Current Expectations and Guidance, including Data Integrity and Compliance With CGMP

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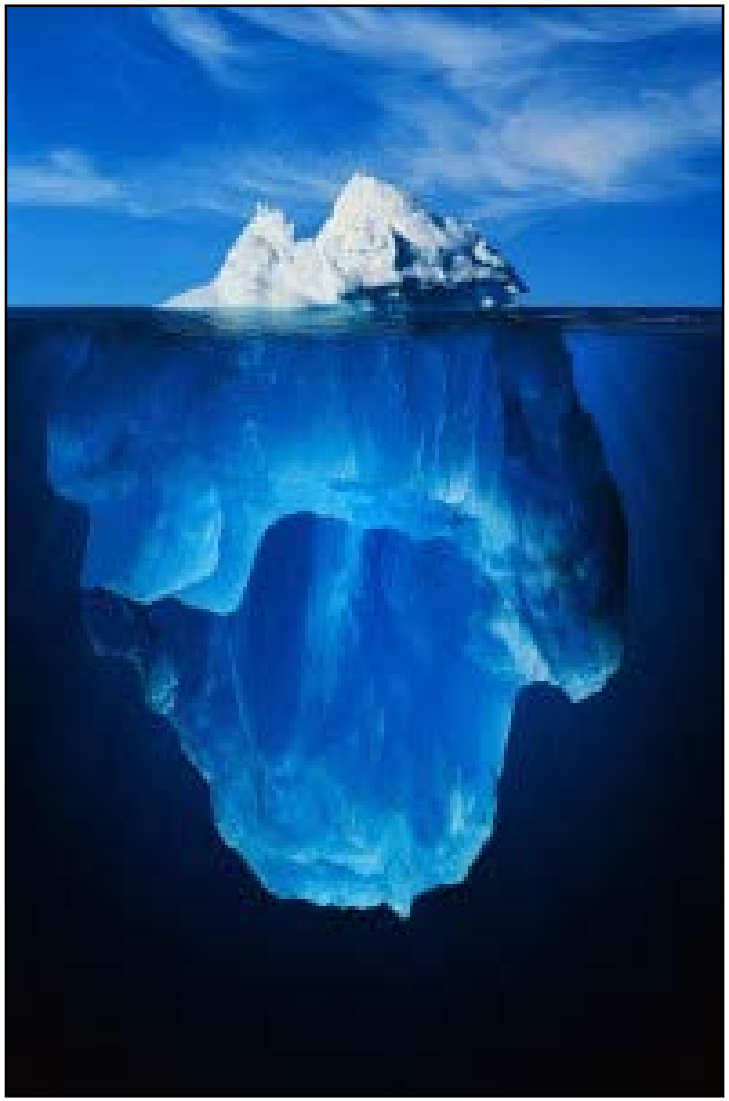
Data Integrity

CGMP – minimum requirements

Data integrity underpins CGMP

Lapses obscure other problems

Tip of iceberg



Draft Guidance

Data Integrity and Compliance With CGMP, draft guidance for industry (April 2016)

Q&A style guidance focused on frequently occurring data integrity lapses with definition of key terms.

When final, will represent our current thinking on data integrity and CGMP compliance.

http://www.fda.gov/downloads/drugs/guidancecompliancereg ulatoryinformation/guidances/ucm495891.pdf

Submit comments to the docket through June 14, 2016 online at www.regulations.gov

Why write a guidance?

FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections

*21 Warning Letters have involved data integrity lapses in drug manufacturing since Jan 2015**

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

NOTE: *21 out of 28 WLs issued to 05/15/16

What the guidance is and isn't

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

What is Data Integrity?

Data integrity – requirements for complete, consistent, and accurate data.

Throughout CGMP

ALCOA
Attributable
Legible
Contemporaneous
Original or true copy
Accurate

Other Important Concepts:

- Metadata
- Audit Trail
- Static vs. dynamic records
- Backup
- Systems

Paper requirements = electronic requirements

The requirements for record retention and review do not differ depending on the data format; paper-based and electronic data record-keeping systems are subject to the same requirements.

Data Integrity: Not a New Concept

Principles from the paper-and-ink era still apply:

- § 211.68 requires that backup data are exact and complete, and secure from alteration, inadvertent erasures, or loss
- § 212.110(b) requires that data be stored to prevent deterioration or loss
- §§ 211.100 and 211.160 require that certain activities be documented at the time of performance and that laboratory controls be scientifically sound
- § 211.180 requires true copies or other accurate reproductions of the original records; and
- §§ 211.188, 211.194, and 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.

APIs - ICH Q7

Computerized Systems (5.4)

- GMP-related computerized systems should be validated.
- Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

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

- "…you must implement documentation controls that ensure actions are attributable to a specific individual."
- When login credentials are shared, a unique individual cannot be identified
- On paper you would sign/initial and date your work or the review of other's work

WL: Forms used a password shared by four or five individuals. December 2015

How should access to CGMP computer systems be restricted?

- FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means where possible (for example, by limiting permissions to change settings or data).
- FDA suggests that the system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content.

WL: Failure to prevent unauthorized access or changes to data, February 2015

When does electronic data become a CGMP record?

- When generated to satisfy a CGMP requirement, **all data** become a CGMP record
- You must document, or save, the data at the time of performance
- Not acceptable to record data on pieces of paper that will be discarded after the data are transcribed

WL: *Substitution of results following failing lab results; failure to record critical values at time activities were performed in cases involving highly potent drugs November 2015*

What is wrong with 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
- It is not acceptable to use an actual sample in *test, prep, or equilibration* runs as a means of disguising testing into compliance

WL: *Unreported product failures, labeled "trial" HPLC injections. Similar failures for gas chromatography, ultra violet spectroscopy and moisture analyses – January 2015*

How often should audit trails be reviewed?

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

WL: Lack of audit trails for lab instruments and turning off audit trails– April 2015

If You Find a Data Integrity Problem

- Disclose it to regulators
- Determine the scope
- Commit to voluntary remediation

FDA is much more willing to work with firms that voluntarily disclose and commit to fixing problems.

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