Difficulties Meeting US FDA Regulatory Requirements

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Three Parts

- Changes in Pharmaceutical Industry
  - Pharmaceutical CGMP Manufacturing
- US FDA Trends
  - 2006-2023
- Difficulties Meeting US FDA Regulatory Requirements
  - Difficulties & Mitigation
- Q&A

Changes in Pharmaceutical Industry

Changes in Pharma

- Technology
- Use of Computerized Systems
  - eQMS, eBRs, CMMS, LIMS, LMS, etc.
- SaaS Cloud Systems
  - Ability to work from any location with secure internet access
- Emerging Technology
  - Artificial Intelligence (AI)

Changes in Pharma

- Digitize Records
  - Increase in use of electronic records
  - Interfaces
    - Training – SOP System Interface
  - Quality Assurance (eQMS (CC, CAPA, OOS, Dev, Complaints, SOP))
  - Manufacturing Automation (PLCs, SCADA, DCS, ERP, eBRs, etc.)
  - Laboratories (QC Analytics and Microbiology)

Changes in Pharma

- 21st Century Quality Programs
  - Right the first time
  - Built-in Quality - Quality by Design (QbD)
  - Above and Beyond
  - Robust Quality Programs
    - Internal / External Audits
  - Risk Management (Probability, Severity, and Complexity, etc.)
    - High, Medium, Low

Changes in Pharma

- Global Regulatory Agencies Involvement
  - US FDA International Regulatory Harmonization (Link)
    - International Council for Harmonisation (ICH)
    - Pharmaceutical Inspection Co-operation Scheme (PIC/S)
    - International Coalition of Medicine Regulatory Authorities (ICMRA)
    - International Agreements & Information Sharing (Link)

