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U.S. FOOD & DRUG ADMINISTRATION

Data Integrity
General Overview

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DISCLAIMER: The views and opinions expressed in this presentation are those of the authors and do not necessarily represent official policy or position of the Food and Drug Administration

Objectives

- Present a general picture of the concept of data integrity
- Discuss the US FDA's expectation regarding data integrity
- Examples of WLs citing breaches of DI
- Examples of EU Non-Conformance Reports due to breaches of DI found
- Discuss the do's and don'ts and questions to be answered when breaches in data integrity is found by regulators or self identified

Data Integrity (DI) Again?

- DI has been a hot topic for the past 5 years, but it's not a new issue for regulators or industry.
- DI discussion has generated more questions than answers about what is a breach in the integrity of data and what is not.
- The high number of DI findings has resulted in publications of guidance documents.
- DI breaches may be CGMP violations.

What is Data Integrity?

- Degree to which the data is complete, consistent, accurate, trustworthy, and reliable, and that these characteristics of data are maintained throughout the data lifecycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy and accurate.
- Assuring data integrity requires appropriate quality unit and risk management systems, including adherence to sound scientific principals and good documentation practices.

WHO Annex 5, Guidance on Good Data and Record Management

What is Data Integrity?

Back to Basics:

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

The concept of data integrity underpins CGMP.

Applies to CGMP and Good Clinical Practice (ICH E6).

ALCOA
ATTRIBUTABLE-**traceable to a unique person**
LEGIBLE-**no pencil, no correction, no liquid fluid, no hidden field that won't allow access, no deletion, overwriting**
CONTEMPORANEOUS no backdating, no prefilling, date and time
ORIGINAL or true copy-in paper world (analytical worksheet); e-world (FTIR-spectra, injection sequence, electronic backup copy of the source TF-IR spectra file, compare to the original electronic data confirming ALL metadata is in the electronic copy set.
ACCURATE- verification and confirmation through QMS

Problem Statement

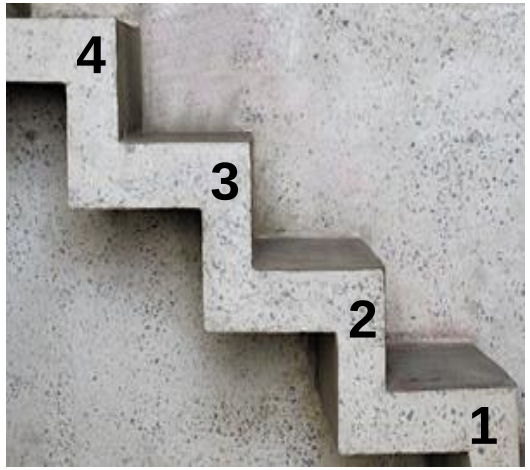
"Testing into compliance," data manipulation, data deletion/record destruction, misreporting, disregarding failing and/or questionable results, all leading to possible breaches in the integrity of critical data, has become one of the most important and relevant topics currently discussed by industry and regulators from around the world.

Basic Principles

- A breach in data integrity is a fundamental failure of the Quality System.

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.

