U.S. FOOD & DRUG ADMINISTRATION

Data Integrity

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GRx + Biosims 2018: Association for Accessible Medicines

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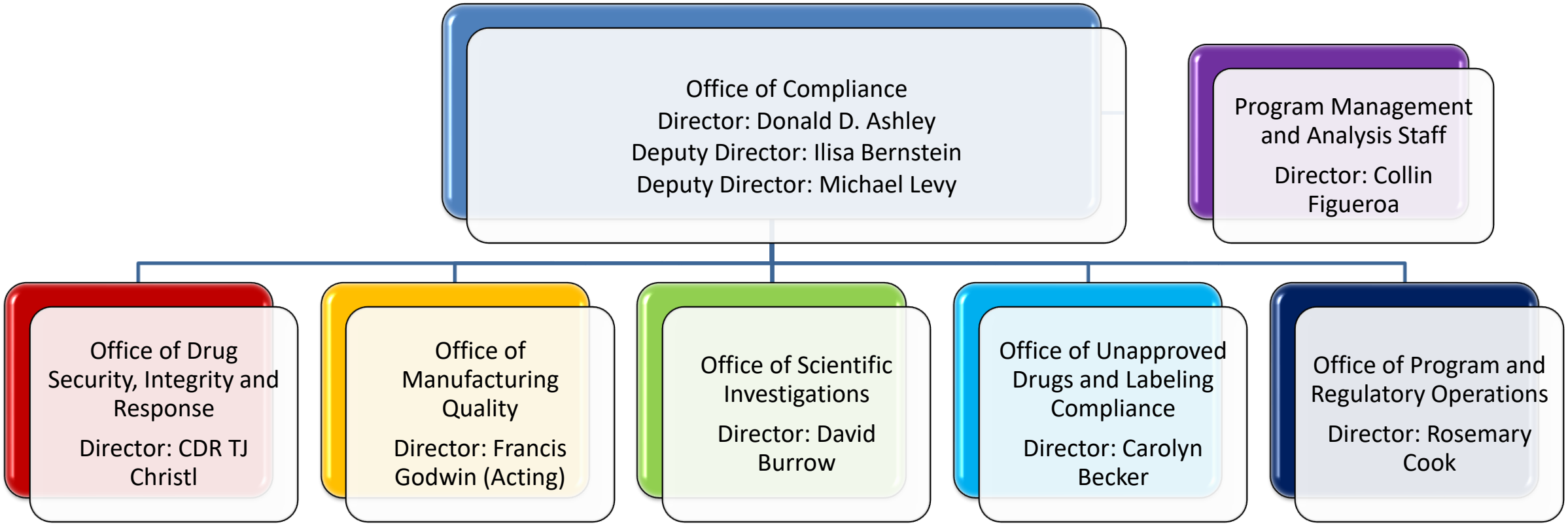
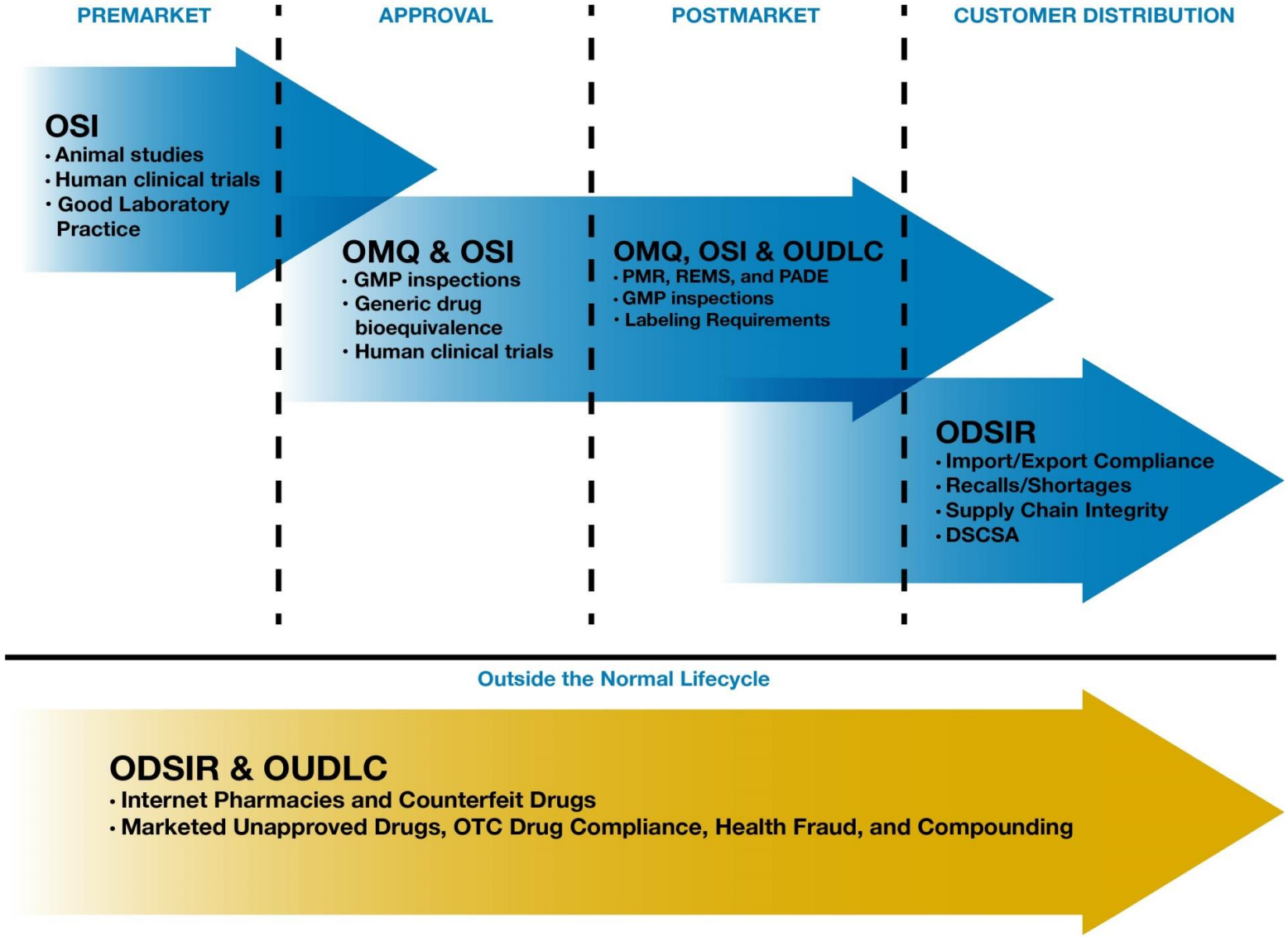
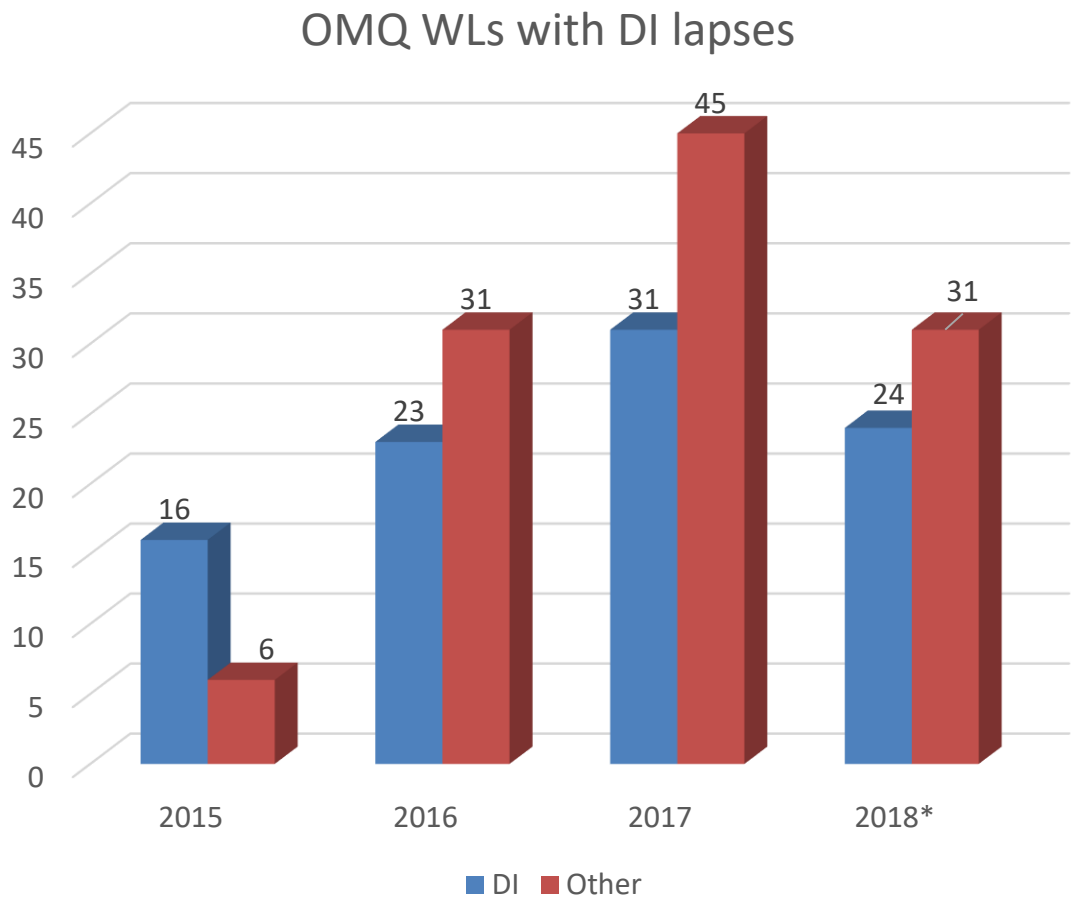
CDER Office of Compliance



