US FDA and Global Guidance for Computer and Software Validation

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Disclosure

- The opinions expressed during this presentation are those of the presenter.
Objectives

- How do US FDA drug and device related computer system regulations compare?
- Review US FDA and global computer systems compliance regulatory requirements and guidelines.
- Present a “new” approach to computer compliance.

References

The Crosswalk relates Annex 11 guidelines to other official regulations, standards and guidance documents.


References


ISBN 9781482243628
Relevant Regulations and Guidelines

- 21 CFR Part 211.2(b), June 1963.
- 21 CFR Part 211.68 (1976) and 820.70(i) (1997).
- FDA CPGs (1982-87).

Compliance Policy Guides

- CGMP Applicability To Hardware and Software (CPG 7132a.11) '84
- Input/Output Checking (CPG 7132a.07) '82
- Identification of “Persons” on Batch Production and Control Records (CPG 7132a.08) ‘82
- Vendor Responsibility (CPG 7132a.12) ‘85
- Source Code for Process Control Application Programs (CPG 7132a.15) ‘87

Relevant Regulations and Guidelines

- 21 CFR Part 211.2(b), June 1963.
- 21 CFR Part 211.68 (1976) and 820.70(i) (1997).
- FDA CPGs (1982-87).
- GAMP 1, March 1995.
Relevant Regulations and Guidelines

- 21 CFR Part 211.2(b), June 1963.
- 21 CFR Part 211.68 (1976) and 820.70(i) (1997).
- FDA CPGs (1987).
- GAMP 1, March 1995.
- MHRA, GMP Data Integrity Definitions and Guidance for Industry, March 2015.
- General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 2002.
- GAMP 5, March 1997.
- 2002 FDA Risk Based Approach.
Computer Compliance

- FDA doesn’t regulate computer systems performing GMP functions.
  - Hardware itself is subject to the GMP requirements that apply to equipment.
  - Software itself is subject to the same GMP requirements applicable to SOPs.
- FDA regulates drug manufacturers and drug products.
- Any computer can be used as long as the intended use is demonstrated.


Data Compliance Maxim

- Regulatory requirements for data do not change whether data are captured on paper, electronically, or using a hybrid approach.
HOW DO US FDA DRUG AND DEVICE REGULATIONS COMPARE?

GMP

- Medical Devices
  - Quality System Software
  - Device Production Software
  - Medical Devices Software

- Pharma/Bio
  - Quality System Software
  - Pharma/Bio Production Software
GMP Medical Devices

- Quality System Software and Device Production Software
  - 21 CFR 820.70(i), Automated Processes
  - 21 CFR 11
- Medical Devices Software
  820.30(c)  820.30(g)
  820.30(i)  820.40
- Medical Device Data Systems
Requirements

- 21 CFR 820.70(i)
  - Validate computer software for its intended use according to an established protocol.
  - All software changes shall be validated before approval and issuance.
  - These validation activities and results shall be documented.

- 21 CFR 11 (See Pharma/Bio)

Requirements

- 21 CFR 820.30(c)
  - Design Inputs
  - Requires a mechanism for addressing incomplete, ambiguous, or conflicting requirements.
Requirements

- 21 CFR 820.30(g)
  - Design Validation
  - The device software (embedded software) in a medical device is validated to assure it performs as intended.

Requirements

- 21 CFR 820.30(h)
  - Design Transfer
  - Manufacturers are prepared to provide evidence that the software used for duplicating the device software, and the software used in automated manufacturing or QA, meet the software design specifications.
Requirements

- 21 CFR 820.30(i)
  - Design Changes
  - Any changes to a computer system including system configurations should only be made in a controlled manner in accordance with a defined procedure.

Requirements

- 21 CFR 820.40
  - Document Control
  - Any changes to a computer system including system configurations should only be made in a controlled manner in accordance with a defined procedure.
Requirements

- 21 CFR 880
  - Feb 2011
  - Medical Device Data Systems
    » are intended to transfer, store, convert from one format to another according to preset specifications, or display medical device data.
    » perform all intended functions without controlling or altering the function or parameters of any connected medical devices.
    » is not intended to be used in connection with active patient monitoring.
US FDA Medical Devices Guidelines

- Off-The-Shelf Software Use in Medical Devices, Sep 1999.
- General Principles of Software Validation: Final Guidance for Industry and FDA Staff, CDRH and CBER, Jan 2002.
- Mobile Medical Applications, Feb 2015.
- Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices, Feb 2015.