Data Integrity: Not a New Concept

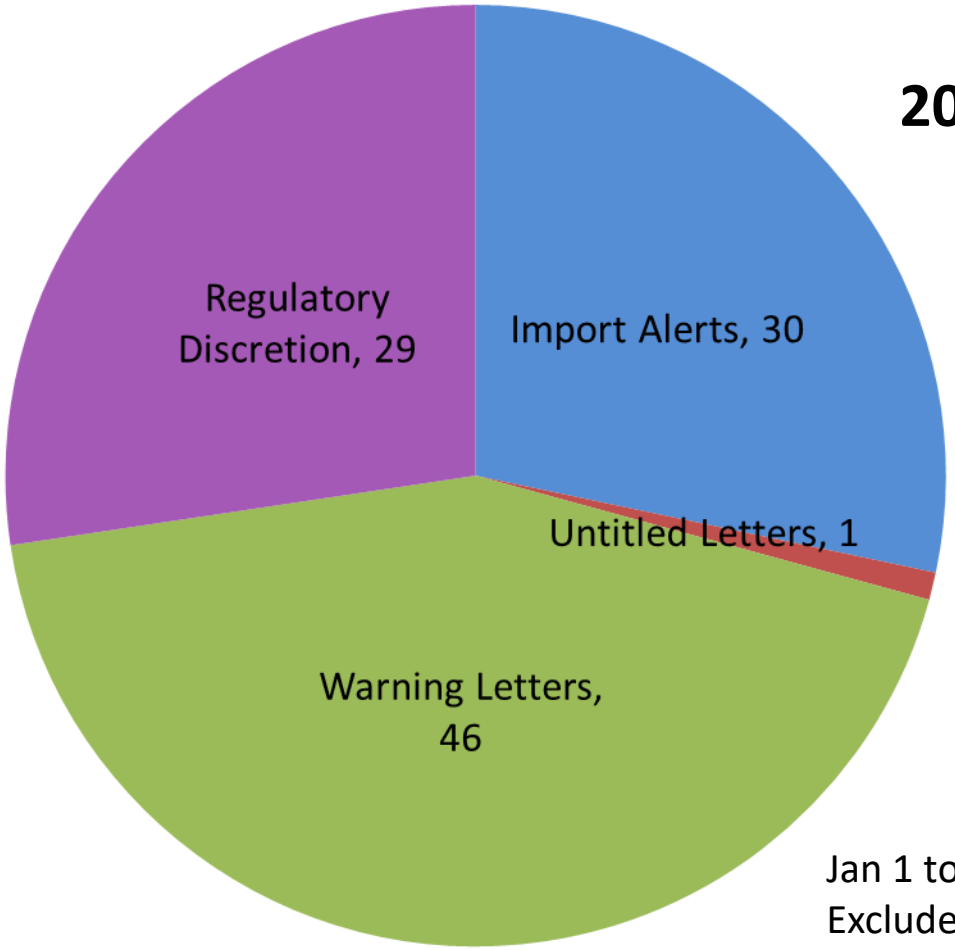
Principles from the paper-and-ink era still apply:

- 21 CFR § 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.

When may FDA Issue an Import Alert, Warning Letter, Injunction, etc.?

- **Significant or systemic CGMP violations or deviations that** could result in a drug quality defect with potential adverse patient health consequences;
- Repeat violations or deviations;
- Refusal or delay of an inspection; or
- Significant data integrity violations or deviations

Enforcement and Advisory Tools



2018 Enforcement and Advisory Actions

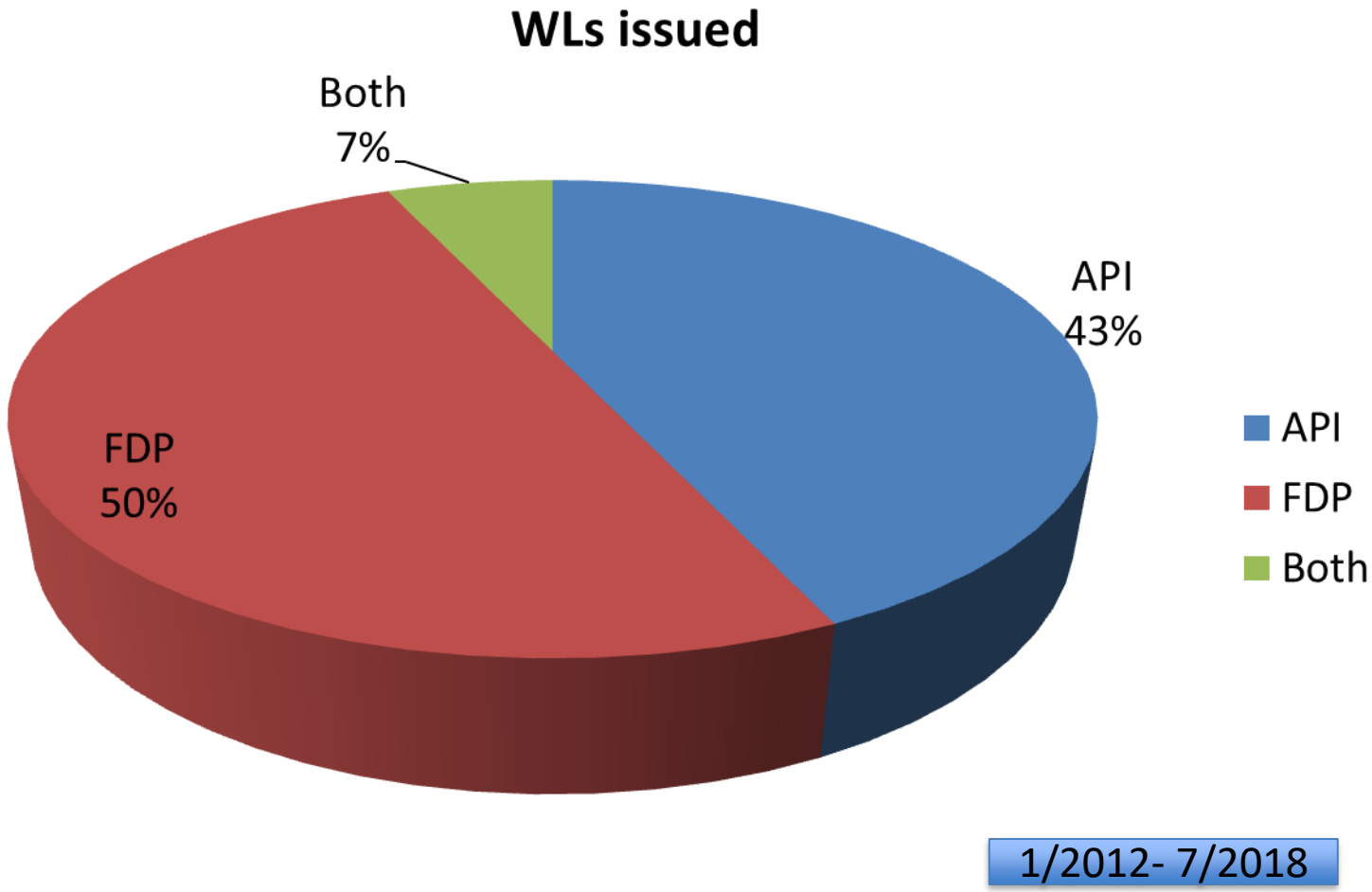
- Import Alerts, 30
- Untitled Letters, 1
- Warning Letters, 46
- Regulatory Discretion, 29

