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Data Integrity and Compliance With CGMP

Guidance for Industry

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1

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Why write a guidance?

FDA has increasingly observed CGMP violations involving data integrity

Ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health

2

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...especially the health of the most vulnerable

A photograph of three young children of diverse backgrounds playing in a field of yellow wildflowers. A girl in a green shirt and blue shorts is on the left, a boy in a light blue shirt and shorts is in the middle, and a girl in a red shirt and blue shorts is on the right, reaching for a large yellow and blue ball. The background shows green trees and a clear sky.

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What is the guidance?

- It is a summary of current problems and how they relate to the CGMPs in 21 CFR 210, 211, and 212
- Clarification of several terms in FDA's regulations
- It is not a comprehensive list of data controls or a "how to" guidance

4



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Data integrity requirements in 21 CFR 211 and 212

- 211.68 “backup data are exact and complete” and “secure from alteration, inadvertent erasures, or loss;”
- 212.110(b) “stored to prevent deterioration or loss;”
- 211.100 and 211.160 certain activities be “documented at the time of performance” and laboratory controls be “scientifically sound;”

5



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- 211.180 records be retained as “original records,” “true copies,” or other “accurate reproductions of the original records;”
- 211.188, 211.194, and 212.60(g) “complete information,” “complete data derived from all tests,” “complete record of all data,” and “complete records of all tests performed.”

6



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What is “data integrity”?

- Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)

7




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What is “metadata”?

- Contextual information required to understand data
- Structured information that describes, explains, or otherwise makes it easier to retrieve, use or manage data
- For example: date/time stamp, user ID, instrument ID, audit trails, etc.
- Relationships between data and their metadata should be preserved in a secure and traceable manner

8


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What is an “audit trail”?

- Secure, computer-generated, time-stamped electronic record that allows for reconstruction of events relating to the creation, modification, or deletion of an electronic record
- Chronology: who, what, when, and why of a record
- Track actions at the record or system level
- CGMP-compliant record-keeping practices prevent data from being lost or obscured

9

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Audit trails capture...

- Overwriting
- Aborting runs
- Testing into compliance
- Deleting
- Backdating
- Altering data

(not an all-inclusive list)

10



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Use of “static” and “dynamic” in relation to record format

- Static: fixed data document such as a paper record or an electronic image
- Dynamic: record format allows interaction between the user and the record content such as a chromatogram where the integration parameters can be modified

11



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How does FDA use the term “backup” in 211.68(b)?

- True copy of the original data that is maintained securely throughout the records retention period
- Should include associated metadata
- Not backup copies that may be created during normal computer use and temporarily maintained for disaster recovery

12



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What are “systems” in “computer or related systems” in 211.68?

- Computer hardware, software, peripheral devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals and standard operating procedures).

13



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When is it permissible to exclude CGMP data from decision making?

- Data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes
- Electronic CGMP data should include relevant metadata
- To exclude data from the release criteria decision-making process, there must be a valid, documented, scientific justification for its exclusion

14



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Does each workflow on our computer system need to be validated?

- Yes, a workflow, such as creation of an electronic MPCR, is an intended use of a computer system to be checked through validation
- If you validate the computer system, but you do not validate it for its intended use, you cannot know if your workflow runs correctly

15



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Federal Register January 1995

manufacturing process. Less dramatic events, such as faulty data entry or programming, can also trigger a chain of events that result in a serious production error and the possible distribution of an adulterated product. Thus, while increasingly sophisticated system safeguards and computerized monitoring of essential equipment and programs help protect data, no automated system exists that can completely substitute for human oversight and supervision.

16



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How should access to CGMP computer systems be restricted?

- Appropriate controls to assure only authorized personnel change computerized:
 - MPCRs
 - Input of laboratory data into records
 - Other records
- Recommend restricting the ability to alter:
 - Specifications
 - Process parameters
 - Manufacturing or testing methods

17



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Continued

- Recommend system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content
- Recommend maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use
- May not be practical for small operations with few employees

18



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Why is FDA concerned with the use of shared login accounts for computer systems?

- A firm must
 - exercise appropriate controls to assure that only authorized personnel make changes to computerized records
 - ensure actions are attributable to a specific individual

19



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Paper Record Comparison

- If actions are not attributable to a specific individual, a BPCR would look like all the values were entered but the people who performed and reviewed every step would be empty.
- Firm would not know if the unidentified individuals are authorized to perform the activity

20



How should blank forms be controlled?