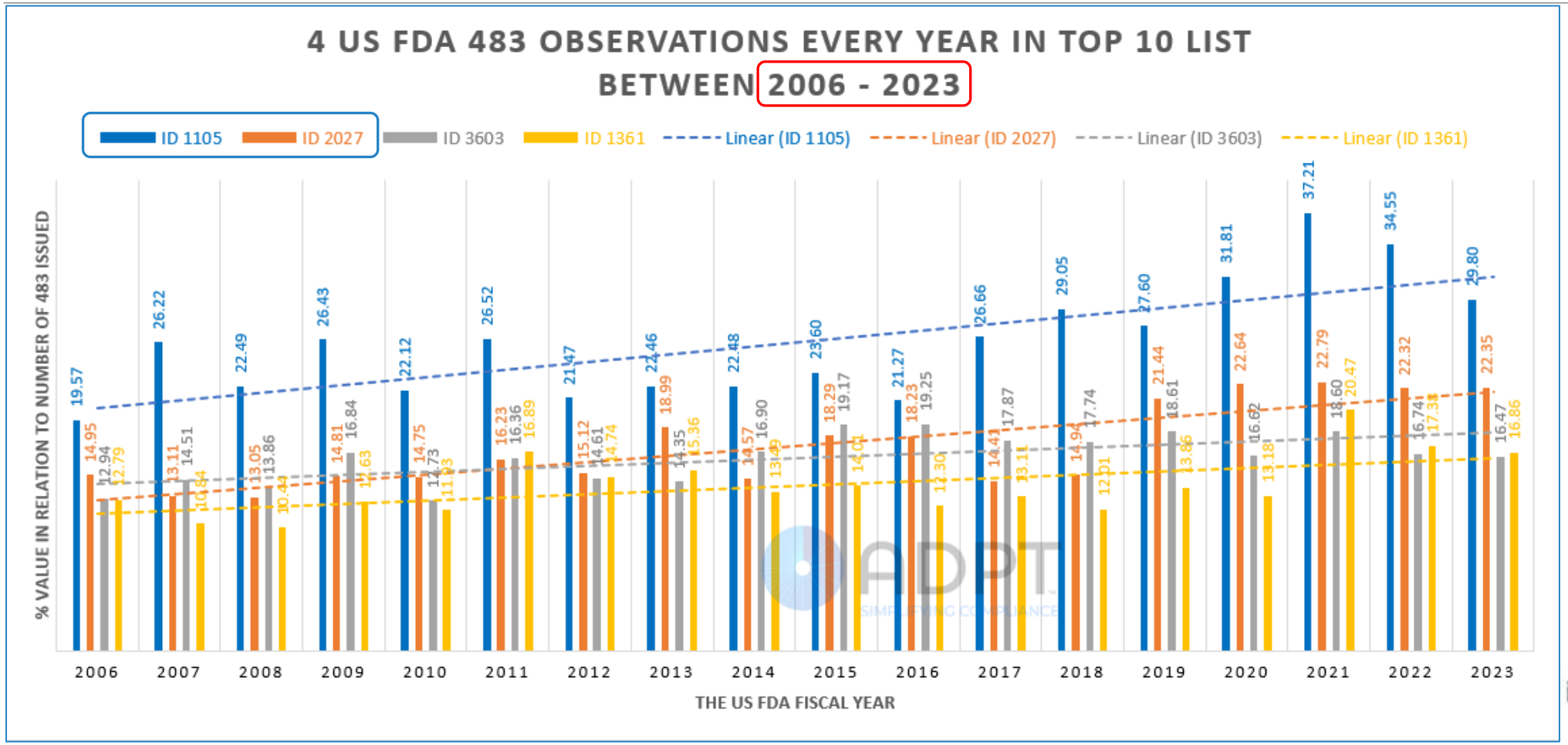
Changes in Pharma

- Global Regulatory Agencies Involvement
  - Industry
    - PDA, ISPE, etc.
      - US FDA Presentations
      - Participate in Guideline Review
      - US FDA Small Business
        - CDER Small Business & Industry Assistance (SBIA)

Trends

US FDA Trends

US FDA Trends



informamarkets

US FDA Trends

Top 4 Observations Detailed Short and Long Descriptions:

Cite ID	CFR Reference Number	Short Description	Long Description
1105*	21 CFR 211.22(d)	Procedures not in writing, fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically…
3603**	21 CFR 211.160(b)	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically…
2027*	21 CFR 211.192*	Investigations of discrepancies, failures	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically…
1361**	21 CFR 211.100(a)	Absence of Written Procedures	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically…

US FDA Trends

Top 10 Observations By Frequency: 2006-2023:

No	Cite ID	CFR Reference Number	Short Description	Long Description	Years in the top 10
1	1105	21 CFR 211.22(d)	Procedures not in writing fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically...	18*
2	3603	21 CFR 211.160(b)	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically...	18
3	2027	21 CFR 211.192	Investigations of discrepancies, failures	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically...	18
4	1361	21 CFR 211.100(a)	Absence of Written Procedures	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically...	18
5	1213	21 CFR 211.67(a)	Cleaning / Sanitizing / Maintenance	Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product. Specifically...	15
6	1451	21 CFR 211.113(b)	Procedures for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically...	10**

US FDA Trends

Top 10 Observations By Frequency: 2006-2023:

No	Cite ID	CFR Reference Number	Short Description	Long Description	Years in the top 10
7	1263	21 CFR 211.68(b)	Computer control of master formula records	Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Specifically...	07**
8	1177	21 CFR 211.63	Equipment Design, Size and Location	Equipment used in the manufacture, processing, packing or holding of drug products is not [of appropriate design] [of adequate size] [suitably located] to facilitate operations for its [intended use] [cleaning and maintenance]. Specifically...	03***
9	1883	21 CFR 211.165(a)	Testing and release for distribution	Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release. Specifically...	14****
10	3585	21 CFR 211.110(a)	Control procedures to monitor and validate performance	Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically...	13****

US FDA Trends

Top 10 Observations by Frequency: 2006-2023:

- *Observation **ID 1105, "Procedures not in writing, fully followed," has been the** Number one by frequency every year since 2006.
- **These observations **ID 1451, 1236, and 1361** are in the **top ten list every year** between **2019 and 2023**.
- ***Observation **ID 1117, "equipment design and size," has been consistently in the top 10 list for the past three years, 2021-2023, and** moved to #8.
- ****These two observations, ID **1883 and 3585**, appear in the top 10 list only **three times between 2019 and 2023**.

US FDA Trends - Data Integrity

Data Integrity Trends

- **Observations related to Records (Data Integrity) since 2012 – 2023**
  - **Record and Data related Data Integrity 483 issued globally**
    - **2012: 21.87% (Maximum before DI Guidance)**
    - 2013: 19.59%f
    - **2014: 18.85% (Minimum before DI Guidance)**
    - 2015: 19.14%
    - **2016: 19.60% (Draft US FDA Data Integrity Guidance)**
    - 2017: 21.39%
    - **2018: 19.16% (Approved US FDA Data Integrity Guidance)**
    - **2019: 18.31% (Minimum after DI Guidance)**
    - 2020: 19.02%
    - 2021: 18.39%
    - **2022: 19.33% (Maximum After DI Guidance)**
    - 2023: 18.36%

US FDA Trends – CAPA vs. Through Investigation

- CAPA Trends (Observation ID 2027)

Corrective Actions and Preventive Actions (CAPA)		
Fundamentals	**CGMP Pharmaceuticals** **21 CFR Part 210 & 211**	**Medical Device** **21 CFR Part 820**
CAPA Regulatory Requirements	None	**21 CFR Part 820.100**
Unexplained Discrepancy Requirements	**21 CFR Part 211.192**	None
CAPA 2023 US FDA 483 Observations	0	**336**
Thoroughly Investigated 2023 US FDA 483 Observations	**175**	0
Warning Letter – FDA Recommendations	Response to Warning Letter	Response to Warning Letter

Data Source US FDA (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations).

Why Difficulties?

"The significant problems we face cannot be solved at the same level of thinking we were when we created them."

