Data Integrity: A Look at the "New" FDA Warning Letter Language

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FDLI
Food and Drug Law Institute

2017 Enforcement, Litigation
& Compliance Conference

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Speaker Introduction

Experience Summary:

- ✓ Thirty years of experience in FDA-regulated operations, quality, compliance, regulatory & law
- ✓ Founder, CEO, Compliance Architects LLC
- ✓ Principal, The Garvey Law Firm

Education / Credentials:

- ✓ Chemical Engineer / Attorney
- ✓ Admitted to practice law in NY and NJ

Companies worked in and for:

- ✓ Johnson & Johnson (Corporate, Consumer, Neutrogena, OCD, Ethicon-Endo, JDx, Lifescan)
- ✓ Bayer
- ✓ Merck
- ✓ Ciba-Geigy (Novartis)
- ✓ BASF Corporation
- ✓ CR Bard
- ✓ Accenture/BMS
- ✓ Ayerst (Wyeth)
- ✓ Aventis-Behring
- ✓ Philips Healthcare

Sample Focus areas:

- ✓ Enforcement remediation (483s, WLs, Import Detention, etc.)
- ✓ Inspection readiness and preparation
- ✓ Quality System development
- ✓ Regulatory / submissions
- ✓ Corporate Compliance
- ✓ HACCP / Process mapping & risk analysis
- ✓ CAPA program development & drafting
- ✓ Computer-based systems, enterprise risk management & quality operations
- ✓ Writing for Compliance®

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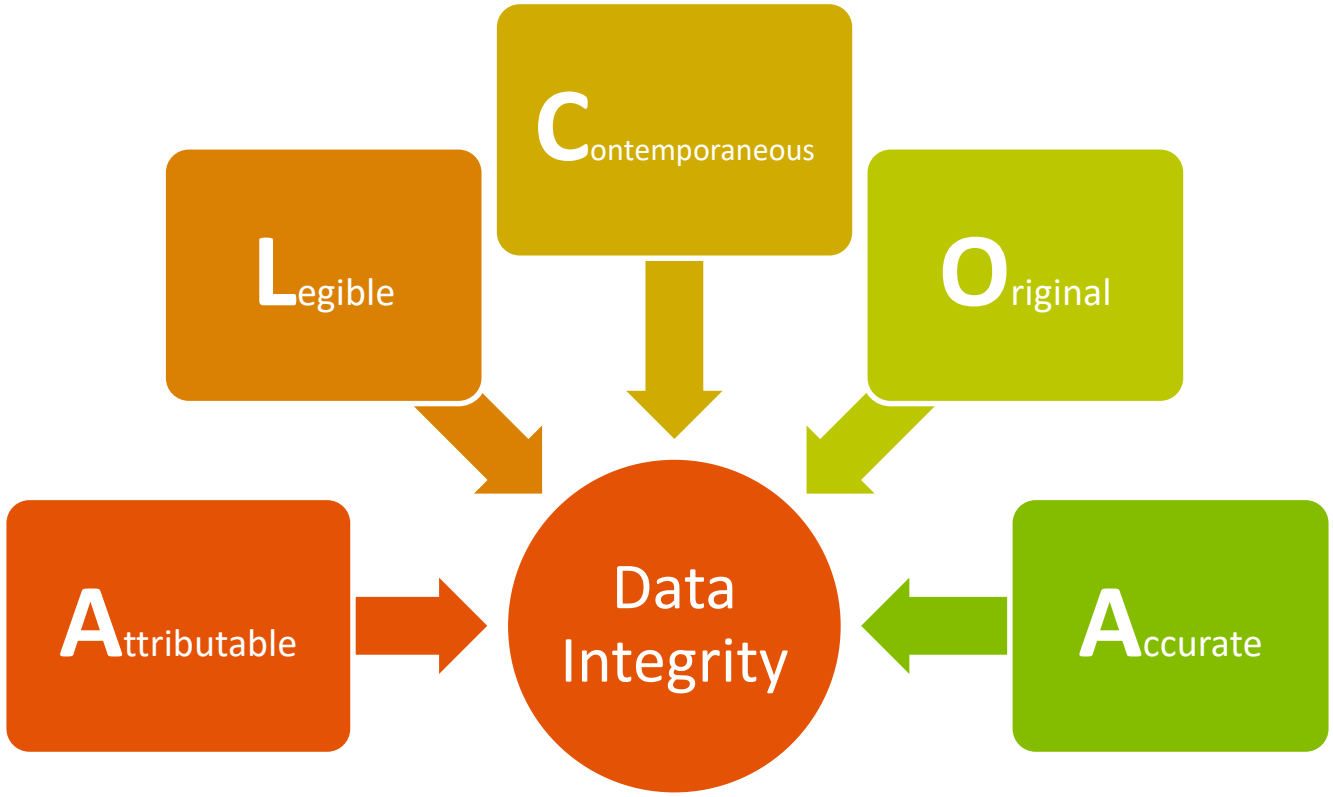
What is Data Integrity?

