
# Data Integrity and the FDA

# AFDO Education Conference

## June, 2018

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OUR EXPERIENCE – YOUR SUCCESS

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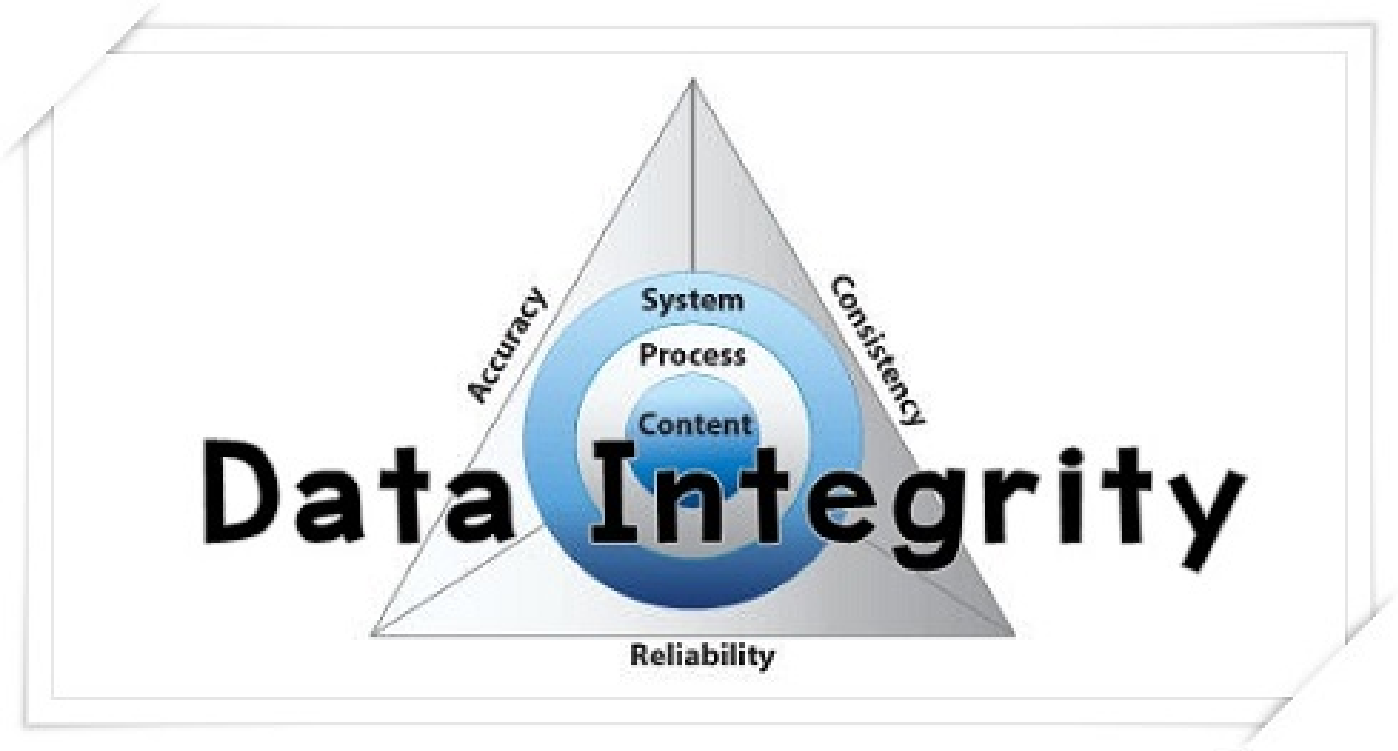
# Data Integrity




What does it mean to you?

