ICH Good Clinical Practice

Review for

Computerized Systems

Of the Revised E6

ICH - International Conference on Harmonisation

Regulations & Guidelines

Guide	Year
	2016
Electronic Source Data in Clinical Investigations (FDA)	2013
EU guide to GMP (Annex 11, Annex 15 p II)	2011
A Risk Based Approach for Good Automated Manufacturing Practice (GAMP5)	2008
Computerized Systems used in Clinical Investigations (FDA)	2007
PIC/S PI011-2 Good Practices for Computer Systems in Regulated GxP Environment	2007
ICH Q9 Risk Management	2005
Good Automated Manufacturing Practice (GAMP4)	2003
Part 11, Electronic Records; Electronic Signatures — Scope and Application	2003
General Principles of SW Validation (FDA)	2002
Guidance for Industry: Off-the-Shelf Software used in Medical Devices	1999
FDA 21 CFR part 11	1997
E6 Good Clinical Practice: Consolidated Guidance	1996

FDA 21 CFR Part 11

- FDA rule dealing with
  Electronic Records (ER) and Electronic Signatures (ES)

- Provides criteria under which
  ER are **equivalent to paper records**
  &
  ES are **equivalent to traditional handwritten signatures**

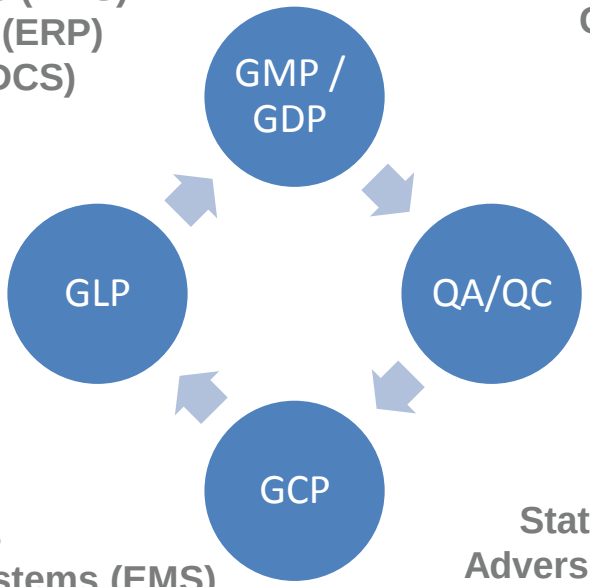
- **Establishes** the requirements under which records may be held in electronic form and electronic signatures may be used in place of handwritten signatures

The rule applies to all regulated records

Systems with Electronic Records

- Manufacturing Execution Systems (MES)
- Maintenance Management Systems (MMS)
- Calibration Management Systems (CMS)
- Building Management Systems (BMS)
- Enterprise Resource Planning (ERP)
- Distributed Control Systems (DCS)
- SCADA Systems
- PLC Systems

Laboratory Information Management Systems (LIMS)
Document Management Systems (DMS)
GXP Training Tracking Systems
SOP Systems



- Stability Systems
- DM&PK Systems
- Toxicology Systems
- Laboratory Robotics Systems
- Environmental Monitoring Systems (EMS)
- Chromatography Data Acquisition Systems
- Laboratory Information Management Systems (LIMS)

Case Report Form Systems
Clinical Data Management Systems
Statistical Analysis Software (e.g., SAS)
Adverse Event Reporting Systems (AERS)
Remote Data Entry/Remote Data Capture (RDE/RDC)

Introduction

"(184)….This guideline has been amended to encourage **implementation of improved and more efficient approaches** to clinical trial design, conduct, oversight, **recording and reporting** while continuing to ensure human subject protection and **data integrity**. **Standards regarding electronic records** and essential documents intended to increase clinical trial quality and efficiency have also been updated."

1. Glossary

1.11.1 Certified copy

A paper or **electronic copy** of the original record that has been verified (e.g. by a dated signature) or has been **generated through a validated process** to produce an exact copy having all of the same attributes and information as the original.

1.60.1. Validation of computerized systems

A process of establishing and documenting that **the specified requirements of a computerized system can be consistently fulfilled**. Validation should ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system or transition to a new system.