A characterization of the reliability, credibility, validity, authenticity, and trustworthiness of a state of data and/or information encompassing multiple foundational dimensions including attributability, legibility, contemporaneous recording, originality and accuracy.

ALCOA: FDA's Data Integrity Focus



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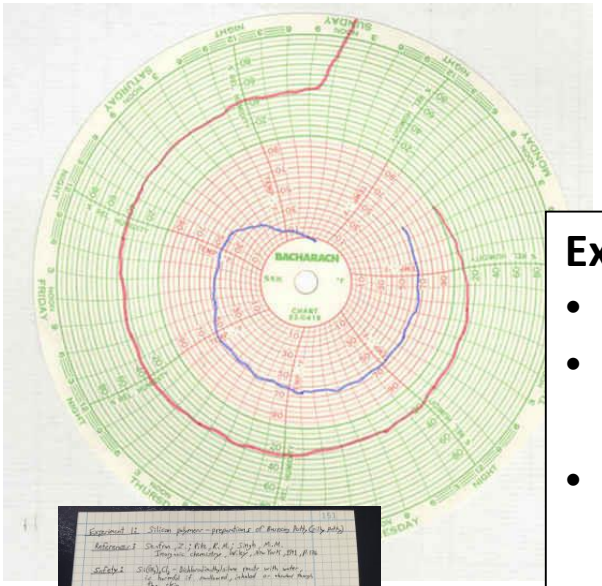
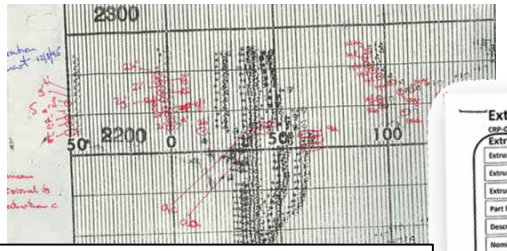
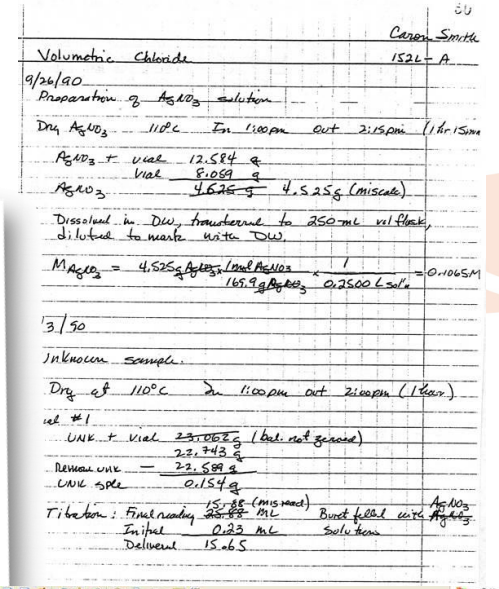
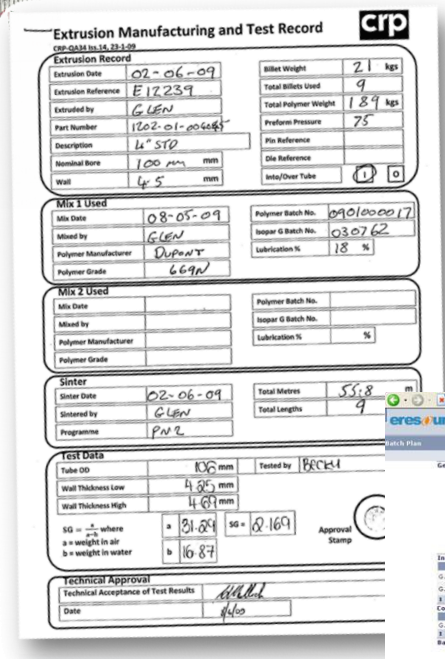
What is Data (and Information)?