# Data Integrity

## *What does FDA say about data integrity…*

*No "legal" definition*

- data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).[1]

[1]Taken from Data Integrity and Compliance with CGMP Guidance for Industry - CDER

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# Data Integrity

*Reference source for dialogue of FDA's perspective and expectations regarding data integrity*

- Data Integrity and Compliance with CGMP – Guidance for Industry (DRAFT GUIDANCE)[1] April 2016

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

[1] Pharmaceutical Quality/Manufacturing Standards (CGMPS)

# Data Integrity

## Why is Data Integrity important from a regulatory perspective?

- Supports the various reporting requirements of the FD&C Act
- Supports the various requirements under the Food Safety and Modernization Act and many others
- Supports manufacturing documentation
- Supports Quality Assurance Requirements (GMPs)
  - Product Design
  - Production
  - Product Life Cycle (expiry dating)

***A fundamental cornerstone for FDA***

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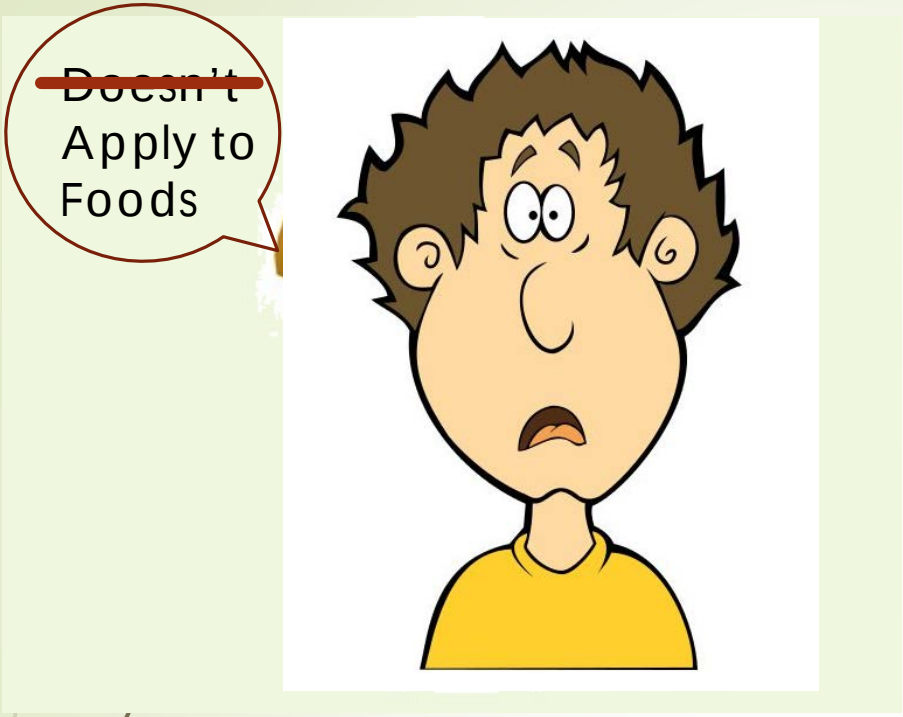
# Data Integrity




- ✓ New Product Applications for Medical Products
- ✓ Clinical Studies
- ✓ Documentation for compliance with cGMPs

An important element in the production of most foods and dietary supplements, just like medical products

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# Data Integrity

PART 101—FOOD LABELING

PART 104—NUTRITIONAL QUALITY GUIDELINES FOR FOODS

PART 110—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKING, OR HOLDING HUMAN FOOD

PART 106—INFANT FORMULA REQUIREMENTS PERTAINING TO CURRENT GOOD MANUFACTURING PRACTICE, QUALITY CONTROL PROCEDURES, QUALITY FACTORS, RECORDS AND REPORTS, AND NOTIFICATIONS

PART 111—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKAGING, LABELING, OR HOLDING OPERATIONS FOR DIETARY SUPPLEMENTS

PART 113—THERMALLY PROCESSED LOW-ACID FOODS PACKAGED IN HERMETICALLY SEALED CONTAINERS

# Data Integrity

PART 115—SHELL EGGS

PART 114—ACIDIFIED FOODS

PART 117—CURRENT GOOD MANUFACTURING PRACTICE, HAZARD ANALYSIS, AND RISK–BASED PREVENTIVE CONTROLS FOR HUMAN FOOD

PART 123—FISH AND FISHERY PRODUCTS

PART 120—HAZARD ANALYSIS AND CRITICAL CONTROL POINT (HACCP) SYSTEMS

Subpart B—Smoked and Smoke-Flavored Fishery Products

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# Data Integrity

| ALCOA |
| --- |
| **A**ttributable |
| **L**egible |
| **C**ontemporaneous |
| **O**riginal or true copy |
| **A**ccurate |