Jan 1 to June 30 , 2018
Excludes pharmacy compounding-related actions

U.S. FDA Warning Letters Related to DI Issues

- Period: 10/2012 to 07/2018
- WLs issued related to DI deficiencies: 111
  - DI issues related to production only: 16
  - DI issues related to laboratory only: 65
  - DI issues related to production and laboratory: 30

U.S. FDA WLs – DI issues related to production activities API vs. FDP



1/2012- 7/2018

Europe Reg. Authorities NCRs with DI Issues

NCRs Evaluated	NCRs with Data Integrity Issues
156	77

Approx. 49% of Europe Agencies Non Compliance Reports, had DI issues

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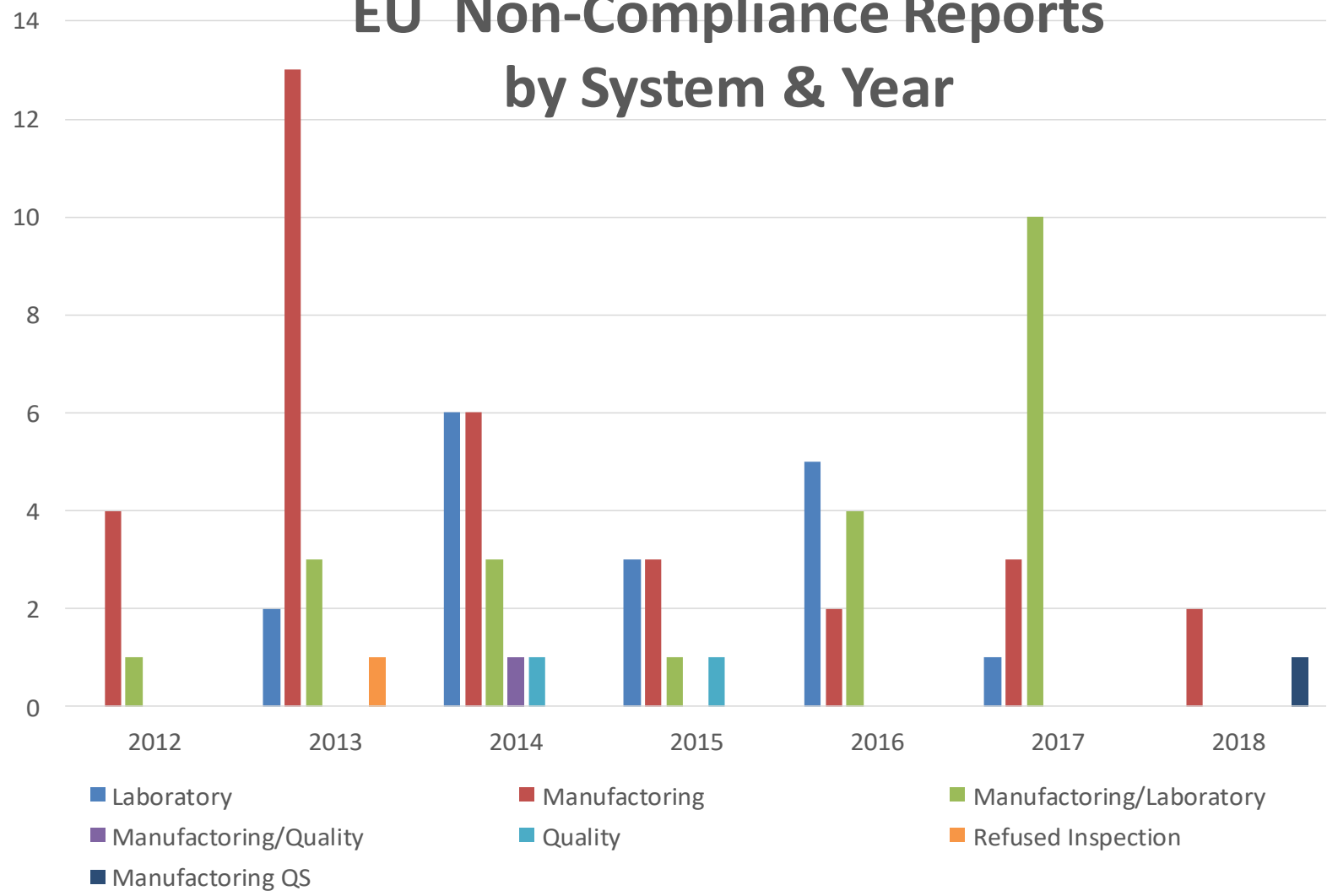
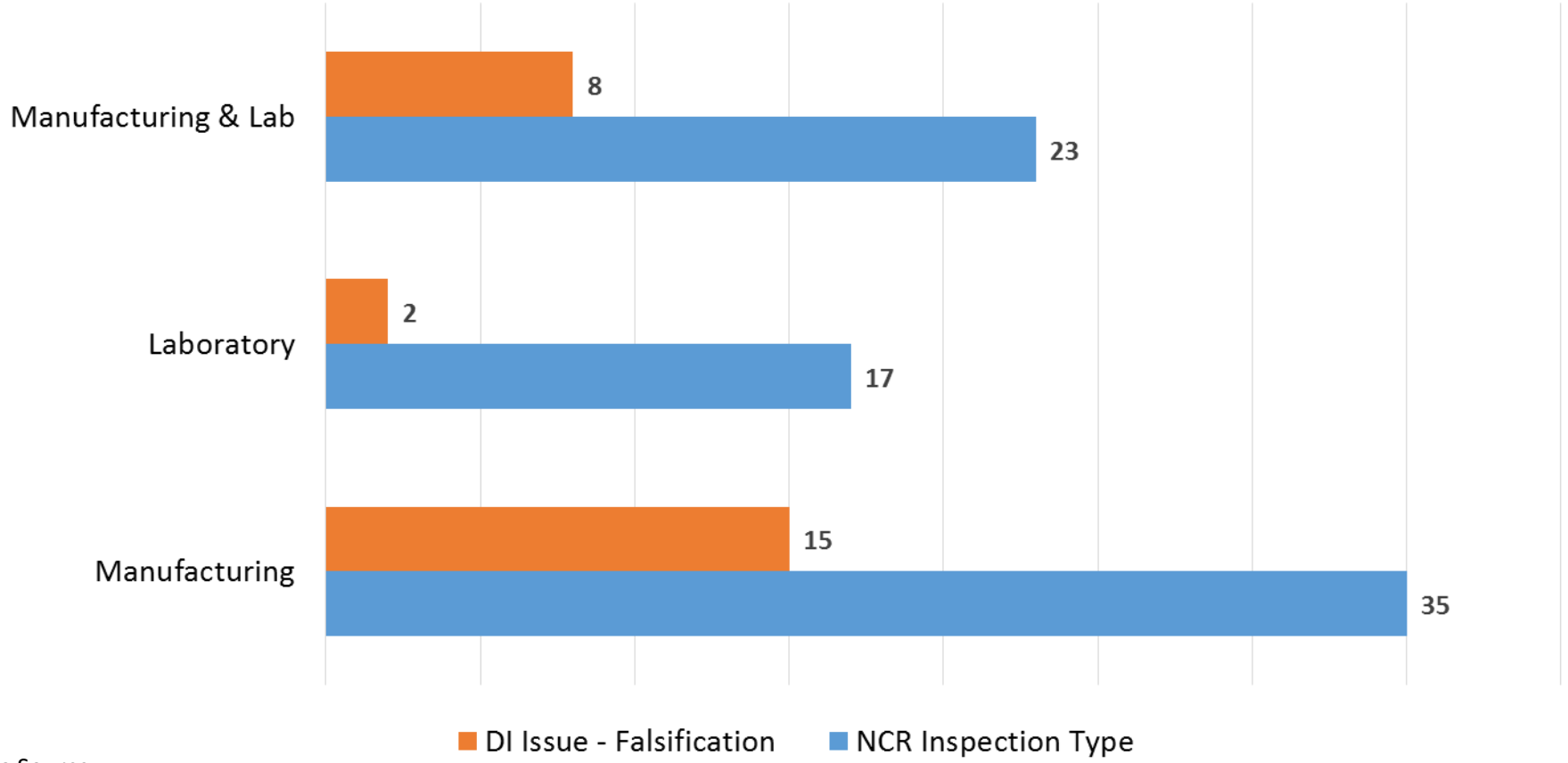
EU Non-Compliance Reports by System & Year