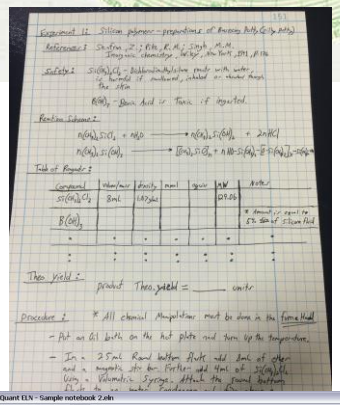


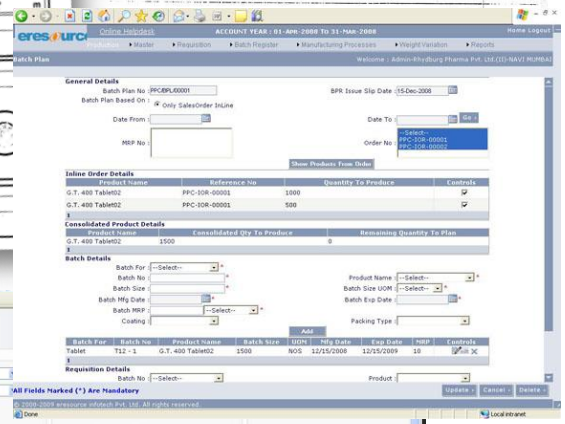


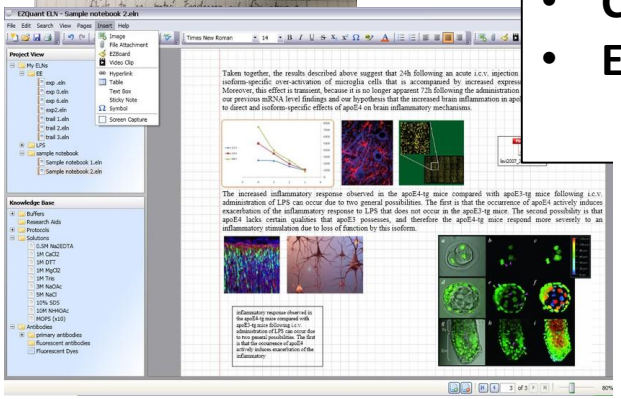


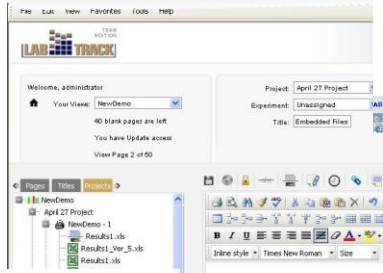
Examples:

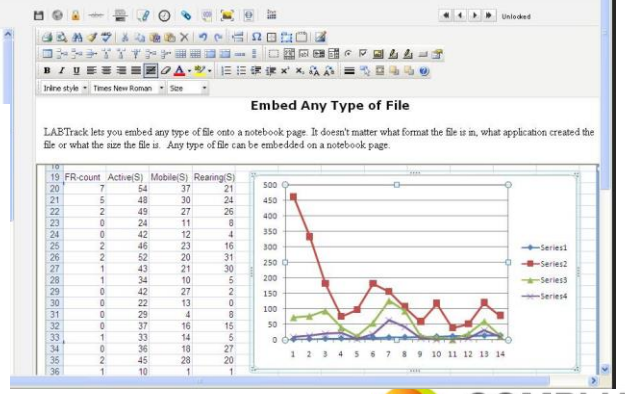
- Chart recorders
- Lab notebooks (paper & electronic)
- Product release / approval data
- Batch release documentation
- C of As
- Raw data
- Instrument printouts
- Computer-based data
- Etc., etc., etc.