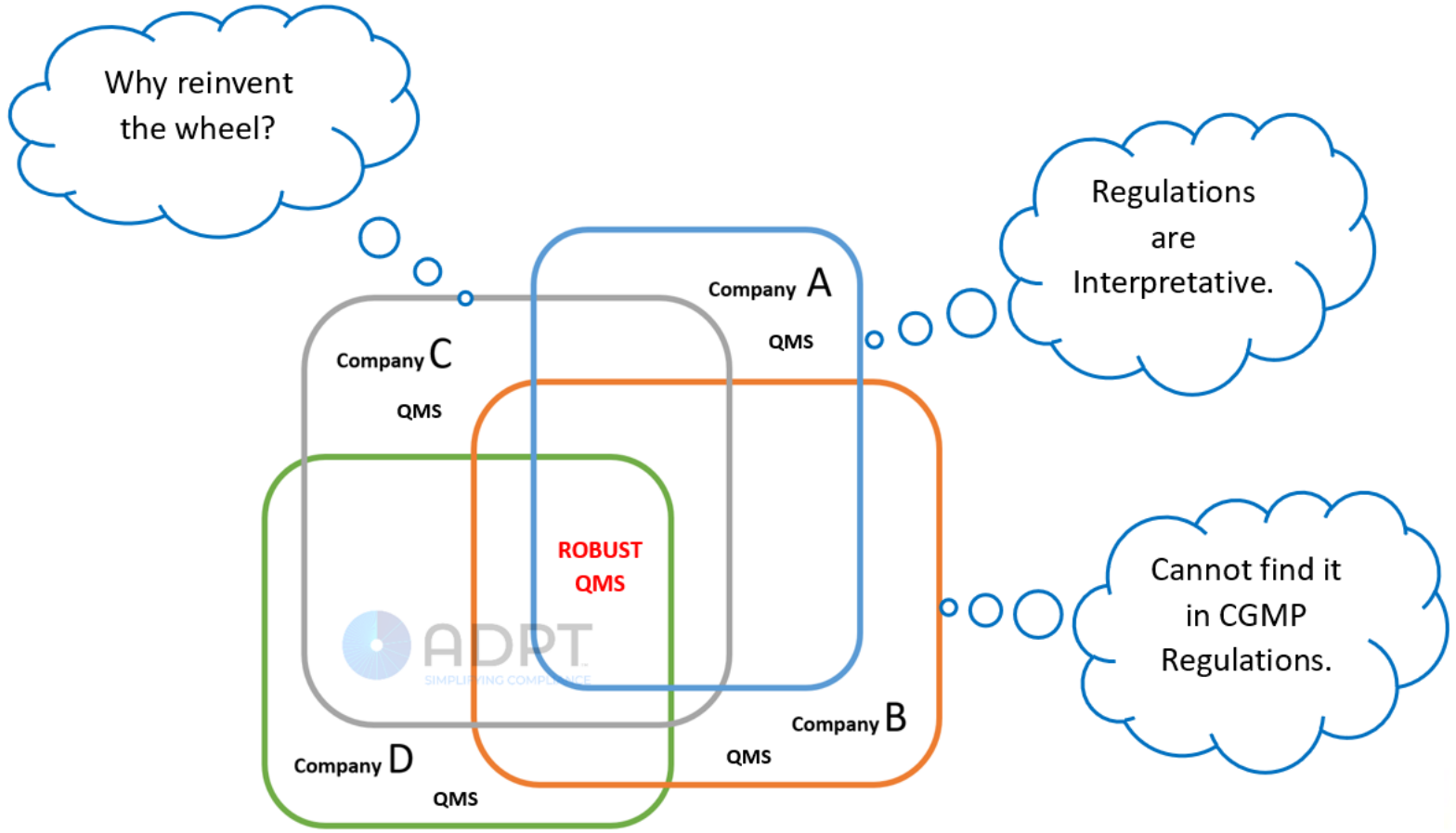
-Albert Einstein

(Source: https://en.wikiquote.org/wiki/Albert_Einstein was not verified)

Difficulty Meeting US FDA Requirements

Difficulties - Mitigation

Quality Management System Design



Quality Management System (QMS) Design

US FDA Guidance – QMS Design

US FDA Guidance - 2006
Quality Systems Approach to Pharmaceutical
CGMP Regulations

https://www.fda.gov/media/71023/download

21 CFR CGMP Regulations Related to Management Responsibilities	
Quality System Element	**Regulatory Citations**
1. Leadership	—
2. Structure	Establish quality function: § 211.22 (a) (see definition § 210.3(b)(15))
	Notification: § 211.180(f)
3. Build QS	QU procedures: § 211.22(d)
	QU procedures, specifications: § 211.22(c), with reinforcement in: §§ 211.100(a), 211.160(a)
	QU control steps: § 211.22(a), with reinforcement in §§ 211.42(c), 211.84(a), 211.87, 211.101(c)(1), 211.110(c), 211.115(b), 211.142, 211.165(d), 211.192
	QU quality assurance; review/investigate: §§ 211.22(a), 211.100(a-b) 211.180(f), 211.192, 211.198(a)
	Record control: §§ 211.180(a-d), 211.180(c), 211.180(d), 211.180(e), 211.186, 211.192, 211.194, 211.198(b)
4. Establish Policies, Objectives and Plans	Procedures: §§ 211.22(c-d), 211.100(a)
5. System Review	Record review: §§ 211.100, 211.180(e), 211.192, 211.198(b)(2)