US FDA Medical Devices Guidelines

- Cybersecurity
US FDA Medical Devices Guidelines

- Blood Establishments

International Medical Devices Guidelines/Standards

- http://www.emergogroup.com/resources/regulations
- IEC 62304 Medical Device Software Development Lifecycle.
- ISO 14971-2012 Medical Devices - Application of Risk Management to Medical Devices.
Other Computer related Medical Devices Regulations/Guidelines

- EC, Green Paper on mobile Health ("mHealth"), Mar 2014.
- TGA Regulation of medical software and mobile medical 'apps', Sep 2013.
- MHRA
  - MHRA - Blood Bank Electronic Issues
  - Guidance on medical device stand-alone software
  - Guidance on the regulations for electronic instructions for use of medical devices

US GMP PHARMA REGULATIONS
GMP Pharma

- Quality System Software and Production Software

211.68(a) Requirements

- Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product.
- If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.
211.68(b) Requirements

- Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.
- Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy.
- The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system.
211.68(b) Requirements

- Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.
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- The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system.

211.68(b) Requirements

- A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes.
- In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.
211.68(c) Requirements

Such automated equipment used for performance of operations addressed by 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements included in those sections relating to the performance of an operation by one person and checking by another person if such equipment is used in conformity with this section, and one person checks that the equipment properly performed the operation.

ICH Requirements
API Q7

- Section 5.4
  - Nov 2000
  - 10 Requirements
  - Risk Assessment, Security, Operation and Maintenance
ICH Requirements
API Q7

- Section 6.60
  - Complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations.

21 CFR Part 11

- 21 CFR 11
Narrowed Scope

- The 2003 FDA guidance on Part 11 redefines the scope of records subject to Part 11 as follows:
  - [Electronic] records that are required to be maintained under predicate rules, provided they are relied on to perform regulated activities.
  - Electronic records submitted to FDA under predicate rule requirements.

Records that are required to be maintained by predicate rules and that are maintained in electronic format *in place of paper format*.

Records that are required to be maintained by predicate rules, are maintained in electronic format *in addition to paper format*, and *are relied on to perform regulated activities*. 
21 CFR 11

(Scope)

- Records submitted to FDA in electronic format, under the predicate rules (even if such records are not specifically identified in Agency regulations)...
- …assuming the records have been identified in the docket as the types of submissions the Agency accepts in electronic format
- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules.

Out of Scope

- Records (and any associated signatures) that are not required to be retained by predicate rules, but that are nonetheless maintained in electronic format.
International Pharma Guidelines/Standards

- ISO 12119-1994 Information technology - Software packages - Quality requirements and testing.

International Pharma Guidelines/Standards

International Pharma Guidelines/Standards


Other Computer-Related Guidelines

  - ISO 17025
  - In-house and commercial software for calculation.
  - Database computer systems.
  - Laboratory Information Management Systems (LIMS), Electronic Laboratory Notebooks (ELN).
  - Computers as part of test equipment.
Other Computer-Related Guidelines

- MHRA
  - MHRA expectation regarding self inspection and data integrity
  - GLP Guidance – Archiving
  - MHRA Good manufacturing practice data integrity definitions
  - Pre-Inspection Compliance Report Document


EMEA’s answers to FAQ on Computerized Systems.

Raw Data vs Results

Q: Must all data maintained, even if the data is manipulated automatically to provide information in “pass or fail” format?

