Laws, Regulations and Guidelines for Computer Validation

Training Course
"GMP Compliance for Computer Validation"

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Topics

- Background / Swiss Inspection System
- EU guidelines relevant for computerised systems
- EU GMP annex 11 / annex 15
- Inspection of computerised systems
- Outlook

New Health Law and Swiss Inspection System (1 January 2002)

- **New Health Law in force since 1 January 2002**
- **PIC/S-GMPs replaced by the EU GMPs (Eudralex Vol. 4)**
- **Federal Agency *swissmedic* replaces OICM / IKS**
  (www.swissmedic.ch)
- **Four regional inspectorates with accredited status according to norm: EN 45'004 / ISO 17'020**

  Zürich : 2000
  Basel : 2001
  Lugano : 2003
  Lausanne : ?

New Health Law and Swiss Inspection System (1 January 2002)

- **Swiss Agency for Therapeutic Products, s*wissmedic* (Bern):**
  - Market authorisations (MA)
  - Site licenses for manufacturers and wholesalers
  - Inspections of blood, blood-products, vaccines
  - Inspections and licenses according to GLP and GCP
  - Supervision of medical devices
  - Interpretation of the GMP/GDP-guidelines for Switzerland
  - Co-ordination of MRAs and foreign inspections
- **Regional Inspectorates (Zürich, Basel, Lausanne, Lugano):**
  - Inspections of manufacturers of finished goods, intermediates and APIs
  - Inspections of wholesalers (incl. importers and exporters)

European Guidelines for GMP

- **EC Directives (http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm):**

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
- Commission Directive 91/356/EEC, of 13 June 1991, laying down the principles and guidelines of good manufacturing practice for medicinal products for human use.

- **Eudralex, vol. 4 (http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm):**

- EU GMP, chapter 4.9 : Electronic Data Storage
- EU GMP, chapter 7 : Contract Manufacturing
- EU GMP Annex 11 : Computerised Systems
- EU GMP Annex 15 : Qualification and Validation

Guideline EU GMP Annex 11: Computerised Systems

- **Principle**

The introduction of computerised systems into systems of manufacturing, including storage, distribution and quality control does not alter the need to observe the relevant principles given elsewhere in the Guide. Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance. Consideration should be given to the risk of losing aspects of the previous system which could result from reducing the involvement of operators.

- **Computerised system part of the overall (GMP-) system**
- **Scope: manufacturing, storage, distribution, quality control**
- **Manual system vs. computerised system**
  - **Failure tolerant operators**
  - **Failure inducing operators**
  - **URS, DQ, testing**

Guideline EU GMP Annex 11: Computerised Systems

- **Personnel**

1. It is essential that there is the closest co-operation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilises computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of computerised system.

- **Responsibility of key personnel**
- **Training need of key personnel**
- **URS, DQ, PQ**
- **Approval of validation**
- **Operative ownership of system**
- **Changes / upgrades / revalidation**
- **User rights / access rights / security levels**

Guideline EU GMP Annex 11: Computerised Systems

- **Validation**

2. The extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether the validation is to be prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and modifying.

- **Classification of system (risk assessment, GAMP4 etc.)**
- **Extent of validation**
- **Owner of validation process (IT, QA, user ?)**
- **Composition of validation team**
- **Method used for validation**
- **Approval of validation / release of system**
- **Training of users**

Guideline EU GMP Annex 15: Qualification and validation

- **Principle**

1. This Annex describes the principles of qualification and validation which are applicable to the manufacture of medicinal products. It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

- **Computerised systems as part of the GMP-environment**
- **Define criticality of process (risk assessment)**
- **Quality of product as target**

Guideline EU GMP Annex 15: Qualification and validation

• Planning for Validation

2. All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

3. The VMP should be a summary document which is brief, concise and clear.

4. The VMP should contain data on at least the following:

(a) validation policy;

(b) organisational structure of validation activities;

(c) summary of facilities, systems, equipment and processes to be validated;

(d) documentation format: the format to be used for protocols and reports;

(e) planning and scheduling;

(f) change control;

(g) reference to existing documents.

5. In case of large projects, it may be necessary to create separate validation master plans.

• Validation performed as a planned process

• Process should be structured, guided, documented

Guideline EU GMP Annex 15: Qualification and validation

• Documentation

6. A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

7. A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.

8. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorisation.