2. The principles of ICH GCP

2.10.

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

This principle applies to all records (paper or electronic) referenced in this guideline.

4. Investigator

4.9. Records and Reports

4.9.1

- The investigator should **maintain adequate and accurate source documents and trial records** that include all pertinent observations on each of the site's trial subjects.
- Source data should be attributable, legible, contemporaneous, original, accurate, and complete.
- **Changes to source data** should be traceable, should not obscure the original entry and should be explained if necessary (e.g. via an audit trail).

4. Investigator

4.9.4

- Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an **audit trail** should be maintained); this applies to both **written** and **electronic changes** or corrections (see 5.18.4 (n)).
- Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections.
- Sponsors should have **written procedures** to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator.
- The investigator should **retain records of the changes** and corrections.

5. Sponsor – Quality Management (1)

5.1 Quality management

- The sponsor should implement a **system** **to manage quality** throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials.
- Sponsors should focus on trial activities essential to ensuring human subject protection and **the reliability** of trial results.
- Quality management includes the efficient design of clinical trial protocols, **data collection tools and procedures**, and the collection of information that is essential to decision making.
- **.**
- **.**
- **The quality management system should use a risk-based approach as described below**.

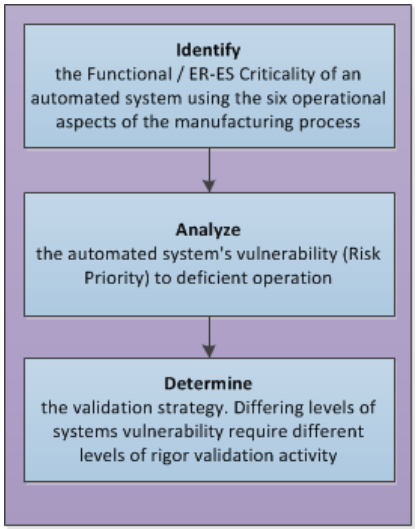
5. Sponsor – Quality Management (2)

5.1.1 Critical process and data identification

- During protocol development, the sponsor should identify those **processes and data** that are critical to assure human subject protection and the **reliability** of study results.

5.1.2 Risk identification

- Risks to **critical study processes and data** should be identified.
- Risks should be considered at both the **system level** (e.g. facilities, standard operating procedures, **computerized systems**, personnel, vendors) and **clinical trial level** (e.g. investigational product, trial design, **data collection and recording**).



5. Sponsor – Quality Management (3)

5.1.3. Risk evaluation

The identified risks should be evaluated by considering:

- The **likelihood** of errors occurring, given existing risk controls.
- The **impact** of such errors on human subject protection and data integrity.
- The extent to which such errors would be **detectable**.

5.1.4. Risk control

5.1.5. Risk communication

5.1.6. Risk review

5.1.7. Risk reporting

5. Sponsor – Quality Management (4)

5.1.3. Risk evaluation

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5.1.4. Risk control

5.1.5. Risk communication

5.1.6. Risk review

5.1.7. Risk reporting

5. Sponsor - Trial management, data handling, and record keeping (1)

5.6. Trial management, data handling, and record keeping

5.6.1.

The sponsor should utilize **appropriately qualified individuals** to supervise the overall conduct of the trial, **to handle the data, to verify the data**, to conduct the statistical analyses, and to prepare the trial reports.

5.6.2.

5.6.3.

When using **electronic** trial data handling and/or remote **electronic** trial data systems, the sponsor should:

- Ensure and document that the **electronic data processing system(s) conforms to the sponsor's established requirements** for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).
- Maintains SOPs for using these systems.

5. Sponsor - Trial management, data handling, and record keeping (2)

5.6.3. (*continued*)

- Maintains SOPs for using these systems.

  - The SOPs should cover **system setup, installation and use**.
  - The SOPs should describe
    - system validation
    - functionality testing
    - data collection and handling
    - system maintenance
    - system security measures
    - change control
    - data backup, recovery, contingency planning
    - System decommissioning

- The **responsibilities** of the sponsor, investigator and other parties with respect to **the use of these computerized systems should be clear**, and the users should be provided with **training** in the use of the systems.