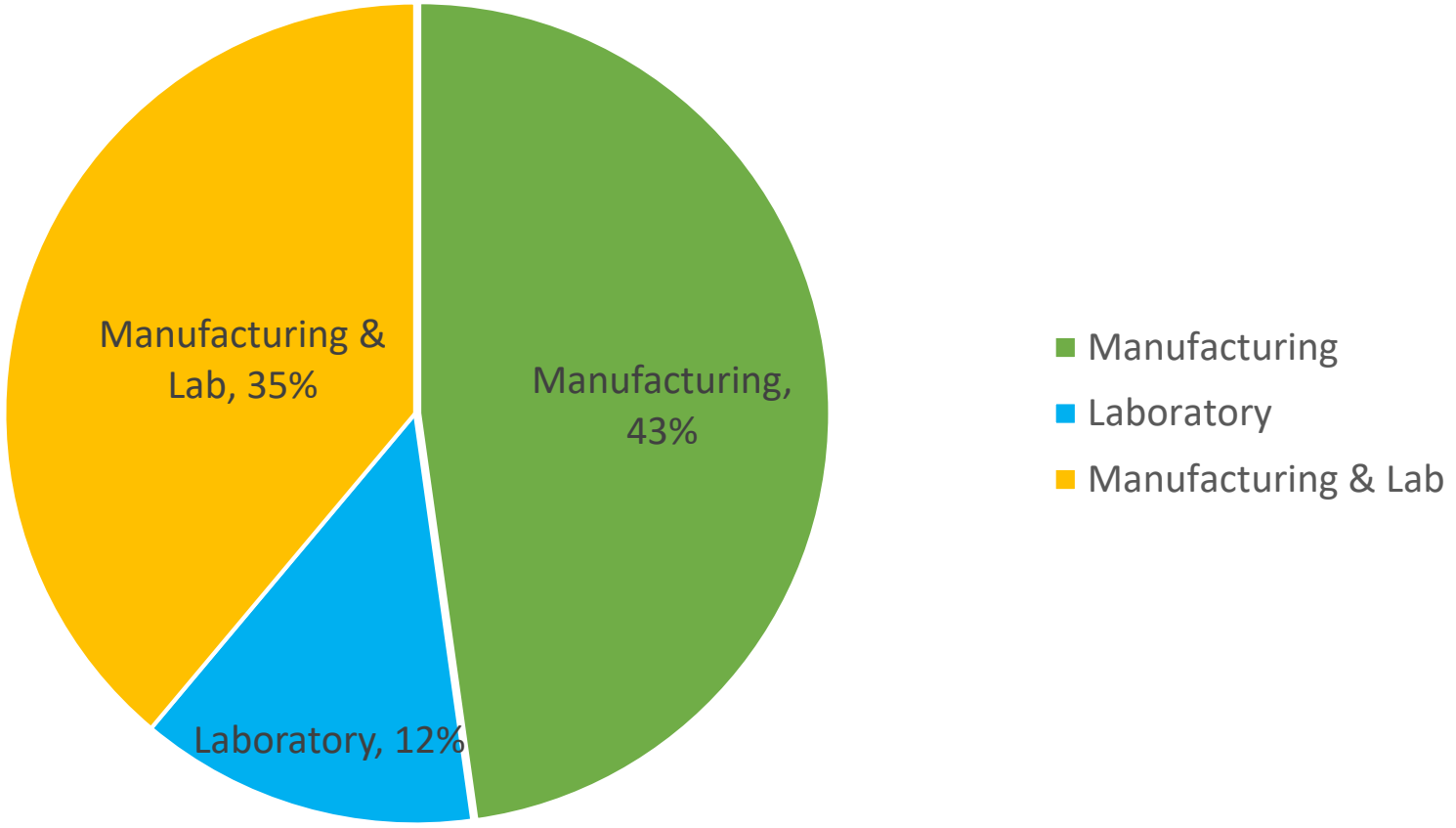


Non-Compliance Inspection Reports with Data Integrity (Falsification) Issues



Data Source:
http://eudragmdp.eudra.org/inspections/gmpc/searchGMPNonCompliance.do; Search: 1/1/12 to 8/16/18 (Include withdrawn documents)