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# Data Integrity

*data integrity refers to the (ALCOA)*

Attributable

Legible

Completeness, (the truth, the whole truth and nothing but the truth)

Consistency

Contemporaneously recorded,

Original or a true copy

Accurate

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# Data Integrity

*data integrity refers to the (ALCOA)*

Attributable **Who Generated the Record** = *Did the Deed*

Legible

Completeness, (the truth, the whole truth and nothing but the truth)

Consistency

Contemporaneously recorded,

Original or a true copy

Accurate

# Data Integrity

*data integrity refers to the (ALCOA)*

Attributable

Legible **Can you read it? Does the nine look like a "9"?**

Completeness, (the truth, the whole truth and nothing but the truth)

Consistency

Contemporaneously recorded,

Original or a true copy

Accurate

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# Data Integrity

*data integrity refers to the (ALCOA)*

Attributable

Legible

Completeness, **(the truth, the whole truth and nothing but the truth)**

**Must include ALL the data for Quality Review – the 'good' and the 'bad'**

Consistency

Contemporaneously recorded,

Original or a true copy

Accurate

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# Data Integrity

*data integrity refers to the (ALCOA)*

Attributable

Legible

Completeness, (the truth, the whole truth and nothing but the truth)

Consistency **Same Process Every Time, initials/signatures**

Contemporaneously recorded,

Original or a true copy

Accurate

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# Data Integrity

*data integrity refers to the (ALCOA)*

Attributable

Legible

Completeness, (the truth, the whole truth and nothing but the truth)

Consistency

Contemporaneously recorded

Original or a true copy

Accurate

**At the same time as accomplished or observed**

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# Data Integrity

*data integrity refers to the (ALCOA)*

Attributable

Legible

Completeness, (the truth, the whole truth and nothing but the truth)

Consistency

Contemporaneously recorded,

Original or a true copy

Accurate

**"true copy" Must be identical to the original record – such as photocopy**

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# Data Integrity

*data integrity refers to the (ALCOA)*

Attributable

Legible

Completeness, (the truth, the whole truth and nothing but the truth)

Consistency

Contemporaneously recorded,

Original or a true copy

Accurate

**The record must reflect the event to the degree required..**

# Other key terms.....

- *What is "metadata" and why is it important?*
- *What is an "audit trail"?*
- *What do the terms "static" and "dynamic" as they relate to record formats mean?*
- *What does the term data "backup" suggest?*

# Data Integrity

- *What is "metadata" and why is it important?*
  - *contextual information required to understand data.*
  - *structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data.*
  - *Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the CGMP activity. The relationships between data and their metadata should be preserved in a secure and traceable manner.*

# Data Integrity

- *What is an "audit trail"?*

  - *secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. An audit trail is a chronology of the "who, what, when, and why" of a record.*

  - *Electronic audit trails include those that track creation, modification, or deletion of data (such as processing parameters and results) and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file).*

# Data Integrity

- *What do the terms "static" and "dynamic" as they relate to record formats mean?*

*static* is used to indicate a fixed-data document such as a paper record or an electronic image,

and *dynamic* means that the record format allows interaction between the user and the record content.

For example, a dynamic chromatographic record may allow the user to change the baseline and reprocess chromatographic data so that the resulting peaks may appear smaller or larger. It also may allow the user to modify formulas or entries in a spreadsheet used to compute test results or other information such as calculated yield.

# Data Integrity

- *What does the term data "backup" suggest?*

  a true copy of the original data that is maintained securely throughout the records retention period. The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format.

# Systems vs. Computer Systems

The American National Standards Institute (ANSI) defines ***systems*** as people, machines, and methods organized to accomplish a set of specific functions.

***Computer*** or related systems can refer to **computer hardware**, **software**, peripheral devices, **networks**, cloud infrastructure, and associated documents (e.g., user manuals and standard operating procedures).