US FDA Guidance – QMS Design

21 CFR CGMP Regulations Related to Resources	
1. General Arrangements	—
2. Develop Personnel	Qualifications: § 211.25(a)
	Staff number: § 211.25(c)
	Staff training: § 211.25(a-b)
3. Facilities and Equipment	Buildings and facilities: §§ 211.22(b), 211.28(c), 211.42 – 211.58, 211.173
	Equipment: §§ 211.63 – 211.72, 211.105, 211.160(b)(4), 211.182
	Lab facilities: § 211.22(b)

US FDA Guidance – QMS Design

21 CFR CGMP Regulations Related to Manufacturing Operations	
Quality System Element	**Regulatory Citation**
1. Design and Develop Product and Processes	Production: § 211.100(a)
2. Examine Inputs	Materials: §§ 210.3(b), 211.80 – 211.94, 211.101, 211.122, 211.125
3. Perform and Monitor Operations	Production: §§ 211.100, 211.103, 211.110, 211.111, 211.113
	QC criteria: §§ 211.22(a-c), 211.115(b), 211.160(a), 211.165(d), 211.188
	QC checkpoints: §§ 211.22 (a), 211.84(a), 211.87, 211.110(c)
4. Address Nonconformities	Discrepancy investigation: §§ 211.22(a), 211.100, 211.115, 211.192, 211.198
	Recalls: 21 CFR Part 7

US FDA Guidance – QMS Design

21 CFR CGMP Regulations Related to Evaluation Activities	
Quality System Element	**Regulatory Citation**
1. Analyze Data for Trends	Annual Review: § 211.180(e)
2. Conduct Internal Audits	--
3. Risk Assessment	
4. Corrective Action	Discrepancy investigation: §§ 211.22(a), 211.192
5. Preventive Action	—
6. Promote Improvement	§ 211.110

Data Integrity – Regulatory Requirements

- FACT: ALCOA word used once in the US FDA Guidance.

a. What is "data integrity"?

For the purposes of this guidance, *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).[5]

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[5] These characteristics are important to ensuring data integrity and are addressed throughout the CGMP regulations for drugs. For *attributable*, see §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for *legible*, see §§ 211.180(e) and 212.110(b); for *contemporaneously recorded* (at the time of performance), see §§ 211.100(b) and 211.160(a); for *original or a true copy*, see §§ 211.180 and 211.194(a); and for *accurate*, see §§ 211.22(a), 211.68, 211.188, and 212.60(g).

[6] For examples of record retention periods, see §§ 211.180 and 212.110(c).

US FDA Perspective – Regulation vs. Guidance

Legal Framework

Federal Food, Drug, and Cosmetic Act (FD&C Act)
Section 505(i) is the statutory authority for FDA's oversight of clinical investigations to test safety and effectiveness

Code of Federal Regulations (CFR)
Regulations promulgated under Section 505(i) describing FDA's authority over the conduct of clinical investigations

Guidances
Advisory only, to assist regulated entities in complying with the regulations

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US FDA Disclaimer

- Global Regulatory Agencies Involvement

Contains Nonbinding Recommendations

Data Integrity and Compliance With Drug CGMP
Questions and Answers
Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

Procedural Requirements – 211.67

211.67(b) **Written procedures shall be established and followed for cleaning and maintenance** of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. **These procedures shall include, but are not necessarily limited to, the following:**

(1) **Assignment of responsibility** for cleaning and maintaining equipment;

(2) Maintenance and cleaning **schedules,** including, where appropriate, sanitizing schedules;

(3) A description in **sufficient detail of the methods,** equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) **Removal** or obliteration **of previous batch identification**;