Falsification Rate in Inspection Types (Non-Compliance Reports)



Europe Non Compliance Reports Evaluated Period 1/1/12 to 8/16/18

What Regulators Find Is Truly The Tip of Iceberg

CGMP – "minimum" requirements

Data integrity underpins basic CGMP principals

Breaches of DI are observed in the U.S., China, India, Europe, around the world

http://khongthe.com/wallpapers/nature/tip-of-the-iceberg-90839.jpg

Common Terminology When Data Integrity is Found

- Falsification of data
- Alteration of data and events
- Misleading information, statements or facts
- Misrepresentation of what really happened
- Untruthful statements
- Deceit
- Forgery

Common Terminology When Data Integrity is Found

- Releasing failing product as if they had passed
- Testing into compliance
- Not saving electronic or hard copy data that would confirm the failing results
- Making up microbiological test (EM) results
- Question – *Why would firms tolerate this behavior?*

Data Integrity Failure Examples

- Lack of controlled access to computer systems
- “Trial” HPLC injections outside a quality structure
- Deleted data
- Not recording activities contemporaneously
- Backdating
- Fabricating data
- Copying existing data as new data
- Discarding or deleting results with no justification and re-running/retesting samples to present better results

Why Data Integrity Matters

- DI is the foundation of pharmaceutical quality
- Breach in DI (records/electronic) erodes confidence/breaks trust of regulator and public.
- FDA CGMP surveillance inspections are usually focused to determine adherence to CGMP, not to verify all data. Changing due to recent events.

Why Data Integrity Matters

Data integrity breaches cast doubt on all results and records.

- When we find firms making up microbiological data during inspection, can/should we trust what we see during an inspection?
- When DI practices are found, will retesting be sufficient to overcome the breach and assure products released are within specifications, safe, and effective?
- Is the data submitted to support pending or approved drug applications, and used to release batches, reliable, truthful, accurate, original?
- Can we be confident in providing these drugs to our patients?

Why Data Integrity Matters

"…the term 'current good manufacturing practice' includes the implementation of **oversight** and controls **over the manufacture of drugs to ensure quality**, including **managing** the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."

Food and Drug Administration Safety and Innovation Act, Sec. 711
Enhancing the Safety and Quality of the Drug Supply