- Blank forms (e.g., worksheets, laboratory notebooks, and MPCRs) should be controlled by the quality unit or by another document control method
- Numbered sets of blank forms may be issued and should be reconciled upon completion of the activity

21



Continued

- Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement

22



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Paper Record Comparison

- Bound paginated notebooks, stamped for official use by a document control group, allow detection of unofficial notebooks as well as of any gaps in notebook pages
- Or, an electronic document management system could have the capability to reconcile and document the number of copies printed

23



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How often should audit trails be reviewed?

- FDA recommends that audit trails capturing changes to critical data be reviewed with each record and before final approval of the record
- Audit trails subject to regular review should include, for example, changes to: finished product test results, sample run sequences, sample identification, critical process parameters

24



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- FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.

25



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Who should review audit trails?

- Audit trails are considered part of the associated records
- Personnel responsible for record review under CGMP should review the audit trails that capture changes to critical data...as they review the rest of the record

26



Paper Record Comparison

Similar to review by:

- Person directly supervising or checking each significant step in BPCR
- Second person showing that the original lab records are reviewed for accuracy, completeness, and compliance with established standards


27



Can electronic copies be used as accurate reproductions of paper or electronic records?

- Yes
- Provided copies preserve the content and meaning of the original data, which includes associated metadata and the static or dynamic nature of the original records

28


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Paper Record Comparison

- True copy of a paper record could be a photocopy that is verified to preserve the content and meaning

29

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Can you retain paper printouts/static records instead of original electronic records from computerized laboratory instruments?

- If it is a complete copy of the original record
- e.g., pH meters and balances may create a paper printout or static image during data acquisition as the original record

30



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- Electronic records from certain types of laboratory instruments are dynamic records, and a printout or a static record does not preserve the dynamic format which is part of the complete original record
- e.g., spectral file created by FT-IR


31



Can electronic signatures be used instead of handwritten signatures for master production/control records?

- Yes
- Part of the intent of the full signature requirement is to be able to clearly identify the individual signing the record
- Appropriate controls to securely link the signature and associated record

32

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Federal Register September 1978

447. Several comments argued that the "full signature, hand written" is not necessary and that the paragraph should be changed to allow for other means of identifying the persons who prepare and check the master production or control cards, such as initials, registered initials and/or signature stamps.

The Commissioner believes the requirement for a full signature is appropriate when applied to master records. In the past, FDA has on occasion found instances where firms could not identify the person or persons whom the initials were intended to represent.

33

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When does electronic data become a CGMP record?

- When it is generated to satisfy a CGMP requirement
- You must document, or save, the data at the time of performance
- Not acceptable to store data in temporary memory; this allows for manipulation, before creating a permanent record

34



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- You may employ a combination of technical and procedural controls to meet CGMP documentation practices
- Computer systems, such as LIMS or EBR systems, can be designed to save after separate entries

35



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Paper Record Comparison

- This is similar to recording each entry contemporaneously on a paper batch record

36



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What is wrong with the using samples during “system suitability” or test, prep, or equilibration runs?

- FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result
 - e.g., using *test, prep, or equilibration* runs as a means of disguising testing into compliance

37



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- If a sample is used for system suitability:
 - Should be a properly characterized secondary standard
 - Written procedures should be established and followed
 - Sample should be from a different batch than the sample(s) being tested

38



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- All data should be included in records retained and subject to review unless there is documented scientific justification for its exclusion

39



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Is it acceptable to only save the final results from reprocessed laboratory chromatography?

- No
- Analytical methods should be capable and stable
- If reprocessed, written procedures must be established and followed
- FDA requires laboratory records include complete data derived from all tests

40



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Paper Record Comparison

- When laboratory notebook mistakes or re-running tests are documented, these should be notated with a single line cross out, initialed and dated
- Analyst should not tear a page out of a notebook and discard it

41




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Can internal quality tips, e.g., suspected data falsification, be handled outside the quality system?

- No
- Determine the effect of the event on:
 - patient safety
 - product quality
 - data reliability
 - root cause
 - ensure the necessary corrective actions

42

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Report suspected data integrity problems:

DrugInfo@fda.hhs.gov

“CGMP data integrity” should be included in the subject line

43


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Should personnel be trained in detecting data integrity issues as part of a routine CGMP training program?

- Yes, detecting data integrity issues is consistent with the CGMP requirements for personnel qualifications
- Personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties

44


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Is the FDA investigator allowed to look at my electronic records?

- Yes
- All records required under CGMP are subject to FDA inspection

45

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How does FDA recommend data integrity problems identified during inspections be addressed?

- Demonstrate effective remediation by:
 - Hiring third party auditor
 - Determining scope of the problem
 - Implementing corrective action plan (globally)
 - Removing individuals responsible for problems from CGMP positions
- FDA may re-inspect

46



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Guidance reference:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf>

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