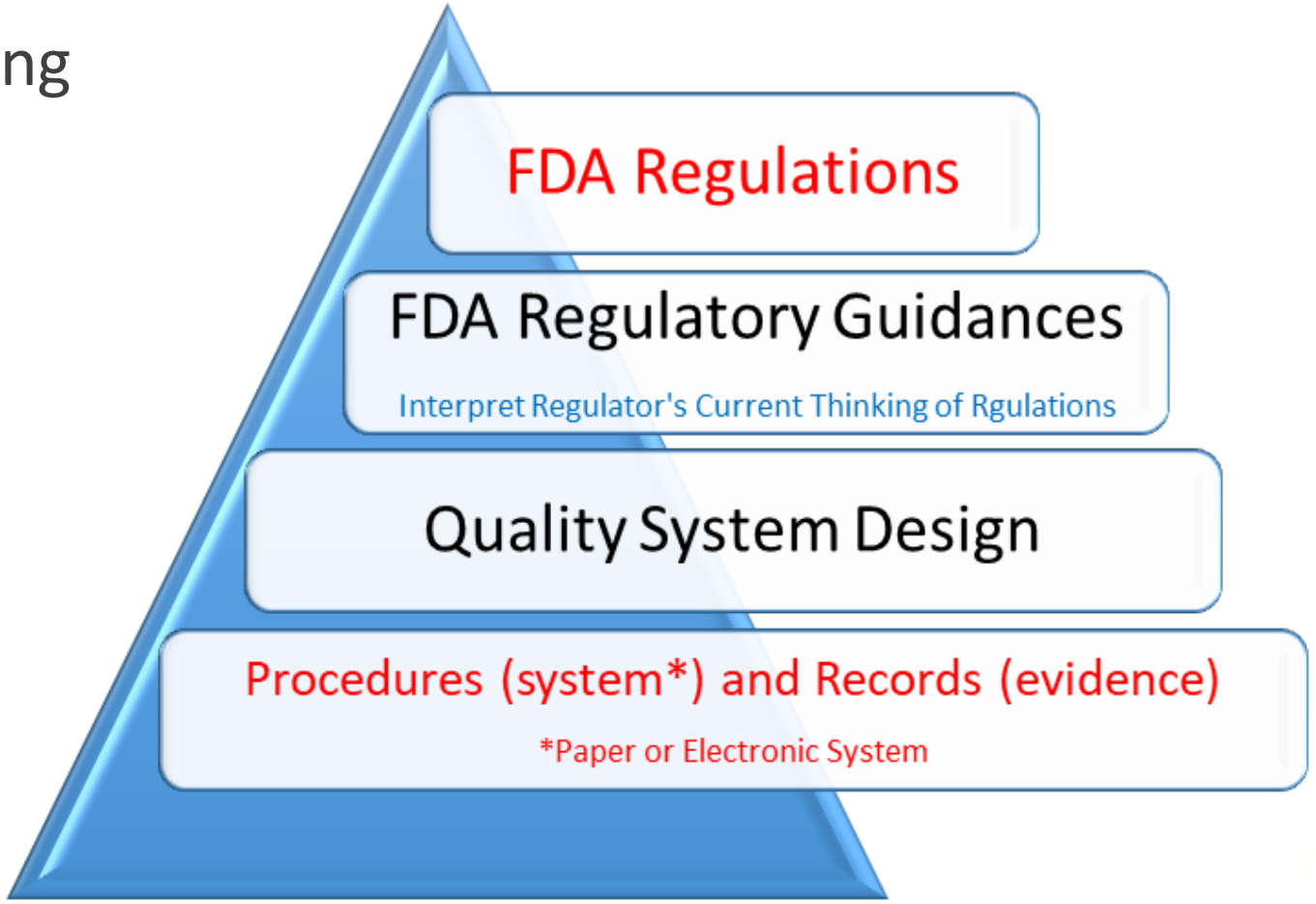
(5) **Protection** of clean equipment from contamination prior to use;

(6) **Inspection of equipment** for cleanliness immediately before use.

(c) **Records shall be kept** of maintenance, cleaning, sanitizing, and inspection as specified in §§ 211.180 and 211.182.