Responsibility Throughout Lifecycle



DI Warning Letters by Year



- About 40% of OMQ's warning letters include data integrity lapses.
- These letters went to manufacturers around the world.

*Through July 31, 2018
Excludes compounding-related actions

Data Integrity

- Data integrity – evidence that data are complete, consistent, and accurate.
- Applies to CGMP via the FD&C Act, CFR 210, 211, 212, ICH Q7 and other guidance.
- Draft FDA guidance document, ***Data Integrity and Compliance with CGMP,*** published April 2016, to clarify the role of data integrity in CGMP for drugs.

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

Data Integrity

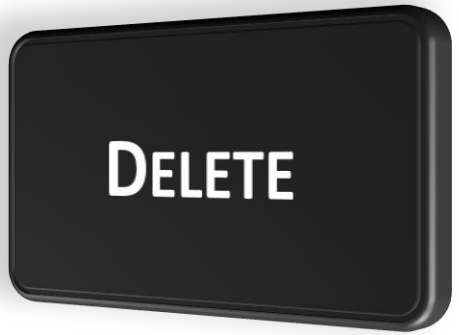
- CGMP is the minimum requirement.
- Data integrity underpins CGMP.
- Lapses obscure other problems.

DI problems you can see are the tip of the iceberg.

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

Data Integrity Case Study: Laboratory Data

- Audit trail review showed results deleted routinely
- Audit trails showed tests being repeated without justification or investigation
- Lab instruments weren’t networked or otherwise backed-up
- Employees shared usernames and passwords
- [] stated that “when chromatograms don't look right, they are deleted” followed by “retesting.”



Audit Trail

Question 1

Failing results on an assay, now what?

a) Conduct an investigation
b) Document the failure
c) Just keep testing until something passes
d) Delete any failing results

You should document the failure and conduct an Out-of-Specification investigation. The firm opted for c and d.