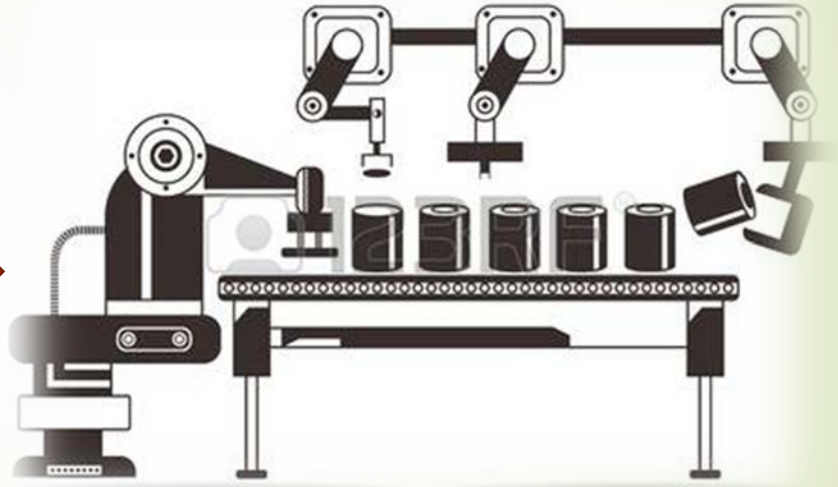
Systems (**people**/machines and methods)
Computer (hardware, software, etc.)