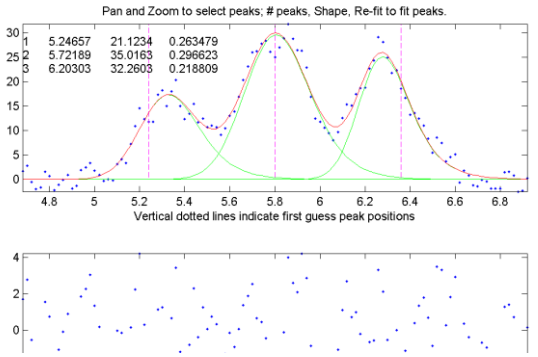












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Our Industry Problem…

Raw materials, intermediates, and finished API analytical results found to be failing specifications or otherwise suspect (e.g. OOT) are retested until acceptable results are obtained. These failing or otherwise suspect results are not reported.

Failure to document production and analytical testing activities at the time they are performed.

Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

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.

Failure to maintain complete data derived from all testing, and to ensure compliance with established specifications and standards.

During our inspection, we observed multiple examples of incomplete, inaccurate, or falsified laboratory records.

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Obstacles to Reliable Data & Information

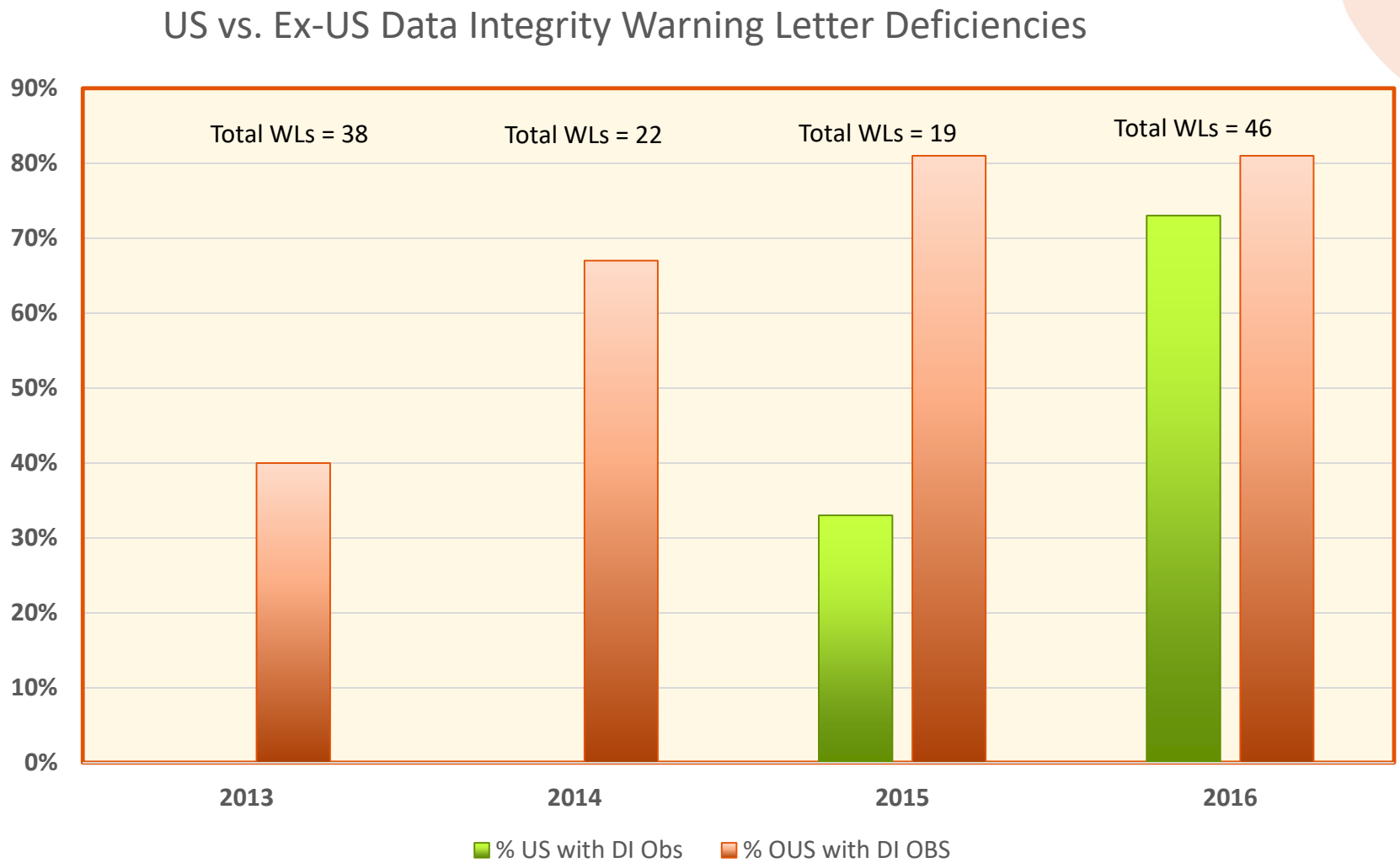
Unintentional / Negligent Conduct

- Lack of awareness
- Lack of defined expectations
- Lack of procedural / positive controls
- Lack of adequate supervision / oversight