Question 2

Reasons to delete CGMP data:

a) Your hard drive is full
b) You only need one passing result
c) They weren't real results in the first place
d) Oops, it was an accident

The firm claimed the deletions were just solvent injections to get a stable baseline or were to decrease the number of saved chromatograms on the computer.

Warning Letter

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

“Our investigators observed systemic data manipulation across your facility. They documented unexplained deletions of laboratory test results. They discovered that you repeated tests until you obtained acceptable results and that you failed to investigate out-of-specification or otherwise undesirable test results. Your firm relied on these falsified and manipulated test results to support batch release and stability data… ”

How to Remediate
aka DI Remediation Three-Step

Recent FDA warning letters with data integrity citations ask firms to respond by taking these three steps:

- Comprehensive investigation
- Risk assessment
- Remediation and management strategy including corrective action plan

Contract Manufacturing Case Study: What You See is What You Get

- Products were not tested for microbial contamination or sterility.
- Firm “lost” qualification data.
- Firm routinely did not record (or measure?) weight of samples, test methods, calculations performed.

Question(s) 3-5

3) If you rely on certificates of analysis, what do you know?

4) If you do a paper audit, what do you know?

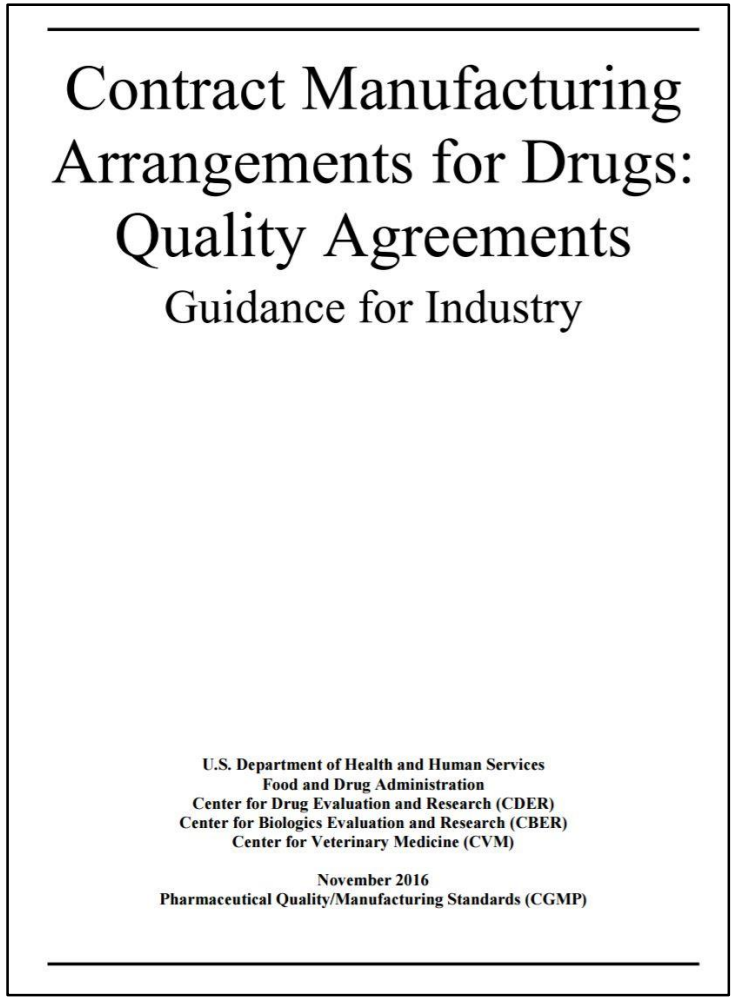
5) If you do a physical audit, what do you know?

Warning Letter

Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

- Your firm was unable to provide complete raw data related to the qualification of your [] water system. You lacked basic information (including missing sanitization data) to assess water system performance. According to your employee, half the data you generated over a year was lost.

FDA Quality Agreements Guidance



Contract Manufacturing Arrangements for Drugs: Quality Agreements

Guidance for Industry

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)

November 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Quality agreements define expectations and responsibilities in a contract manufacturing arrangement up front.

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf

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Thank you

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