5. Sponsor - Trial management, data handling, and record keeping (3)

5.6.3. (*continued*)

- **Ensure that the systems are designed** to permit **data changes** in such a way that the data changes are **documented** and that there is **no deletion of entered data** (i.e. maintain an audit trail, data trail, edit trail).
- **Maintain** a **security system** that **prevents unauthorized access** to the data. (e) Maintain a list of 1104 the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
- **Maintain** adequate **backup** of the data.
- **Safeguard the blinding**, if any (e.g. maintain the blinding during data entry and processing).

- **Ensure the integrity of the data** including any data that describe the context, content and structure of the data. This is particularly important when making changes to the computerized systems, such as **software upgrades** or **migration of data**.

MAIN CRITERIA FOR DATA INTEGRITY

#	Term		Explanation
1	**Accurate**	**דיוק**	No errors or editing without documented amendments
2	**Attributable**	**שניתן לייחסו למישהו**	Who acquired the data or performed an action and when?
3	**Available**	**זמין**	For review and audit or inspection over the lifetime of the record
4	**Complete**	**שלם**	All data is present and available
5	**Consistent**	**עיקבי**	All elements of the record, such as the sequence of events, follow on and are dated or time stamped in expected sequence
6	**Contemporaneous**	**בו-זמני**	Documented at the time of the activity
7	**Enduring**	**בר-קיום**	On proven storage media (paper or electronic)
8	**Legible**	**קריא**	Can you read the data?
9	**Original/Reliable**	**מקורי\עותק אמין**	Written printout or observation or a certified copy thereof
10	**Trustworthy**	**אמין**	The data and the record have not been tampered with

5. Sponsor - Trial management, data handling, and record keeping (4)

5.6.4.
Data transformed - possible to compare the original data with the processed data.

5.6.5.
Unambiguous subject identification code that allows identification of all the data reported for each subject.

5.6.6.
Retain all of the sponsor- specific essential documents pertaining to the trial.

5.6.7.
Retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s)

5.6.8.
Trial discontinuation - maintain all sponsor specific essential documents for at least 2 years after formal discontinuation…

5. Sponsor - Trial management, data handling, and record keeping (5)

5.6.9.
Trial discontinuation – notification to all the trial investigators/institutions and all the regulatory authorities.

5.6.10.
Transfer of data ownership - reporting to the appropriate authority(ies),

5.6.11.
Retained of Sponsor specific essential documents at least 2 years after the last approval…

5.6.12.
Inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no 1145 longer needed.

5. Sponsor - Extent and nature of monitoring (1)

5.19.3. Extent and nature of monitoring

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials.

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Centralized monitoring processes provide additional monitoring capabilities that can **complement and reduce the extent and/or frequency** of on-site monitoring by such methods as:

- **Routine review of submitted data**.
- **Identification of** missing data, inconsistent data, data outliers or unexpected lack of variability and protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site or across sites, or may be indicative of potential data manipulation or data integrity problems.

5. Sponsor - Extent and nature of monitoring (2)

5.19.3. Extent and nature of monitoring (*Continued*)

- Using statistical analyses to identify **data trends** such as the range and consistency of data within and across sites.
- Analyzing site characteristics and **performance metrics**.
- Selection of sites and/or processes for targeted on-site monitoring.

5.19.6. Monitoring Report

- ….**Results of monitoring activities** should be documented in sufficient detail to allow verification of compliance with the monitoring plan.

6. Clinical trial protocol and protocol amendment(s)

6.4. *Trial design*

…A description of the trial design, should include:

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6.4.9.

- The **identification of any data to be recorded directly** on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

What is Added in the Guide?

- The principles (2.10)
- (Electronic) Records & Reports (4.9.1)
- Quality Management – Risk Based Approach (5.1)
- Trial management, data handling, and record keeping – Validation of Computerized Systems and relevant SOPs (5.6.3)
- Data Integrity (5.6.3)
- Data Monitoring (5.19.3)

Thank You

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