- Failure to prioritize importance of data integrity
- Tolerance for sloppy / unprofessional work
- Lack of periodic “checks” on performance
- Lack of technology controls
- Pressure on personnel to achieve outcomes
- “Whatever it takes” culture

Purposeful / Knowing Conduct

- Substantial opportunity for monetary gain – stock options, bonuses, etc.
- Opportunity for personal / professional gain
- Risk from non-performance greater than risk of wrongful conduct
- Management direction to fudge or make up numbers driven by customer service requirements, greed or significant financial gain
- Management creates a culture that data manipulation is victimless and that conduct can’t create harm

FDA Data Integrity Enforcement Trends



Data from Pharmaceutical Online, Guest Column, January 16, 2017,
Barbara Unger, Unger Consulting
https://www.pharmaceuticalonline.com/doc/an-analysis-of-fda-fy-drug-gmp-warning-letters-0001

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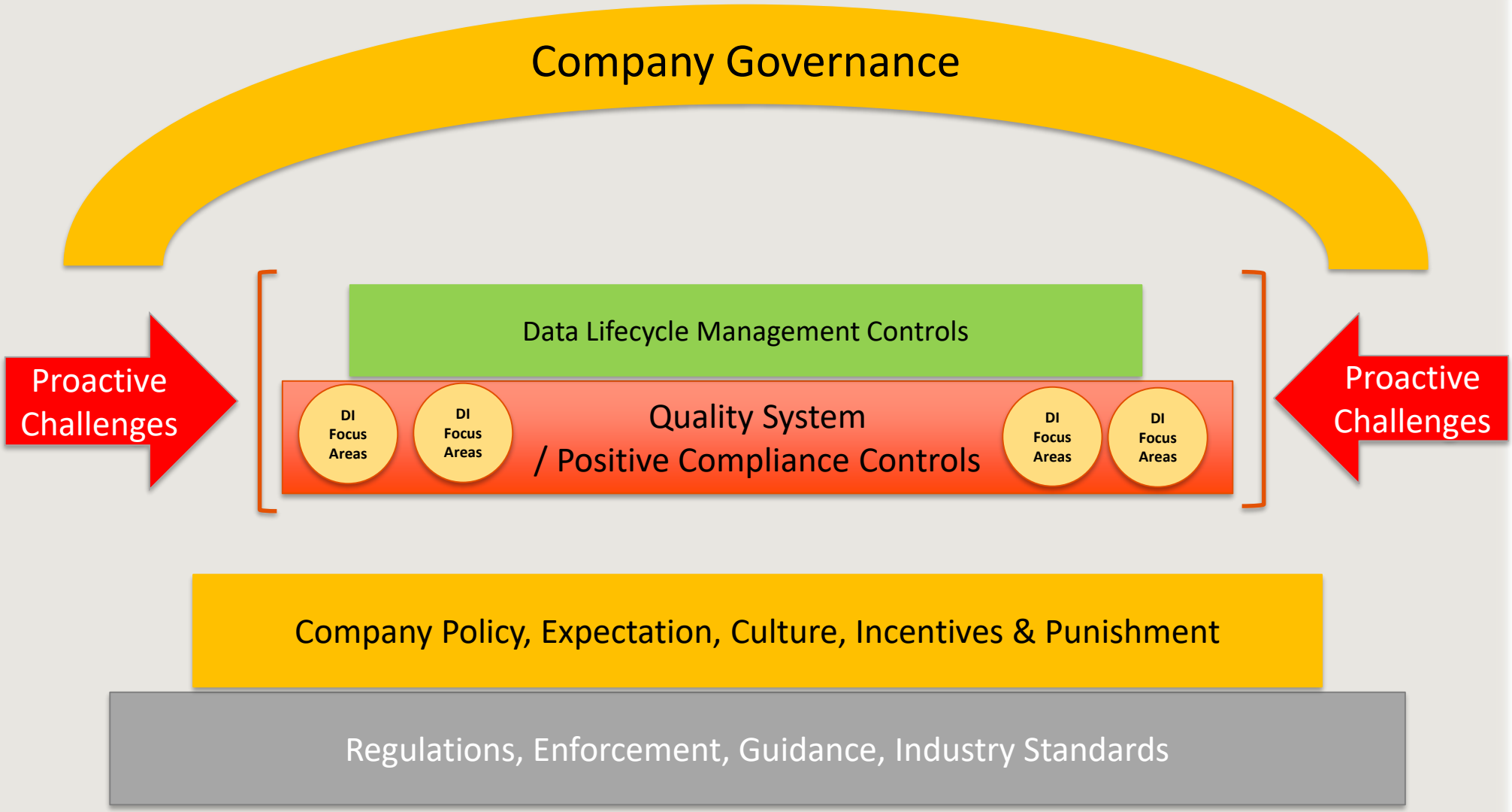
Compliance Architects®
Seven Elements Program for Data Integrity Success