Quality Management System (QMS) Design

- Different Thinking

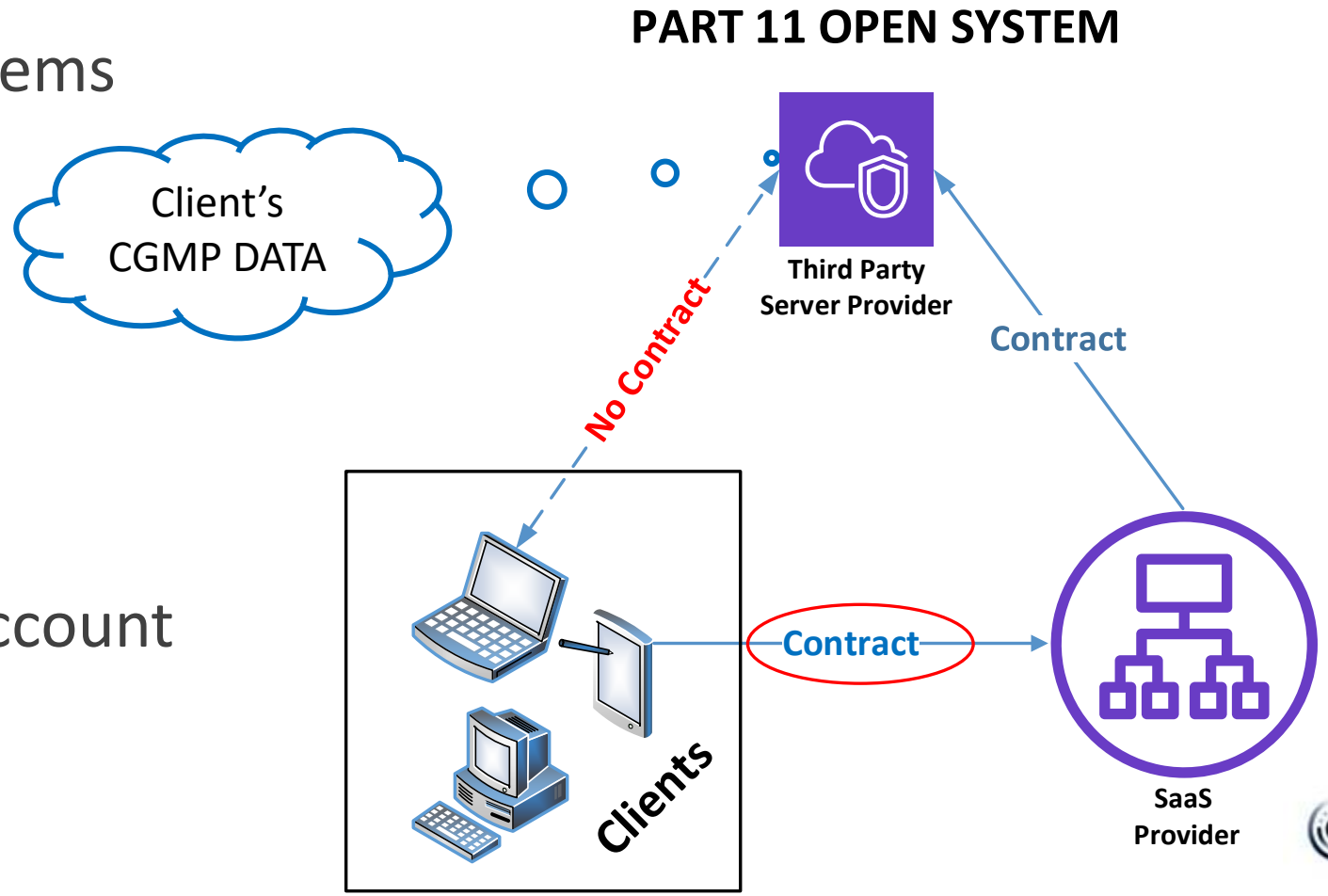


System Design – Open System

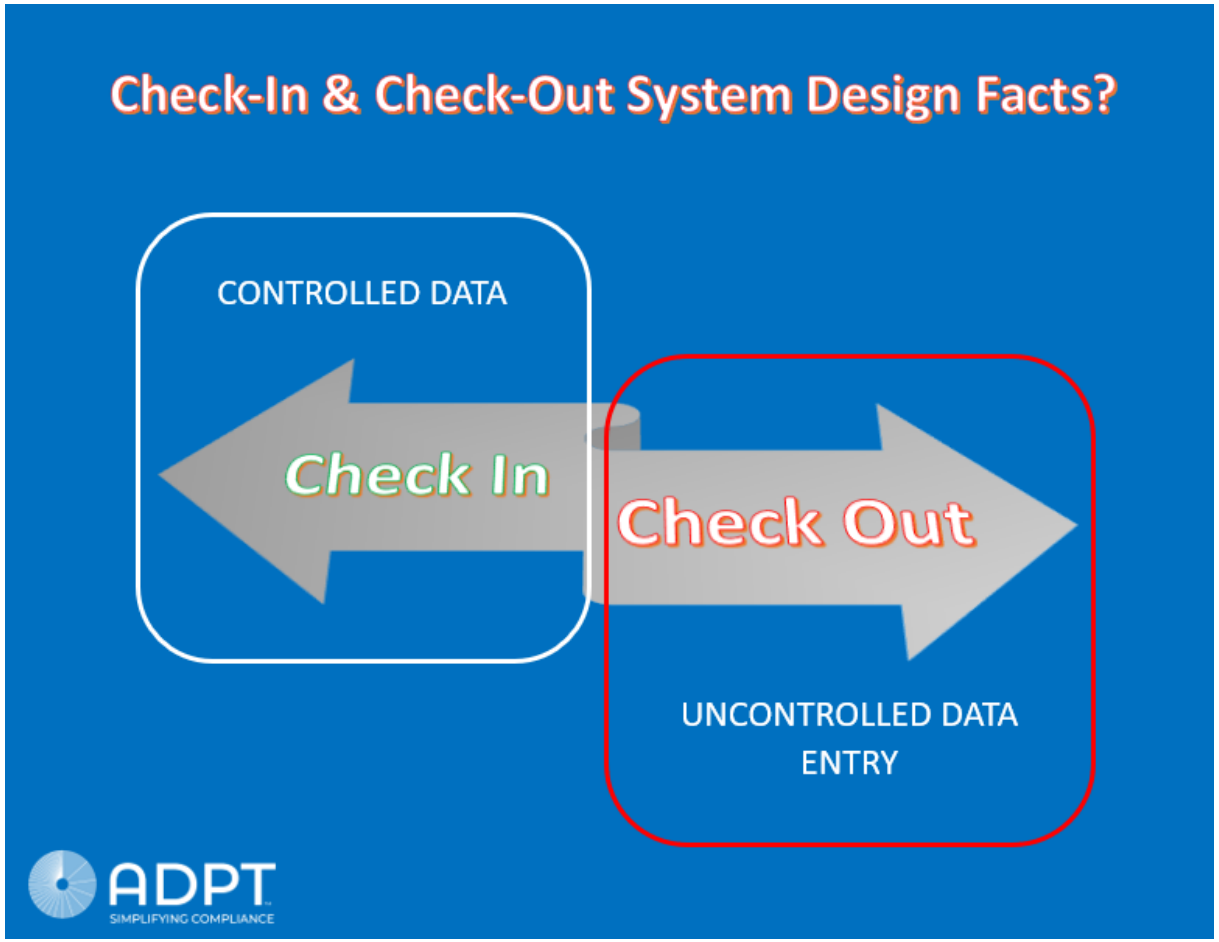
- SaaS Cloud Systems

Data and System