**VALIDATION required = Restrict Access**

**Companies must create and control systems to insure only authorized access NO SHARING OF PASSWORDS**

# Systems vs. Computer Systems

Hardware
Software

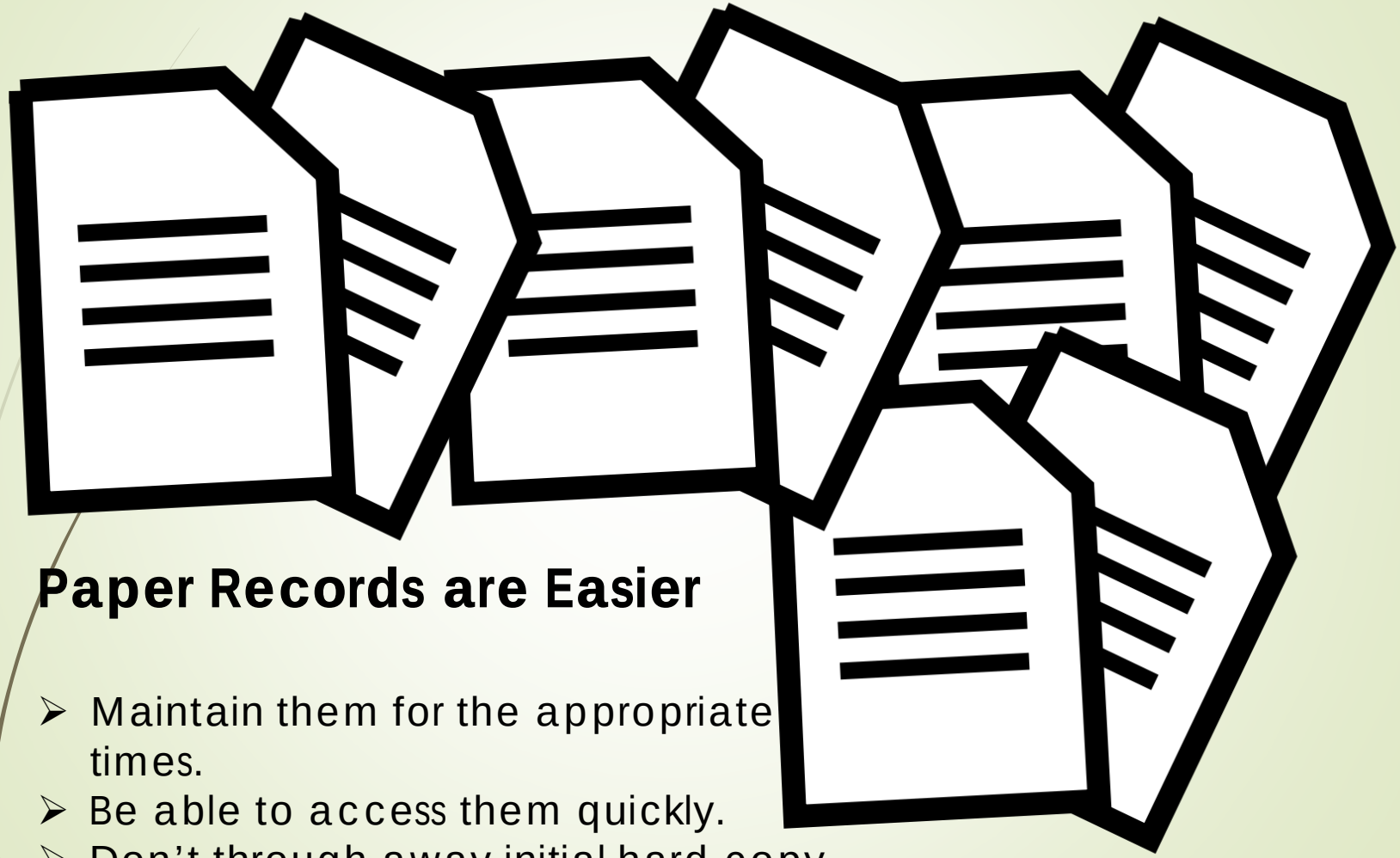


# Systems vs. Computer Systems

**L M S**


**Laboratory Analysis**

# Data Integrity



## Paper Records are Easier

- Maintain them for the appropriate times.
- Be able to access them quickly.
- Don't through away initial hard copy data.

# Data Integrity and Part 11

**The Regulatory Framework:**

## PART 11—ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

### Subpart A—General Provisions

Sec.
11.1 Scope.
11.2 Implementation.
11.3 Definitions.

### Subpart B—Electronic Records

11.10 Controls for closed systems.
11.30 Controls for open systems.
11.50 Signature manifestations.
11.70 Signature/record linking.

### Subpart C—Electronic Signatures

11.100 General requirements.
11.200 Electronic signature components and controls.
11.300 Controls for identification codes/passwords.

## Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

- Records that are required to be maintained under predicate rules, that are maintained in electronic format *in addition to paper format*, **and that *are relied on to perform regulated activities*.**

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

**Overall Approach to Part 11 Requirements**

As described in more detail below, the approach outlined in this guidance is based on *three main elements:*

- Part 11 will be *interpreted narrowly;* FDA clarified that fewer records will be considered subject to Part 11.
- For those records that remain subject to Part 11, FDA intends to exercise enforcement discretion with regard to Part 11 requirements for validation, audit trails, record retention, and record copying for systems that *were operational before the effective date of Part 11 (also known as legacy systems).*

# Data Integrity and Part 11

Does maintaining Data Integrity include Part 11 (electronic records)


Electronic Record = GMP Record (when the predicate regulation requires the record)

# Data Integrity and Part 11

*Electronic Record = GMP Record (when the predicate regulation requires the record)*


FDA Regulatory Requirement (GMP or Required Submission)

Paper Documentation Required by the Regulations

Electronic Documentation in Lieu of Paper Record

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

***A. Narrow Interpretation of Scope***

- with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, Part 11 would apply


***Does QA review the electronic record or the paper record to approve product? (Part 11 applies if the electronic record is relied upon for approval).***

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

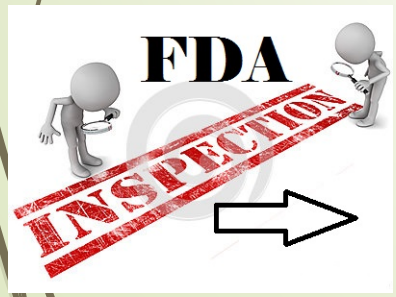
***A. Narrow Interpretation of Scope***

- with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, Part 11 would apply


***What computer records/systems did you use to generate data for your required submissions to FDA? (not necessarily covered under Part 11)***

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**




*A. Electronic Signatures* that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. *approved, reviewed,* and *verified*).

***Do you consider electronic signatures as verification that quality decisions are being made by the appropriate individuals? (Part 11 Applies)***

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

***Validation*** - The FDA intends to exercise enforcement discretion regarding specific Part 11 requirements for validation of computerized systems. Although persons **must still comply with all applicable predicate rule requirements for validation.**


***This is a critical computer system controlling your processing. Have you validated the software? (Although the specific requirements of Part 11 may not apply, computer system validation MAY.***

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

***Validation*** – FDA recommends that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity.


***This computer system executes and documents a critical production process. Has this system been validated? (Validation requirement, not necessarily a Part 11 requirement.***

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

***Audit Trail***

The FDA intends to exercise enforcement discretion regarding requirements related to computer-generated, time-stamped audit trails. Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date, time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries.

