# DATA INTEGRITY: PARADIGMS, PROBLEMS & SOLUTIONS

*Why We Still Have Data Integrity Issues 20 Years After Part 11 & What You Can Do About It*

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# Discussion Questions

- Why is Data Integrity FDA's current focus?
- Why is Data Integrity still an Issue…after Part 11?
- What is FDA looking for?
- What are the Data Integrity Best Practices?
- *"My CSV Program is a mess – what do I do?"*
- FDA's Draft Guidance for Industry –
  *Data Integrity and Compliance With CGMP:*
  What are the main topics & challenges?
- *Bonus slides* – Useful Agency & Industry Resources



# Why is Data Integrity FDA's current focus?

## Data Integrity is the current focus!

- Main emphasis in recent inspections by the FDA
- Increasing finding in 483's and Warning Letters
- Guidance issued in April 2016

**Data Integrity** is a primary enforcement focus because the data integrity problems are **pervasive** and represent a **high safety risk!**

# Why is Data Integrity still an Issue? …even after almost 20 years since Part 11?

## Data Integrity is old & persistent issue

- "Integrity" issues led to 1906 Pure Food & Drugs Act
- Data Integrity issues in submissions led to GLPs
- Multiple Data Integrity concerns led to Part 11
  - Generic Drug Scandal
  - Therac-25
  - New England Blood Bank
  - Source Code Availability
  - eBPR Citizen's Petition
  - DIA Red Apple Report



# Why is Data Integrity still an Issue? …even after almost 20 years since Part 11?

## Means, Motive & Opportunity

- More people are more computer-literate and more computer-proficient than ever before
  - People are able to use computers almost anywhere
  - People easily "program" configurable computers
- People make errors
- People can be unaware, negligent, lazy or greedy
- FDA inspections don't focus on means & motive, though these may be assessed if issues are found

# Why is Data Integrity still an Issue? …even after almost 20 years since Part 11?

## Means, Motive & Opportunity

- **An FDA inspection primarily evaluates opportunity**
- **CSV documentation is a primary means of demonstrating to the FDA that your company has limited the opportunity for data integrity issues**
- **Have Data Integrity controls been adequately…?**
  - **Designed** (requirements, specifications & configurations)
  - **Validated** (traceable, verified, challenged & tested)
  - **Implemented** (procedures & training)



# What is FDA looking for?

## Understand the Agency's Perspective

- **Oversight over 25% to 35% of the US economy**
- **From the eyes of Congress and the Public, the FDA is "responsible" for public (patient) safety**
- **Limited resources & time – more limited than industry**
- **Lack of control and/or non-compliance is assumed to be a patient safety issue**
- **Looking for well-documented, quick demonstration that the computerized systems are under control**

# CASE STUDIES – What has FDA often found?

## What would FDA assume if your…?

- Management – No knowledge of systems & CSV
- Security – minimal, users can do practically anything
- Audit trails – turned off or unsecured & not reviewed
- Records – duplicate, unauthorized, uncontrolled, incomplete &/or unchecked records
- Stand-alone systems – lax security, no data back-up
- Calculations – incorrect, not verified or validated
- Documentation – minimal CSV for major GxP systems & Validation Reports that say absolutely nothing



# What are the Data Integrity Best Practices?

1. Corporate Ethics & Compliance Program
2. Good Documentation Practices (GDP)
   - ALCOA – applied to electronic records
3. Quality Risk Management
   - Serious risks are taken seriously
   - Applied to CSV
     - Higher risk systems prioritized
     - Lower risk systems planned & scheduled
4. Good Computer System Validation (CSV) Practices

# What are the Data Integrity Best Practices?

## CSV Best Practices – Data Integrity Perspective

1. **Identify all computerized systems & their components**
2. **Assess the risk associated with each system & data**
3. **Identify, map & characterize all data in the system***
4. **Identify & characterize all user roles in the system**
5. **Trace, verify, challenge & test functionality***
6. **Document the CSV Effort in a comprehensive VSR***

**Main areas where industry is not doing an optimal job*



# What are the Data Integrity Best Practices?

## *CSV*

1. **Identify all computerized systems**
   - **List of all systems**
     - Intended use, including GxP data & records
     - Written justification for non-validated systems
   - **Identify all components of the computerized system**
     - Hardware, OS and application software (w/ versions)
     - Include On-site & Remote: hosted, cloud-based

# What are the Data Integrity Best Practices?
## *CSV*

2. **Assess the risk associated with each system & data**
   - **Patient safety** (The FDA's primary concern)
   - **Product Quality** (Often affects patient safety)
   - **Compliance Status**
     - Validated to current regulatory expectations?
     - Clear, concise, self-explanatory documentation?
     - SME's who understand & can explain regulatory requirements, system operation & validation effort?