A Defined Operational Model to Reduce Data Integrity Risk



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The "NEW" FDA Data Integrity Warning Letter Language (2015 – 2017)

WARNING LETTER

Introduced with…

"Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture."

All Warning Letters contained a virtually identical detailed request for a comprehensive response including

1. investigation as to the extent of bad data,
2. risk assessment on potential product quality impacts, and
3. management strategy for corrections/preventions, including CAPA.

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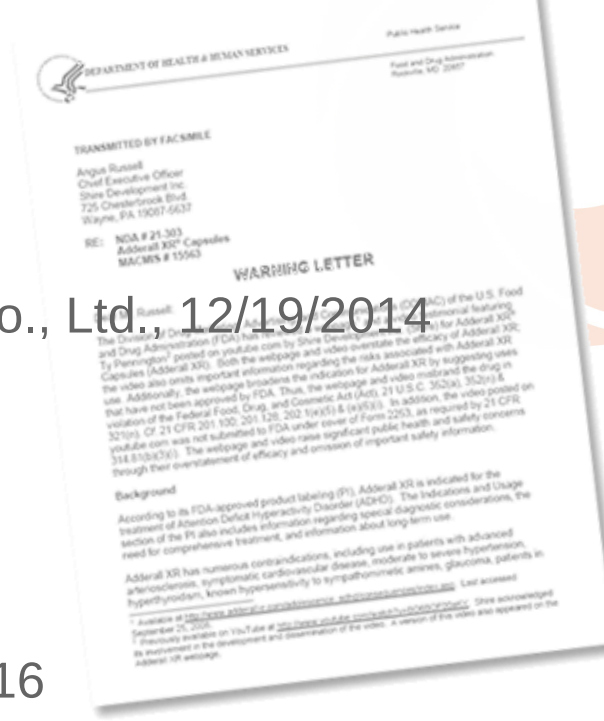
The "NEW" FDA Data Integrity Warning Letter Language (2014 – 2017)


DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

TRANSMITTED BY FACSIMILE

Angus Russell
Chief Executive Officer
Shire Development Inc
725 Chesterbrook Blvd
Wayne, PA 19087-5637

RE: NDA # 21-303
Adderall XR® Capsules
MACMIS # 15563

WARNING LETTER

Background

- First use of *basic* language: Novacyl Wuxi Pharmaceutical Co., Ltd., 12/19/2014
- Apotex, Toronto, January 2015
- Mahendra Chemicals, Inida, July 2015
- Ipca Labs, India, January 2016
- Megafine Pharma Ltd., India, May 2016
- Shanghai Desano Chemical Pharmaceutical, China, June 2016
- TEVA, Hungary Site, October 2016
- Wockhardt Limited, India Site, December 2016
- Megafine Pharma, India Site, February 2017
- Jinan Jinda Pharmaceutical Chemistry, India Site, February 2017
- USV Private Limited, India Site, March 2017
- Badrivishal Chemicals & Pharmaceuticals, India Site, March 2017
- Mylan Pharmaceuticals, Inc., India Site, April 2017
- Divi Laboratories Ltd., India Site, April 2017
- Kim Chemicals, India Site, October 2017