into an Escrow Account



System Design – Check-In & Check-Out



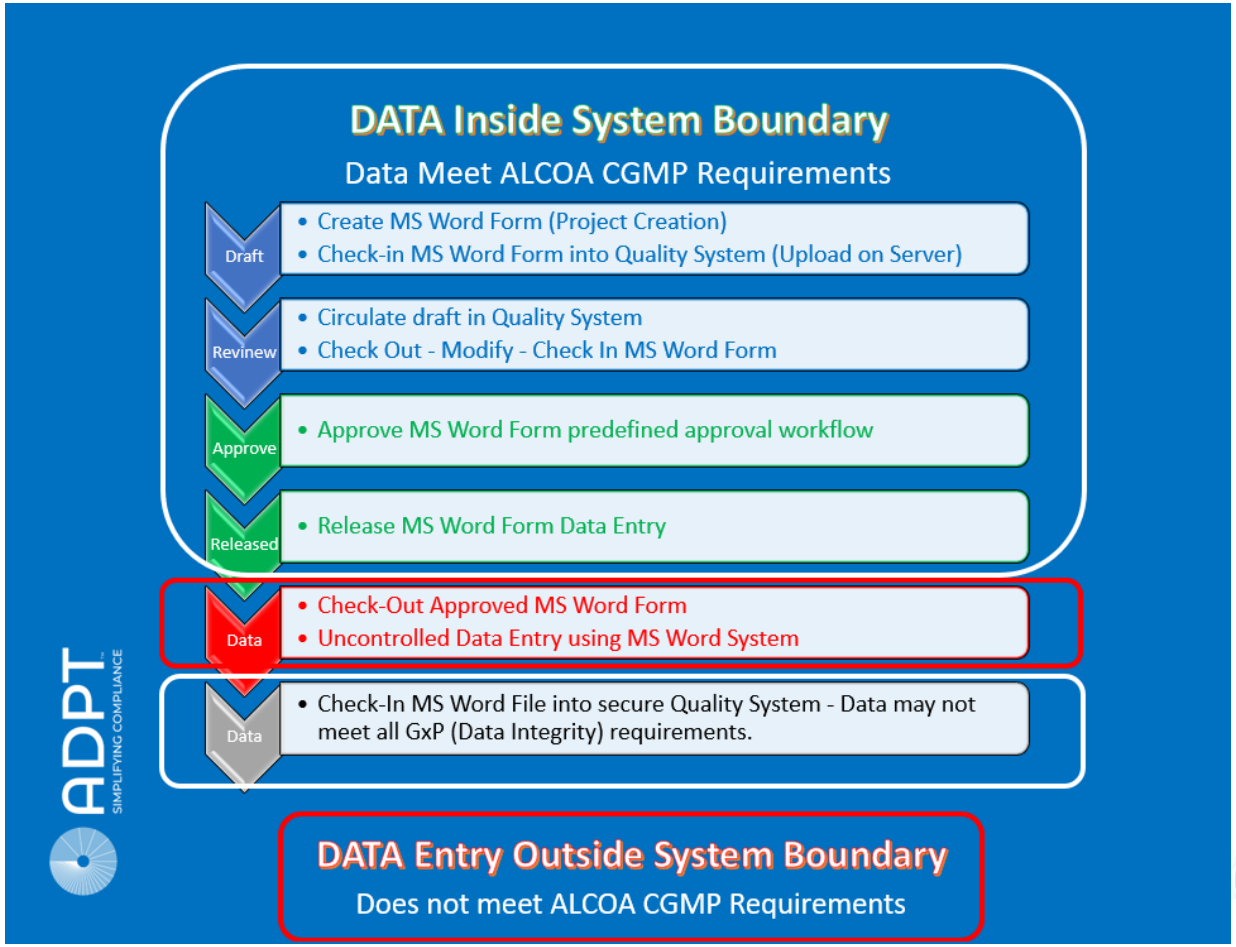
System Design – Check-In & Check-Out

Print the approved form.

Handwritten data entry and signature.