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

***Audit Trail***

Although an audit trail, in all incidents, may not be a specific requirement under Part 11, data integrity expectations include a defined audit trail with meta data.


***You had a Product Defect investigation that relied on computer data. How confident are you that your computer data is accurate and has not been changed?***

# Part 11 became effective in August 1997

**Guidance for Industry**
**Part 11, Electronic Records; Electronic Signatures - Scope and Application**
**Contains Nonbinding Recommendations**

***Copies of Records***

You should provide an investigator with reasonable and useful access to records during an inspection. All records held by you, required by a predicate rule, are subject to inspection.


***I would like to conduct my own trend analysis of your complaints and product defect investigations and I would like to have that database electronically in an Excel® format..***

# Data Integrity and Part 11

ENFORCED

I. limiting system access to authorized individuals
II. use of operational system checks
III. use of authority checks
IV. use of device checks
V. determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
VI. establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
VII. appropriate controls over systems documentation
VIII. controls for open systems corresponding to controls for closed systems
IX. requirements related to electronic signatures

# Data Integrity

## FDA Access:

Access to all records required by the GMPs to be maintained

AND

All records to support submissions to FDA whether Part 11 applies or not

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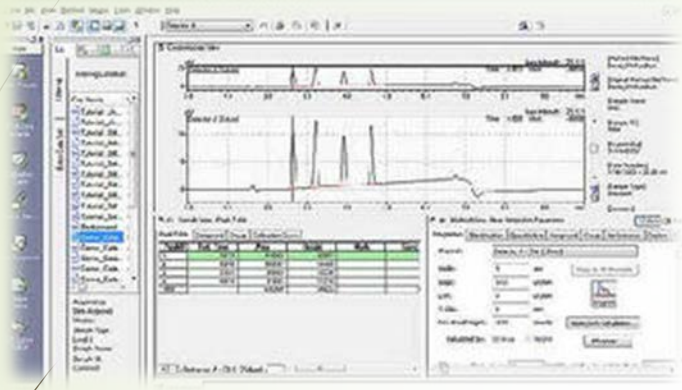
# Data and Control Systems



Process Control

Analytical

Process Monitoring

# Critical Systems

# Data Integrity in Foods

21 CFR 123.9(f) 21 CFR 120.12(g)
Computerized records
**Your computerized records do not provide that appropriate controls are implemented to ensure the integrity of the electronic data and signatures.**

21 CFR 111.325(b)(2)(i)
Documentation; laboratory methodology followed
**The person who conducted the testing and examination did not document [at the time of performance] that established laboratory methodology was followed.**

21 CFR 111.325(b)(2)(ii)
Records - document; results
**The documentation for laboratory tests and examinations did not include the results of the testing and examination. Specifically, ***

# Data Integrity in Foods

21 CFR 120.8(a)
HACCP plan not implemented
**You did not [fully] implement the [monitoring] [validation] [verification] [recordkeeping] procedures listed in your HACCP plan. Specifically, ***

21 CFR 123.9(a)
Records entries - timing
**Processing or other information was not [always] entered on your records at the time it was observed. Specifically, ***

21 CFR 123.6(c)(7)
Records system
**Your HACCP plan does not provide for a recordkeeping system that documents the monitoring of the critical control points. Specifically, ***

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# Data and Control Systems



| | |
|---|---|
| **Software validation for automated processes** | **Software used as part of [production] [the quality system] has not been [adequately] validated for its intended use according to an established protocol. Specifically, ***** |
| **Documentation of software validation** | **Software validation activities and results for computers or automated data processing systems used as part of [production] [the quality system] have not been [adequately] documented. Specifically, ***** |
| **Validation of changes to automated process software** | **Changes to software used as part of [production] [the quality system] were not [adequately] validated before approval and issuance. Specifically, ***** |
| **Documentation of validated process performance** | **There is [no] [inadequate] documentation of [monitoring and control methods and data] [the date performed] [the individual performing the process] [the major equipment used] for a validated process. Specifically, ***** |