• Formal structure as for any qualification / validation-step:

- protocol / approved (by QA)
- testing (qualified environment and personnel)
- evaluation / deviation handling
- report / approved (by QA)

• Formal release of system for operative use

Guideline EU GMP Annex 11: Computerised Systems

- **System (cont.)**

3. **Environment**
4. **Written detailed description of system**
5. **Software**
6. **Data entry and data processing**
7. **Testing / Validation**
8. **User identification**
10. **Change of critical data / audit trail**
11. **Change control / system modifications / revalidation**
12. **Printed copies for audit purposes**
14. **Back-up**
16. **System failure / break down**
17. **Record and analyse errors / corrective actions**

- **Issues well established through IT**

Guideline EU GMP Annex 11: Computerised Systems

- **System (cont.) : Critical data entry**

9. When critical data are being entered manually (for example the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by validated electronic means.

- **Decision required by QA**
- **Compatible / comparable with manual procedures**
- **Risk assessment required**
- **"Second operator" vs. "validated electronic means"**
- **Fall-back system**

Guideline EU GMP Annex 11: Computerised Systems

- **System (cont.): Electronic data**

13. Data should be secured by physical or electronic means against wilful or accidental damage, in accordance with item 4.9 of the Guide. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.

- **Data integrity / safety / security**
- **Cross reference to EU GMP chapter 4.9**

  Availability requirements depend strongly on type of data:

  - clinical batches (production, analytics)
  - analytical data of evaluation of reference standards
  - validation data (production process, analytical testing methods)
  - qualification data of equipment (production, HVAC, water)
  - etc.
- **Accessibility, durability, accuracy**
- **Life cycle of storage medium**

Guideline EU GMP Annex 11: Computerised Systems

• System (cont.): Alternative systems

15. There should be available adequate alternative arrangements for systems which need to be operated in the event of a breakdown. The time required to bring the alternative arrangements into use should be related to the possible urgency of the need to use them. For example, information required to effect a recall must be available at short notice.

• Critical steps should be identified via risk assessment:

- Release status of raw material and intermediates
- Release status of finished goods
- Master batch records / analytical testing instructions
- Monitoring systems (storage, water, HVAC)
- Distribution / pharmcovigliance / recall procedures
- etc.

Guideline EU GMP Annex 11: Computerised Systems

• System (cont.): Contracts

18. When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency (see Chapter 7).

• Link to GMP guide chapter 7
• Need for formal, binding contract
• Need for profound technical agreement

Guideline EU GMP Annex 11: Computerised Systems

- **System (cont.): Batch release**

19. When the release of batches for sale or supply is carried out using a computerised system, the system should allow for only a Qualified Person to release the batches and it should clearly identify and record the person releasing the batches.

- **Responsibility of release of product stays with QP**
- **Identification of user**
- **Signature-type of activity required**

Inspection of Computerised Systems

Issues to expect during inspections

- GxP-inspector is trained to find deviations
- System must be "inspectable" and presented in order to demonstrate compliance with general principles of GMP
- Ownership and responsibilities of all parts of the system (hardware, software, application, network, business process, network etc.) is of interest, including interfaces
- The computerised system must be sufficiently understood by the persons involved and as a GMP-relevant process under control
- Inspection focus is usually directed to the whole system and not only to the computerised part of it

Inspection of Computerised Systems (cont.)

- Interfaces between computerised system and rest of site / systems / processes are of interest (including other systems, humans, environment etc.)
- Control over objects from outside the GMP-environment (i.e. software, hardware, expertise, contracted work, support, training etc.) Key word: suppliers and supplier qualification
- VMP, change control, validation / revalidation documents, failure handling and investigation
- Fall-back systems, disaster recovery
- Data handling: back-up, migration, accuracy, availability
- Security, access control, user profiles, authorisation
- Training records, job descriptions (IT departments !)

Outlook

- IT is a fast evolving field
- Keeping up with state of the art is required for pharmaceutical companies, since guidelines can change very fast
- Liability of pharmaceutical companies is not limited to compliance with guidelines but also with the state of the art (depending on national legal system)
- Export of products requires compliance with the regulations of the receiving country (EC, USA etc.)