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Standard Data Integrity Warning Letter Response Demand

1. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

2. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

From Diva Laboratories Warning Letter, April 2017

For further information, contact:

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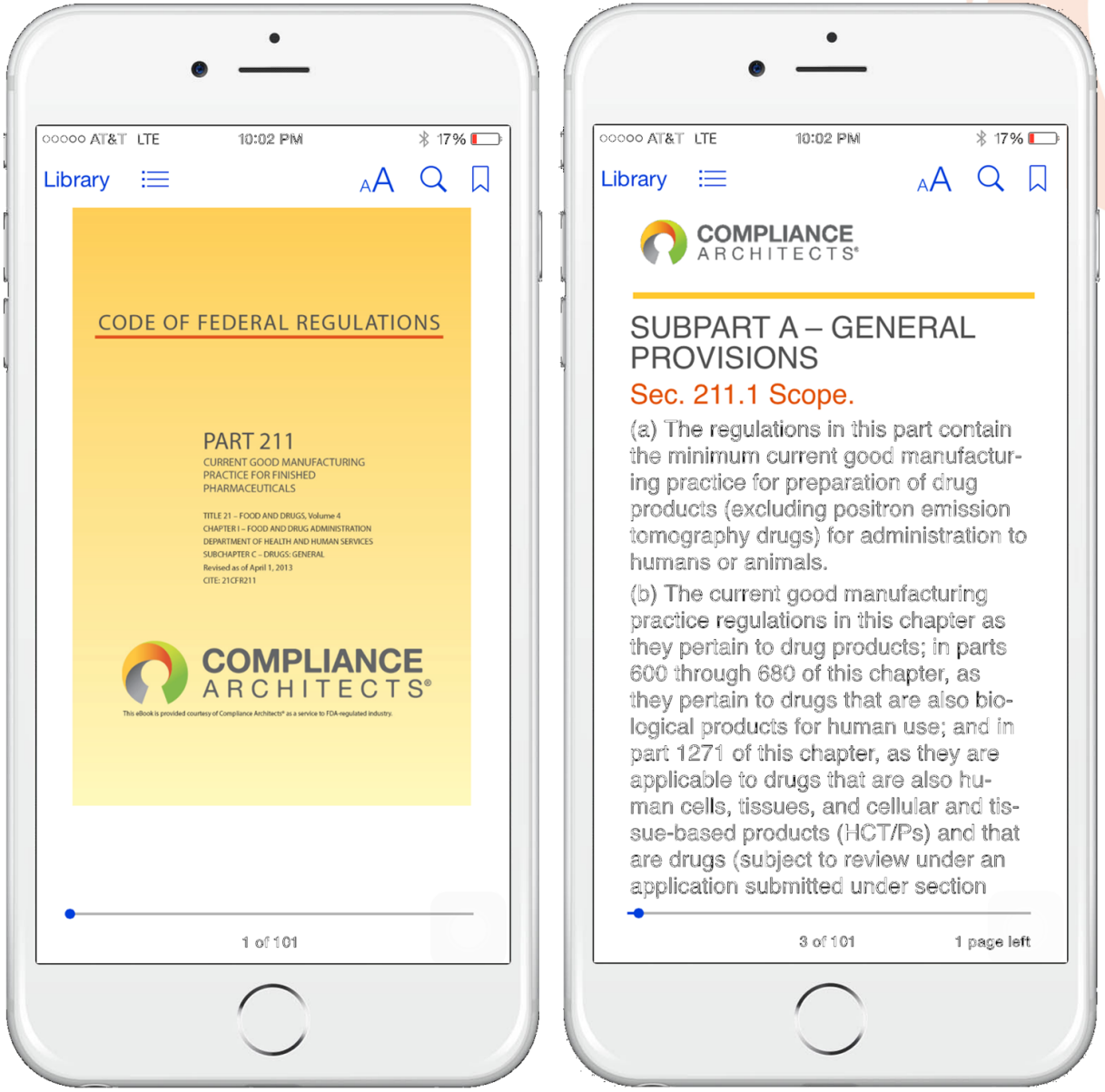

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