# What are the Data Integrity Best Practices?
## *CSV*

3. **Identify, map & characterize all data in the system**
   - **Should already be in requirements & specifications**
   - **Map the data flow – inputs, transformations, outputs**
   - **How is data transformed** (i.e., calculations, logic)**?**
   - **Data ranges, limits, results/effects at limits?**
   - **Data migrations & transfers**
   - **Metadata**
   - **Impact of sw upgrades on data & data structures**
   - **Audit Trails** (What audit trail functionality is available?)

# What are the Data Integrity Best Practices?
## *CSV*

4. **Identify & characterize all user roles in the system**
   - **List of User types & permissions/privileges**
     - Restrict access to relevant workflows
     - Restrict permissions to change or delete data
   - **Differentiate administration functions**
     - Not involved in data entry or data review/approval
     - User Admin – Specifications, parameters
     - IT Admin – User account management



# What are the Data Integrity Best Practices?
## *CSV*

5. **Trace, verify, challenge & test functionality**
   - **Calculations**
   - **Limits of ranges, boundary conditions, alerts/alarms – what happens at the extremes?**
   - **Security – access & approval privileges?**
   - **Audit Trails – changes to records** (data, parameters, limits) **& system changes** (users, permissions)
   - **Regression testing – upgrade, DB changes**
   - **Retention – backup, archival & restoration**

# What are the Data Integrity Best Practices?
## *CSV*

### 6. Document the CSV Effort Comprehensively in the VSR

- **Validation Summary Report (VSR) shows that**
  - All components qualified or assessed/audited
  - Intended use or purpose specified & validated
  - Complete validation with adequate test challenges
  - Deviations identified, risk-assessed & redressed
  - Conclusion for system accuracy, integrity & reliability
  - Supported by the rest of the Validation package
- **Administration, operation & maintenance SOPs established (**i.e., defined, written & implemented**)**



# *My CSV Program is a mess – what do I do?*

### A. Assess the Scope of the Problem

a. Audit your computerized systems, including data integrity

b. Escalate issues to Quality & Management

c. If you suspect or find a data integrity issue, call in a competent 3rd-party auditor (as recommended in the FDA's *Data Integrity* Guidance).

### B. Build The Remediation Plan

a. Assess risk (patient safety, product quality, compliance)

b. Estimate required resources (oversight & implementation)

c. Develop a plan & prioritized schedule according to risk

# My CSV Program is a mess – what do I do?

## C. Conduct the Remediation

a. Appoint a Multidisciplinary Team with the right SME's

b. Do the remediation according to GMP – use the Quality System deviations, investigations and CAPA functions

c. Begin CSV on the system(s) with the highest risk

d. Consider concurrently doing smaller systems to get some "quick wins" and to go up the learning curve faster

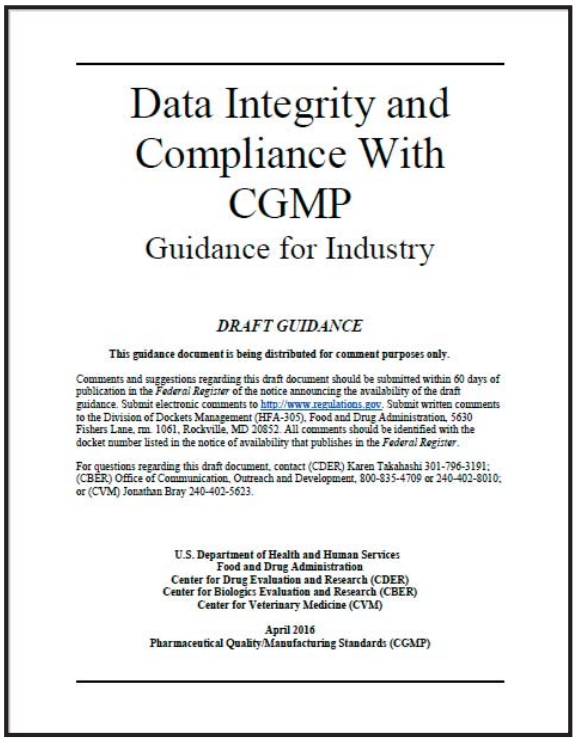
e. Escalate issues & regularly report progress/schedule

f. Revise plan and schedule as needed



# Data Integrity and Compliance With CGMP

- **Issued April 2016**
- **18 (or maybe 23) Questions**
- **Helpful!**
- **A Few Difficulties**
  - Terminology
  - Older system functionality
- **Some Challenges**