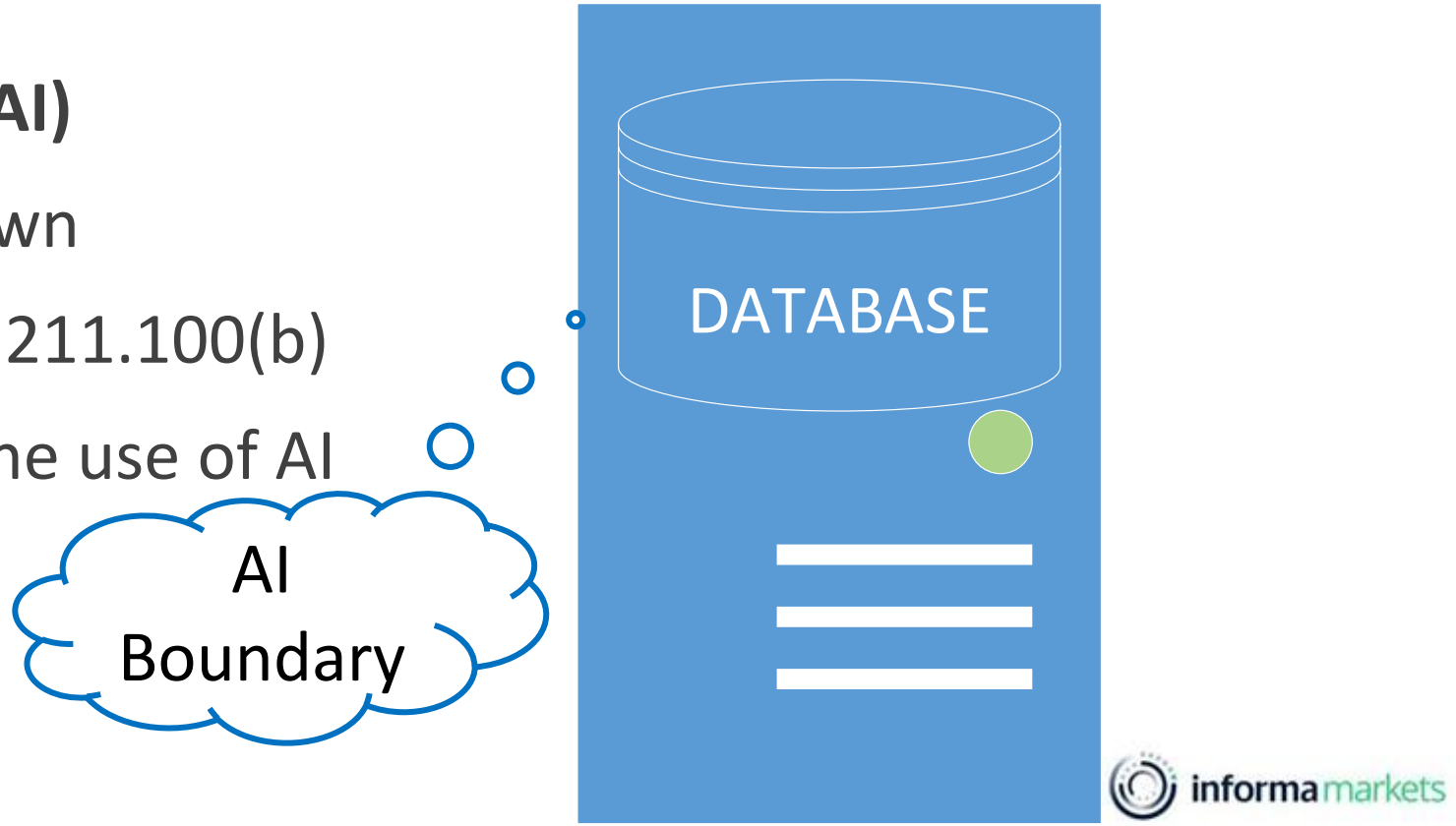
Check-in scanned copy.

Maintain original hardcopy and dynamic data.



System Design - AI

- Emerging Technology
  - **Artificial Intelligence (AI)**
    - Source of data unknown
      - Deviation Search vs. 211.100(b)
    - System boundary in the use of AI
    - Failure Prediction
    - Training AI



Quality Maturity

DI: Reflection of a Firm's Quality System Maturity

Level 4: *Routinely* acts preventively as described in level 3. Fully institutionalizes and reinforces (rewards) a vigilant culture that makes lasting manufacturing & system improvements.

Level 3: More proactive. *Increasingly* detects emerging adverse trends, surfaces major issues, and makes meaningful manufacturing & system improvements.

Level 2: Nearly always reactive, but there is willingness to change. Patchwork corrections are the norm.

Level 1: Small problems ultimately snowball into larger ones, and management becomes aware only when there is a crisis.

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Achieve and Sustain Compliance

Understanding, Interpreting, and Implementing US FDA CGMP regulatory requirements (21 CFR Part 211) will help Achieve and Sustain US FDA CGMP compliance.

Difficulty Meeting US FDA CGMP Requirements

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