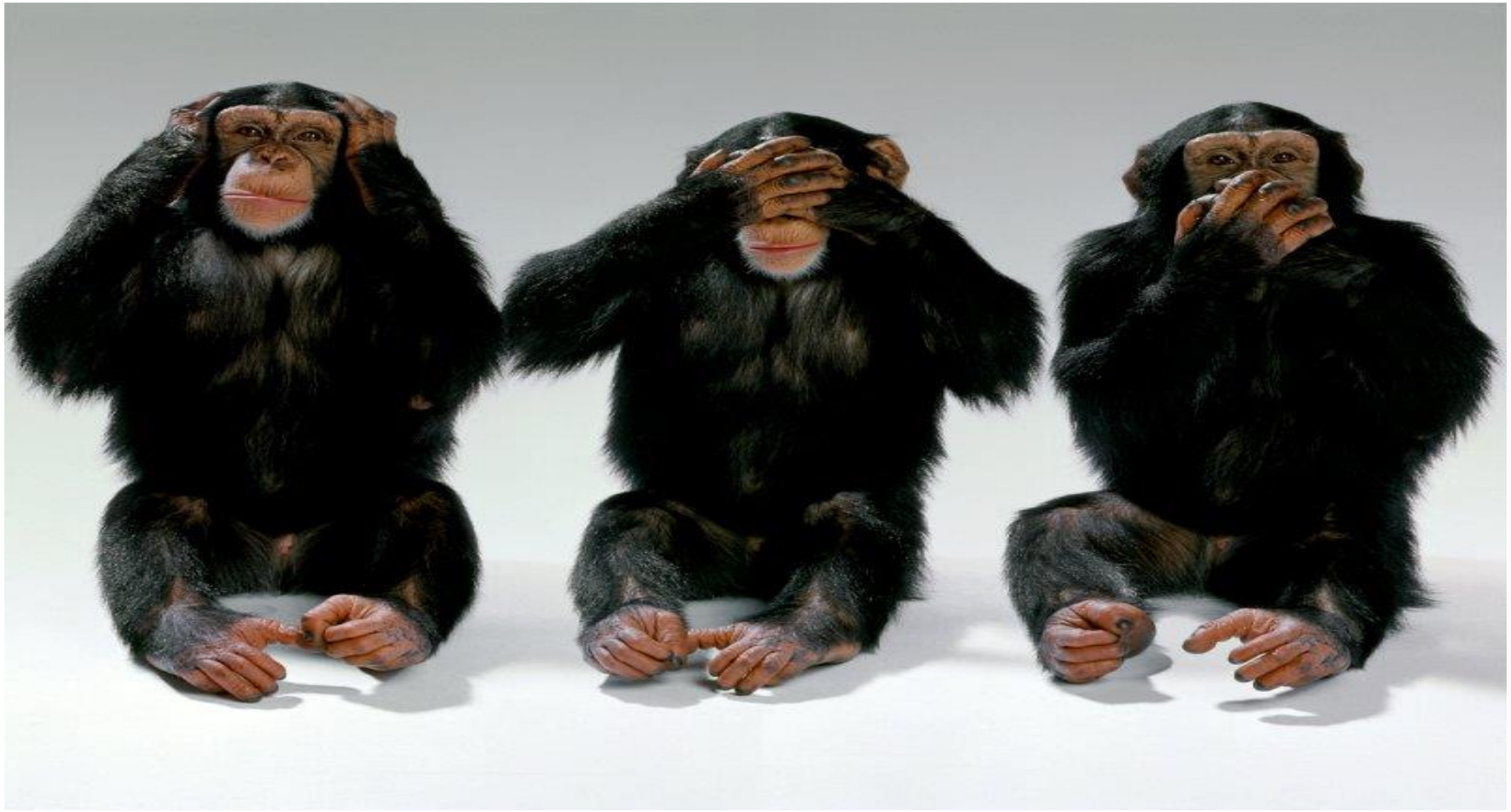
Why Data Integrity Matters

Drug can be deemed adulterated under section 501(a)(2)(B) of the FD&C Act because data integrity breach is a violation of CGMP.

- Under U.S. law, adulterated drug is subject to detention.
- Generally, significant CGMP issues require re-inspection.
- Firms must fix problems and be re-inspected.

Who is responsible for the integrity of the data ?

Everyone involved in the "manufacturing" is responsible for assuring the integrity of the data. "What you see, hear and say matters" Otherwise, we are silent conspirators.



Factors That May Be Associated With DI Problems

1. Production-first business model (driven by economic pressure), where allocating resources and robust systems to predict, prevent, and detect DI issues are not a priority.
2. More CMOs manufacturing and testing of drugs occurring under different quality systems, where often the owner or sponsor of the drug has little control, oversight, or access to the contracted operations.

Factors That May Be Associated With DI Problems

3. Incorporation of new technology, software, and systems without the appropriate **understanding** of the gaps and challenges, and **risk-based controls needed to prevent and detect** DI practices.

4. Deficient or immature quality system.

5. Systems and SOPs are outdated, little training and oversight by QA/QC, complacent approach.

Factors That May Be Associated With DI Problems

6. Complex supply chain/more globalization.
7. Firms relying on regulators to serve as

QU to find the problems.

“Regulatory Significance Considerations”

General Considerations During Review of DI Cases:

- Impact of the CGMP violations/deviations on the product attributes (drug quality, released, pending/approved applications);
- Associated risk of the substandard product or deficiency to the patient;
- Clinical significance;
- Batches released, submitted to support drug approved and pending applications;
- Firm’s compliance history (e.g., **a history of serious deficiencies**, or failure to prevent the recurrence of violations), showing pervasive behavior;

“Regulatory Significance Considerations”

- Nature of the violation (e.g., was the firm aware of the DI issues & failed to correct, or were they discovered by

FDA and the firms was unaware);

- Was it an inadvertent or minor error ? (e.g., mathematical

calculation error and does it have a significant impact on product quality);

- Severity, likelihood of harm, affected product in market;
- State of control (pattern or single instance, how do you know);

“Regulatory Significance Considerations”

- How does a firm mitigate the impact of a deficiency?
- Has the firm voluntarily corrected and prevented recurrence?
- Assessment of scope and extent of the problems
- Can the firm detect or prevent future problems?
- Has the firm addressed the issue in a systemic or global manner? Have similar violations been cited at other sites?