A: Not for devices. See part 820 preamble pp. 52631 and 52646. Part 820 requires that “results” of acceptance activities be recorded but not necessarily all raw data. “Results” must have audit trails. Be sensitive to need for raw data during failure investigations under CAPA.
New Approach Computer Compliance

- Trustworthy System
  - It is one that produces consistent reliable and authentic records. The focus of all controls and IT security mechanism should be the assurance that this trustworthy condition is maintained.
New Approach Computer Compliance

- **Trustworthy System**
  - Are reasonably suited to performing their intended function (21 CFR 11.10(a)).
  - Provide a reasonably reliable level of availability, reliability and correct operation (21 CFR 11.10(a)).
  - Are reasonably secure from intrusion and misuse.
  - Adhere to generally accepted security principles.

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EMA ANNEX 11

- European Medicines Agency GMP guideline applicable to computer systems.
- Two (2) revisions: 1992 and 2011.
- Annex 11 (like the rest of Eudralex Volume) is a guidance.
EMA Annex 11

- Used as a model to other regulated applications and other countries.
  - PIC/S Guidance on Good Practices for Computerised Systems in Regulated GxP Environments (PI 011-3)
  - EU GCP inspectors and ASEAN use PI 011-3
  - Health Canada (Health Products and Food Branch Inspectorate) (Medicinal Products and API)
  - China (SFDA) (GMP Annex 2 Computerized System (Draft))
  - Australia Therapeutic Goods Administration (TGA) (GMPs and Blood Establishments)

EMA Annex 11

- Principles
  - This annex applies to all forms of computerized systems used as part of a GMP regulated activities. A computerized system is a set of software and hardware components which together fulfill certain functionalities.
  - The application should be validated; IT infrastructure should be qualified.
  - Where a computerized system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.
# EMA Annex 11

## General
- Risk Management
- Personnel
- Suppliers and Service Providers

## Project Phase
- Validation

## Operational Phase
- Data
- Accuracy Checks
- Data Storage
- Printouts
- Audit Trails
- Change and Configuration Management
- Periodic Evaluation

## Security
- Incident Management
- Electronic Signature
- Batch Release
- Business Continuity
- Archiving
Summary

- One of the significant differences between computer systems compliance in 1992 and today, is that today’s regulatory methodologies and guidelines requires a risk based approach throughout the lifecycle of the computer system taking into account patient safety, data integrity and product quality.
Summary

Scalability is based on....

- Risk
- Complexity and Novelty
- Supplier

Summary

- Computer systems can be used to perform operations covered by the drugs GMP regulation.
- These computer systems require a written validation process.
- Computers systems documentation and validation documentation shall be maintained.
- There must be procedural controls for managing changes to infrastructure and application software, including documentation.
Computer systems can be used to perform operations covered by the drugs GMP regulation. (Principle 1)

These computer systems require a written validation process. (Principle 2, Annex 11-4)

Computers systems documentation and validation documentation shall be maintained. (Annex 11-4.1)

There must be procedural controls for managing changes to infrastructure and application software, including documentation. (Annex 11-10 and Annex 11-4.2)

Computer systems electronic records must be controlled including records retention, backup, and security.

Based on the complexity and reliability of computer systems there must be procedural controls and technologies to ensure the accuracy and security of computer systems I/Os, electronic records and data.
Computer systems electronic records must be controlled (Annex 11-1, 11-4.8, 11-5, 11-6, 11-7, 11-8, 11-9, 11-13, 11-14, 11-17) including records retention, backup (Annex 11-7.2), and security (Annex 11-12).

Based on the complexity and reliability of computer systems (Annex 11-1) there must be procedural controls and technologies to ensure the accuracy and security (Annex 11-12) of computer systems I/Os (Annex 11-5), electronic records and data.

Computer systems must have adequate controls to prevent unauthorized access or changes to data, inadvertent erasures, or loss.

There must be written procedural controls describing the maintenance of the computer system, including an on-going performance evaluation and periodic reviews.

Verification by a second individual may not be necessary when automated equipment is used.
Summary

- Computer systems must have adequate controls to prevent unauthorized access or changes to data (Annex 11-12), inadvertent erasures, or loss.
- There must be written procedural controls describing the maintenance of the computer system (Annex 11 Operational Phase), including an on-going performance evaluation and periodic reviews (Annex 11-11).
- Verification by a second individual may not be necessary when automated equipment is used (Annex 11-6).

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