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# Data and Control Systems



| | |
|---|---|
| **input/output verification** | **Input to and output from [the computer] [related systems of formulas] [records or data] are not checked for accuracy. Specifically, ***** |
| **Backup file not maintained** | **Failure to maintain a backup file of data entered into the computer or related system. Specifically, ***** |
| **Written record not kept of program and validation data** | **A written record of the program along with appropriate validation data has not been maintained in situations where backup data is eliminated by computerization or other automated processes. Specifically, ***** |

# Data and Control Systems



**Backup data not assured as exact and complete**

**Backup data is not assured as [exact] [complete] [secure from alteration, erasure or loss] through keeping hard copy or alternate systems. Specifically, *****

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# Data and Control Systems


| | |
|---|---|
| **Data secured in course of each test** | **Laboratory records do not include a complete record of all data secured in the course of each test, including all [graphs] [charts] [spectra] from laboratory instrumentation, properly identified to show the [specific component] [drug product container] [closure] [in-process material] [lot tested] [drug product tested]. Specifically, *** ** |
| **Record of all test data** | **Laboratory records did not contain a complete record of all data obtained in the course of each test. Specifically,*** ** |

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# Data and Control Systems


| | |
|---|---|
| **Complete Test Data** | **Laboratory records are deficient in that they do not include a complete record of all data obtained during testing. Specifically, *** ** |
| **Laboratory Records Lack Required Data** | **Laboratory records did not contain [all graphs, charts, and spectra from the laboratory instrumentation] [properly identified graphs, charts, and spectra from laboratory instrumentation] to show the specific [component] [in-process material] [drug product] for each lot tested. Specifically.*** ** |

# Data and Control Systems


- ✓ Identify “systems” that may impact product quality.
- ✓ Validate both process and electronic systems that are critical to consistently produce a quality product.
- ✓ Limit access to computer systems to qualified personnel.
- ✓ Maintain data integrity and traceability.
- ✓ Provide for adequate documentation of each significant step in the process or monitoring of the process.
- ✓ When transferring data from paper to electronic KEEP THE PAPER RECORD.
- ✓ Focus on new computer systems to “get it right on the front end”.

## Critical Systems

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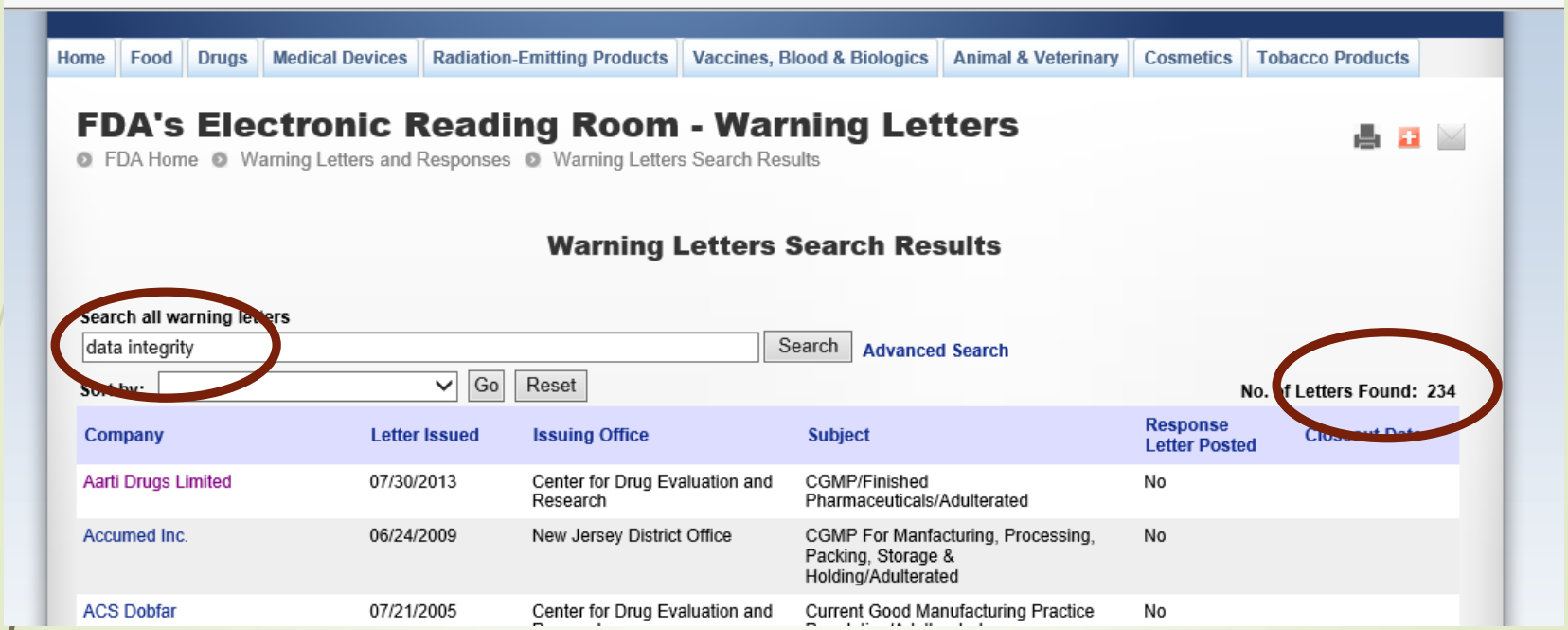
# FDA Warning Letters