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)

# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 1-a | *Data integrity* definition<br>• Data is complete, consistent, accurate (≈ MHRA)<br>• ALCOA |
| **Challenges** | **No** – we should be used to this requirement. |

| Question | Main Topic |
|---|---|
| 1-b | *Metadata* definition<br>• All data about the data<br>• Contextual, meaningful, attributable, identifiable |
| **Challenges** | **Maybe** – Identifying all the data & meta data can be difficult. |



# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

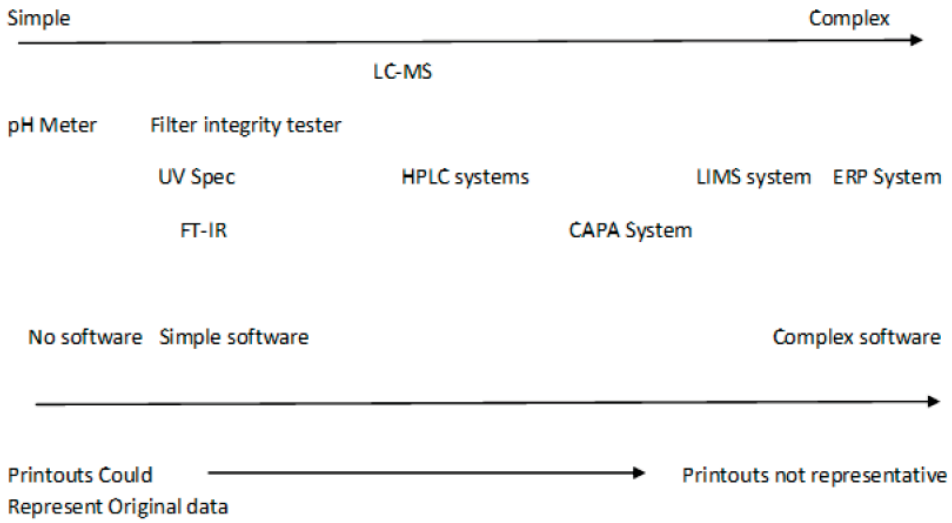
| Question | Main Topic |
|---|---|
| 1-c | *Audit trail* definition<br>• Chronology of data generation & changes<br>• May be at data or record/system levels |
| **Challenges** | **Maybe** – Not everyone is aware of a system's audit trail capabilities, but all personnel involved need to understand. |

| Question | Main Topic |
|---|---|
| 1-d | *Dynamic/static record formats* definitions<br>• ***Static*** ≈ fixed data (e.g., paper or image)<br>*Can the results be completely captured on paper?*<br>• ***Dynamic*** ≈ modifiable data (e.g., HPLC, Excel)<br>• *See M. Cahilly's diagram in MHRA DI Guidance?* |
| **Challenges** | **Yes** – MHRA terms. There's a learning curve with new terms.<br>**Yes** – Current CSV documentation does not have these terms and some FDA investigators may not understand. |

# Static (Print-outs) vs. Dynamic E-records

## *Diagram from MHRA Data Integrity Guidance*

**Figure 1: Diagram to illustrate the spectrum of simple machine (left) to complex computerised system (right), and relevance of printouts as 'original data'**



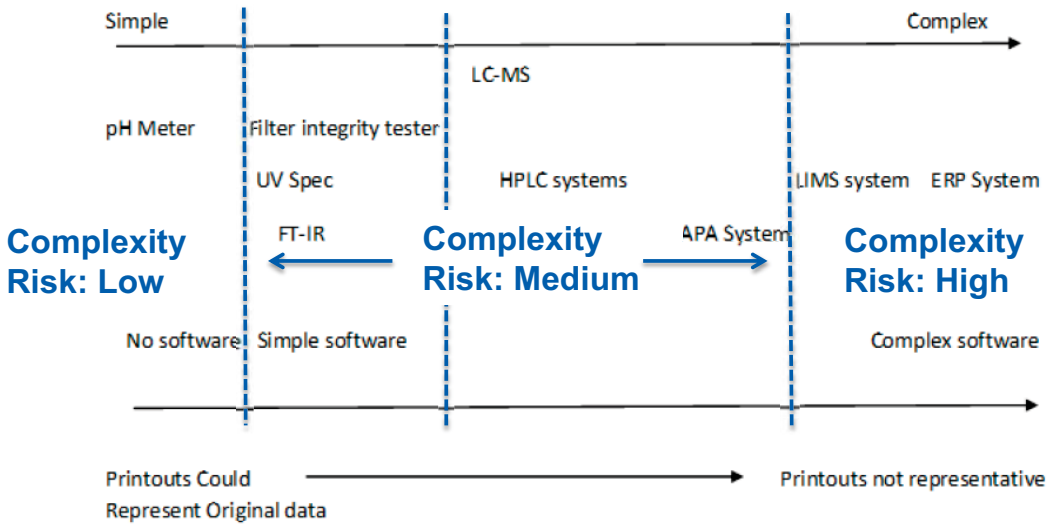

(diagram acknowledgement: Green Mountain QA LLC)