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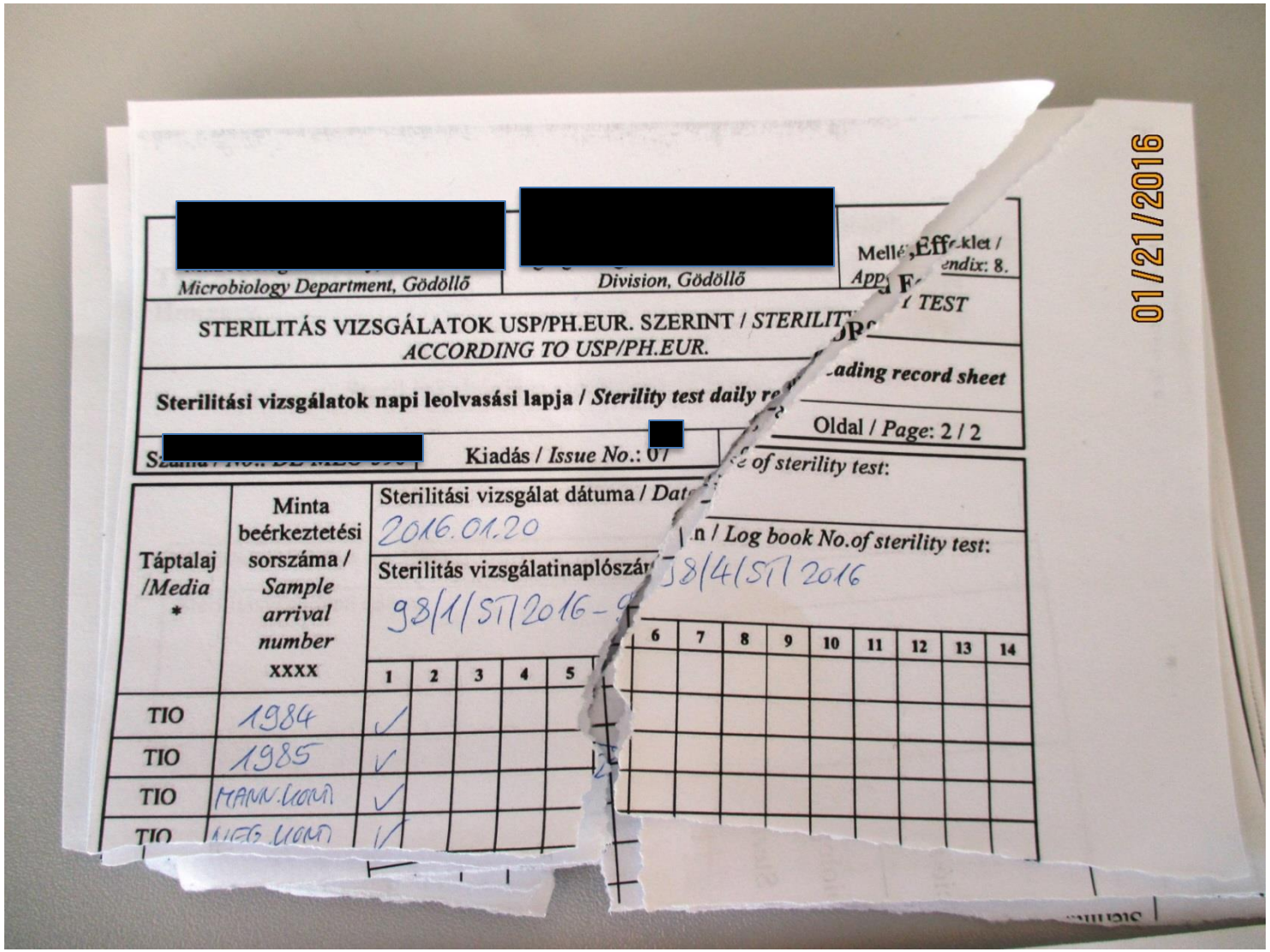
Four contact slides with uncounted colonies found in the waste bin.

Contact slides from Grade B area (e.g., aseptic corridor for autoclave; gown hood of the cleanroom) retrieved from waste bins.

A Picture Tells a Thousand Words!

Sterility test data sheets dated January 20, 2016, found in a waste bin.



FDA compliance information online:

www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm081992.htm

Acknowledgements

- Rick Friedman, Deputy Director, Office of Manufacturing Quality, Office of Compliance, CDER
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