EU GMP Requirements

- Validation -

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Contents covered

- Legal basis
- Interface regulatory vs. supervisory authorities
- General aspects of qualification & validation
- Qualification of premises and equipment
  - incl. water systems, dedicated systems
- Specific validations
  - Manufacturing process
  - Cleaning
  - Test methods
  - Computer systems
- Recent trends with respect to validation
- Supplier qualification and outsourcing

Definitions

- **Qualification** [EC GMP-Guide, Glossary]:
  Action of proving that any equipment works correctly and leads to the expected results.
  The word **validation** is sometimes widened to incorporate the concept of qualification.

- **Validation** [EC GMP-Guide, Glossary]:
  Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results:

- **Process Validation** [Annex 15 to EC GMP-Guide, Glossary]:
  Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting ist predetermined specifications and quality attributes

- (**further definitions** see Annex 15)

Legal Frame for Validation

- Regulatory guidances to obtain Market Authorisations (see later)
- Principles of GMP
  - Directive 2003/94/EC (human, incl. investigational)
  - Directive 91/412/EEC (veterinary)
- EudraLex Volume 4 – EC GMP-Guide
  - Part I – Basic Requirements for Medicinal Products [human + vet.]
  - Part II – Basic Requirements for Active Substances (= ICH Q7)
  - Annexes, e.g.
    - Annex 15 (Qualification and Validation)
    - Annex 11 (Computerised Systems)
    - Annexes for specific products,
      e.g. Annex 1 (Sterile), Annex 2 (Bio), etc.

GMP Principles for Validation

- Directive 2003/94/EC (GMP for Human Products)
  - Article 8 No. 3:
    Premises and **equipment** to be used for manufacturing operations, which are critical to the quality of the products, shall be subjected to appropriate qualification and **validation**
  - Article 9 No. 2:
    When **electronic, photographic or other data processing systems** are used **instead of written documents**, the manufacturer shall first **validate** the systems by showing that the data will be appropriately stored during the anticipated period of storage. …'
  - Article 10 No. 3:
    […] any new manufacture or important modification of a **manufacturing process** of a medicinal product shall be **validated**. Critical phases of manufacturing processes shall be regularly re-validated.

Integration into Quality System

- EC GMP Guide Part I Chapter 1.1:
  The system of QA should ensure that […]
  - (v) any **validations** are carried out

- EC GMP Guide Part I Chapter 1.2:
  - GMP is that part of QA which […]
  - the basic requirements of GMP are that […]
    (ii) critical steps of **manufacturing processes** and significant changes to the process are **validated**

- EC GMP Guide Part I Chapter 1.3:
  - Quality Control ist that part of GMP which […]
  - the basic requirements of QC are that […]
    (iii) **test methods** are **validated**

- EC GMP Guide Part I Chapter 1.4:
  the manufacturer and the marketing authorisation holder should evaluate the results of this [**periodic quality] review** and an assessment made whether […]
  any **revalidation** should be undertaken

Responsibilities for Validation

- EC GMP Guide Part I Chapter 2.4:
  a **Qualified Person** must ensure that each batch has been produced and tested/checked in accordance with the **directives** […]

- EC GMP Guide Part I Chapter 2.5:
  The **Head of Production Department** generally has the following responsibilities […]:
  (v) to ensure that the appropriate **validations** are done

- EC GMP Guide Part I Chapter 2.6:
  The **Head of Quality Control Department** generally has the following responsibilities […]:
  (vii) to ensure that the appropriate **validations** are done

- EC GMP Guide Part I Chapter 2.7:
  The heads of Production and Quality Control generally have some **shared**, or jointly exercised, responsibilities […]. These may include […]:
  - **process validation**
  - plant hygiene [cleaning validation]

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