# Risk Assessment: Static vs. Dynamic

## *Diagram from MHRA Data Integrity Guidance*

**Figure 1: Diagram to illustrate the spectrum of simple machine (left) to complex computerised system (right), and relevance of printouts as 'original data'**

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# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 1-e | 211.68(b) *backup* definition<br>• True copy, original data, securely maintained<br>• Through retention period & not temporary files |
| **Challenges** | **Maybe** – Use of *backup*; is not the typical IT usage.<br>**Maybe** – Define the retention copy & maintain good recordkeeping |

| Question | Main Topic |
|---|---|
| 1-f | 211.68 *systems* definition<br>• Hardware, software, peripheral devices<br>• Networks, cloud infrastructure<br>• Operators & associated documents |
| **Challenges** | **Yes** – Qualification of networks (not many are doing this well)<br>**Yes** – Cloud-based infrastructure (requires Supplier Management) |



# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 2 | Cannot exclude CGMP data from decision making<br>• Includes relevant metadata<br>• Decision-making (e.g., release, investigations) |
| **Challenges** | **Maybe** – Defining all the data & understanding the data flow |

| Question | Main Topic |
|---|---|
| 3 | Each workflow requires validation<br>• Intended use includes each workflow<br>• Design & implement controls to manage risks<br>• Validate the system controls |
| **Challenges** | **Maybe** – Validation effort should be proportional to the risk & the complexity of the computerized system |

# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 4 | Access restrictions to authorized personnel<br>• Security & privileges<br>• List of authorized individuals<br>• Independent security role assignments |
| **Challenges** | **No** – Security requirements should be well understood |

| Question | Main Topic |
|---|---|
| 5 | Shared login accounts<br>• Only authorized personnel make changes<br>• Actions attributable to specific/unique individual |
| **Challenges** | **Maybe** – Old equipment may still permit or require shared login accounts. For example, some older computers may have OS level limitations on the number of users. |



# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 6 | Control blank forms<br>• Controlled, numbered, issued & reconciled<br>• Incomplete/erroneous forms retained & justified |
| **Challenges** | **No** – Forms should be well controlled. Most understand this. |

| Question | Main Topic |
|---|---|
| 7 | Audit trails must be reviewed<br>• Reviewed before final record approval<br>• Focus on changes to results & key parameters<br>• Scheduled audit trail reviews based on complexity & intended use |
| **Challenges** | **Yes** – Need to review for data integrity & invalid data. Resources are required to perform reviews, though some reviews may be able to be automated. |

# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 8 | Record reviewers should review audit trails<br>• Audit trails that capture changes to critical data<br>• Records being reviewed must be complete |
| **Challenges** | **Yes** – Need to review for data integrity & invalid data. Resources are required to perform reviews, though some reviews may be able to be automated. |

| Question | Main Topic |
|---|---|
| 9 | Electronic copies of records are permitted<br>• True copies of original data preserving:<br>○ Content & meaning<br>○ Metadata & static/dynamic nature of data |
| **Challenges** | **Maybe** – Define all the data & validate how the original data is preserved and maintained. |



# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 10 | Paper/static records cannot always be used as a "true copy" for any and all electronic records<br>• Some (simple) uses are permitted (e.g., pH)<br>• Static records are not adequate copies of dynamic records (e.g., FT-IR, HPLC) ≈ *A printout is not enough!*<br>• 2nd person review should make certain results are complete per § 211.194(a)(8) |
| **Challenges** | **Yes** – Need to review for data integrity & completeness of data. Identify/Define:<br>• Complete records<br>• Static Format vs. Dynamic Format records |

# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 11 | E-sigs are permitted for master records<br>• Clear identification of responsible individuals<br>• Document controls for identifying individuals |
| **Challenges** | **No** – Proper system design for e-signatures and standard validation should be sufficient, but mind the workflow. |

| Question | Main Topic |
|---|---|
| 12 | CGMP-required data becomes a CGMP record<br>• Data should not be temporarily recorded<br>• Immediately/promptly save/store data long-term<br>• Combination of technical & procedural controls is allowed |
| **Challenges** | **Maybe** – Requires personnel to be diligent & rigorous in their GDP practices. Systems must be designed to promptly save. Controls must be well-defined. |



# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 13 | Testing into compliance is forbidden<br>• Use appropriate standards for system suitability<br>• Follow written procedures & retain all data |
| **Challenges** | **No** – OOS paradigm should be part of GMP culture, but there may be similar issues not readily or easily recognized. For example, is filter integrity being tested into compliance? |

| Question | Main Topic |
|---|---|
| 14 | Save all data and results, including “invalid” data<br>• When chromatography is reprocessed, original results are part of the complete data record |
| **Challenges** | **Maybe** – Define all the “original” data & make certain / validate how the “original” data is to be saved |

# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 15 | Data integrity issues must be investigated and documented within the CGMP Quality system<br>• Determine effect on patient safety, product quality & data reliability<br>• Mechanism to report issues to the FDA<br>• ***Application Integrity Policy*** cited |
| **Challenges** | **Yes** – Conducting data integrity investigations is difficult. Investigate promptly & thoroughly. Typically, the scope of impact must initially assume a broad effect. Lots of CAPA. |



# *Data Integrity and Compliance With CGMP*
## What are the Main Topics & Challenges?

| Question | Main Topic |
|---|---|
| 16 | Routine CGMP training includes detecting data integrity issues as part of assigned duties:<br>• Data Reviewers<br>• Supervisors |
| **Challenges** | **Maybe** – Defining duties which include reviews to detect DI issues |

| Question | Main Topic |
|---|---|
| 17 | Allow the FDA access to CGMP e-records<br>• Allow authorized inspection, review & copying |
| **Challenges** | **Maybe** – If requested, only permit read-only use of computerized systems during inspections, if at all! Establish a rationale and policy for what is permitted without "*refusing access*."<br>**Maybe** – Beware of data dump requests. |

# *Data Integrity and Compliance With CGMP*
# What are the Main Topics & Challenges?

| Question | Main Topics | ? |
|---|---|---|
| 18 | To remediate Data Integrity problems, the FDA recommends:<br>1. Hire a third-party auditor (implication - *to obtain an independent and unbiased assessment*)<br>2. Determine the scope of the problem<br>3. Implement CAPA globally<br>4. Remove personnel responsible for problems from CGMP positions<br>• The FDA may conduct an inspection to verify<br>• ***Application Integrity Policy*** cited again<br>• ***Points To Consider*** document cited | |
| **Challenges** | **Yes** – Once a data integrity problem occurs, there are difficulties with the additional costs, the drain on internal resources, as well as finding the right 3rd-party auditor and preparing for your "For Cause" FDA inspection (who will then inform the EMA, Health Canada, PMDA, TGA, etc.) | |



# Useful Resources – FDA

- **21 CFR Part 11 Electronic Records; Electronic Signatures**
- **§ 211.68 Automatic, mechanical, and electronic equipment**
- **Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Records and Reports – Question 3**
- **Guidance for Industry, Part 11, Electronic Records; Electronic Signatures — Scope and Application 2003**
- **Computerized Systems Used in Clinical Investigations 2007**
- **Electronic Source Data in Clinical Investigations 2012**
- **CDRH – General Principles of Software Validation 2002**
- **CDRH – Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices 2005**

# Useful Resources – Other Agencies

- WHO – Guidance on Good Data and Record Management Practices (June 2016)
- MHRA GMP Data Integrity Definitions and Guidance for Industry January 2015
- EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Annex 11 Computerised Systems (2011)
- PE 009-10 Guide To Good Manufacturing Practice For Medicinal Products – Annex 11 Computerised systems
- PI 011-3 Good Practices For Computerised Systems In Regulated "GXP" Environments (2007)



# Useful Resources – Industry 1

- ISPE GAMP® 5 *A Risk-Based Approach to Compliant GxP Computerized Systems*
- ISPE GAMP Good Practice Guides
  (*10 different guides on a variety of GAMP-related topics*)
- ISA-88 Batch Control Systems
- ISA-95 Enterprise Control Systems

# Useful Resources – Industry 2

- Computerized Data Systems for Nonclinical Safety Assessment: Current Concepts and Quality Assurance (DIA Red Apple Report II)
- Computerized Systems in Clinical Research: Current Data Quality and Data Integrity Concepts (DIA Peach Report)
- PDA TR-18 Report on the Validation of Computer-Related Systems
- PDA TR-31 Validation and Qualification of Computerized Laboratory Data Acquisition Systems
- PDA TR-32 Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations



# THANK YOU!

## QUESTIONS?

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