# FDA Warning Letters

2. Failure to establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met, as required by 21 CFR 820.75(b). For example, your firm has not established procedures for the monitoring of process parameters for processes such as (b)(4) used in the manufacturing of the Urisys 1100 device. Your firm did not establish procedures which identify the data to be monitored, control limits, or how the data generated from the monitoring of the validated processes are to be reviewed and analyzed. During the inspection, Mr. Rudolf Tolgyesi, QA Director, indicated that your firm did not have any procedures that identified what data was required to be collected and evaluated and the control limits for (b)(4).

# FDA Warning Letters

1. Failure to establish and maintain procedures to include requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing, and potential causes of nonconforming product or other quality problems and to employ appropriate statistical methodology, where necessary, to detect recurring quality problems, as required by 21 CFR 820.100(a)(1). For example, your firm's

# FDA Warning Letters

2. Your firm does not have laboratory records that include complete data derived from all tests necessary to assure compliance with established specifications and standards [21 C.F.R. § 211.194(a)].

For example, in some cases, the analytical testing documentation for raw materials did not include sample solution preparations, sample weight, the method number used, the initials of the analyst who performed the test, and the date of the analysis.

# FDA Warning Letters

d. The investigator observed that a QC analyst had recorded completion times of laboratory analyses that had not yet occurred. …Moreover, our investigator also found that weights for these three samples were recorded on blank pieces of paper and not directly onto the test data sheets.

The above practices observed during the inspection raise concerns regarding the reliability and accuracy of the data generated at your firm, including any other inappropriate data-related practices permitted by your firm when an inspection is not in progress.

# FDA Warning Letters

e) There were no data available to demonstrate that the incubation parameters for test samples specified in your SOP STR-MIC-0021 entitled "Facility Routine Environmental Monitoring Program" promote the growth/identification of all organisms, including yeasts and/or molds. Further, these incubation parameters do not conform to the parameters specified in your SOP for growth promotion testing of microbiological medium…

2. Failure to establish and maintain adequate procedures to analyze appropriate sources of quality data to identify existing and potential causes of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(1). For example:

# FDA Warning Letters

1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.

a. Raw data (e.g., chromatograms, standard and sample weights, calculations, standards, reagents, and instrument information) for the Albuterol Sulfate (June 2001) and Lorazepam (June 2006) related substances, method validation were not available during the inspection.

# FDA Warning Letters

5. Failure to establish and maintain adequate procedures and documentation for the design history file, as required by 21 CFR 820.30(j). For example,
a) No raw data for the interim report or for the final study results were available for review

www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf

# Data Integrity and Compliance With CGMP

## Guidance for Industry

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Karen Takahashi 301-796-3191; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CVM) Jonathan Bray 240-402-5623.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**
**Center for Veterinary Medicine (CVM)**

**April 2016**
**Pharmaceutical Quality/Manufacturing Standards (CGMP)**


www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf

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# What's buggin u?

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# The End…