailed regulations on the aims and execution of process validation on a **European** level can be found in the *EU Guidelines to Good Manufacturing Practice for Medicinal Products* (see chapter C.4). According to section 5.22, when any new manufacturing formula or processing method is introduced, steps should be taken to demonstrate its suitability for routine operation. It should be demonstrated that the defined process using the established materials and equipment will consistently produce a product of the required quality.

In the **USA**, validation has been a legal requirement for more than 30 years. References in the GMP regulations from Section 211.100 and 211.110 are the historical basis for what today is commonly referred to by FDA as the foundation of validation.

"There shall be written procedures for production and process control designed to assure that drug products have the identity, strength, quality and purity they purport or are represented to possess ... these written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit". "Designed to assure" can be interpreted as the beginning of the concept for "Validation".

The process for executing validation on a **European** level is described in Annex 15 of the EU Guidelines to *Good Manufacturing Practice for Medicinal Products* (see chapter C.6.15 *Annex 15 Qualification and Validation*). As Annex 15 contains only the principles of qualification and validation, the PIC/S document PI 006 (see chapter F.1 *PIC/S PI 006-3: Recommendations on Validation Master Plan Installation and Operational Qualification Non-Sterile Process Validation Cleaning Validation*) can assist with the interpretation and the implementation. This document applies primarily to inspectorates of the PIC/S member states, for whom it is intended as instruction for preparing an inspection, and as an advanced training aid for qualification/validation. As, for PIC/S purposes, this reflects the latest scientific and technological developments, valuable information regarding the implementation of the specifications in Annex 15 may also be found here for the industry.

The **USA** has similar documents, which can be referred to for guidance when implementing validation activities and practices, especially the *Guidance for Industry on Process Validation*, which has been revised and published in January 2011 (see chapter D.2). Some more Guidance documents and Inspection Guides are included in Chapter D of this manual (chapter D *USA: CFR and FDA Guidelines*). The Inspection Guides and Guidances issued by FDA provide greater detail in acceptable validation practices than can be found in regulations issued by FDA. It is also suggested that the FDA homepage (www.fda.gov) be periodically searched for new information being considered (draft) or issued by the FDA on relevant subjects. Since the United States, the EU, and Japan all participate in

ICH as equal partners, any ICH issued guidances can also be seen as important reference documents (chapter E *ICH-Guidelines* and ICH homepage www.ich.org).

The US FDA *Compliance Program Guidance Manual* can also provide invaluable information about what can be expected by the FDA. These Compliance programs were written for FDA personnel, and provide manufacturers with greater insight into what the FDA expects.

It is suggested that the FDA website should be searched for applicable inspection guides such as Program Numbers:

- 7346.832 *Pre-Approval Inspections/Investigations* (see chapter D.17)
- 7346.843 *Post-Approval Audit Inspections*
- 7356.002 *Drug Manufacturing Inspections*, and
- 7356.002A *Sterile Drug Process Inspections*

It is important to note that the *United States Food and Drug Administration* (FDA) has become a member of the PIC/S as of January 2011. As a result of this new membership, it is likely to see a greater impact of PIC/S upon FDA expectations whether or not such practices are officially acknowledged. Process Validation expectations and applications are likely to migrate into a more homogeneous application as inspectional findings are shared among PIC/S members.

Figure 7.A-1 gives an overview of relevant text passages in the regulations.

Regulations relating to process validation	
Directive 2003/94/EC, article 10 §3	Validation of new manufacturing procedures and all important changes
EU Guidelines to Good Manufacturing Practice for Medicinal Products, chapter 5.22	When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.
Annex 15 of EU Guidelines to Good Manufacturing Practice for Medicinal Products	Description of the validation process
PIC/S PI 006 "Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation"	As interpretation and implementation aid for Annex 15 of the EU GMP Guideline

Figure 7.A-1 Regulations relating to process validation