



Focused Trends from the FDA

Regulatory Developments and Areas of Concern

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AGENDA

- Ongoing Issues with Data Integrity
- FDA's Program Alignment Initiative
- EU / FDA Mutual Recognition Initiative
- Responsible Corporate Officer Doctrine



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Data Integrity Issues

CDER's Current
Expectations and
Guidance

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Data Integrity

Best Practices

- Corporate Ethics and Compliance Program
- Good Documentation Practices
 - **ALCOA – applied to Electronic Records**
- Quality Risk Management
 - **Serious risks are taken seriously**
 - **Applied to Computer System Validation**
 - Higher risk systems are prioritized
 - Lower risk systems planned and scheduled
- Good Computer System Validation Practices

Source: ISPE Presentation (June 2016) by Robert Wherry



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Data Integrity

Current Expectations and Guidance from FDA

- Representatives of FDA's Office of Manufacturing Quality (Office of Compliance) and the Office of Policy for Pharmaceutical Quality (Office of Pharmaceutical Quality) delivered a presentation at the Society of Quality Assurance Annual Meeting National Harbor, MD
- Key slides from that March 30, 2017 presentation follow (reformatted, otherwise *verbatim*)
- The presentation provides a useful supplement to the April 2016 Draft Guidance.



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Current expectations and guidance, including data integrity and compliance with CGMP

Sarah Barkow, Ph.D.
Office of Manufacturing Quality
Office of Compliance

Karen Takahashi
Office of Policy for Pharmaceutical Quality
Office of Pharmaceutical Quality

**Center for Drug Evaluation and Research
March 30, 2017**

**Society of Quality Assurance Annual Meeting
National Harbor, MD**

Data Integrity Concepts

- Metadata
- Audit Trail
- Static vs. Dynamic Records
- Backup Data
- System Validation



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What is Metadata?

- Contextual information required to understand data
- Structured information that describes, explains, or otherwise makes it easier to retrieve, use or manage data
- For example: date/time stamp, user ID, instrument ID, audit trails, etc.
- Relationships between data and their metadata should be preserved in a secure and traceable manner



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What is an Audit Trail?

- Secure, computer-generated, time-stamped electronic record that allows for reconstruction of events relating to the creation, modification, or deletion of an electronic record
- Chronology: who, what, when, and sometimes why of a record
- CGMP-compliant record-keeping practices prevent data from being lost or obscured



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Audit Trails Capture:

- Overwriting
- Aborting runs
- Testing into compliance
- Deleting
- Backdating
- Altering data

(Note: not an all-inclusive list)



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Use of “Static” and “Dynamic” in relation to record Format

- Static: fixed data document such as a paper record or an electronic image
- Dynamic: record format allows interaction between the user and the record content such as a chromatogram where the integration parameters can be modified



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How Often Should Audit Trails Be Reviewed?

- For audit trails that capture changes to critical data, FDA recommends review of each record before final approval of the record.
- Audit trails subject to regular review should include changes to:
 - History of finished product test results
 - Sample run sequences
 - Sample identification
 - Critical process parameters
- FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.



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Case Study: Audit Trails Off

- Raw data was being deleted or altered on IR spectrometer
- No access controls
- No active audit trails on IR
- File names altered to make it appear tests supported additional lots of API

Warning Letter: Lack of audit trails for lab instruments and turning off audit trails. (April 2015)



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Case Study: Audit Trail Review

- Observed repeat GC injections in the audit trail in June 12, 2013.
- Audit trail showed the computer date/time settings were set back in July 2013 to June 12, 2013 (audit trails go in chronological order, but the dates didn't and showed multiple June 12ths).
- Results were reprocessed and printed to show that they had achieved passing results on June 12, 2013.
- Firm relied on this data to release the batch.
- Similar situation was observed for HPLC testing.

Warning Letter: *Because your quality unit did not review the original electronic raw data, you were unable to detect rewritten, deleted, or overwritten files.* (January 2015)



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Who Should Review Audit Trails?

- Audit trails are considered part of the associated records
- Personnel responsible for record review under CGMP should review the audit trails that capture changes to critical data...as they review the rest of the record



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When is it permissible to exclude CGMP data from decision making?

- Data created as part of a CGMP record must be evaluated by the Quality Unit as part of release criteria and maintained for CGMP purposes.
- Electronic CGMP data should include relevant metadata.
- To exclude data from the release criteria decision-making process there must be a *valid, documented scientific justification* for its exclusion



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Program Alignment Process

Reorganization of the
Office of Regulatory
Affairs

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Reorganization of Office of Regulatory Affairs (ORA)

- Program Alignment is one of the major FDA Initiatives listed on FDA's website. ORA is the organization within FDA consisting of field operational personnel (Investigations, Compliance and Laboratory Branches)
- Regional and District (i.e. geographic) configuration will be eliminated (although Boundary Maps have been created). Product categories will now be basis for ORA's organization.
 - Biological Products
 - Bioresearch Monitoring
 - Pharmaceutical Quality (Office of Pharmaceutical Quality Operations)
 - Medical Devices and Radiological health
 - Human and Animal Food
 - Tobacco



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Reorganization of Office of Regulatory Affairs (ORA)

- Commodity based vertically integrated regulatory programs will be developed. Multi-year Action Plans have been developed for each program area.
- The Pharmaceutical Quality Action Plan entails several key objectives:
 - Transition to the new commodity-based and vertically integrated structure
 - Training, recruitment, employee skill development and career enhancement
 - Planning and allocation of resources
 - Compliance Policy and Enforcement Strategy
 - Imports
 - Labs
 - IT



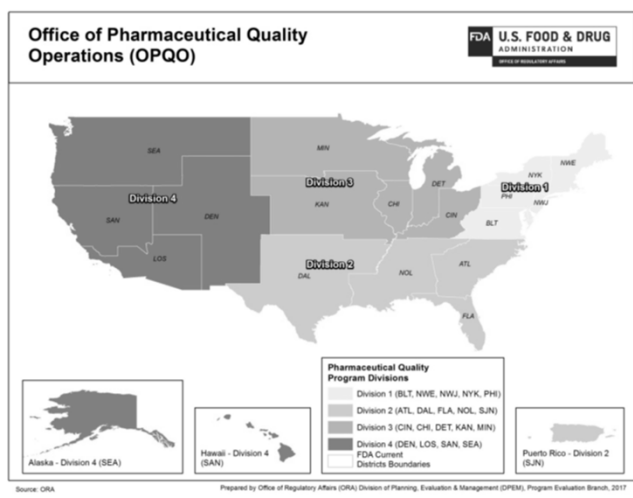
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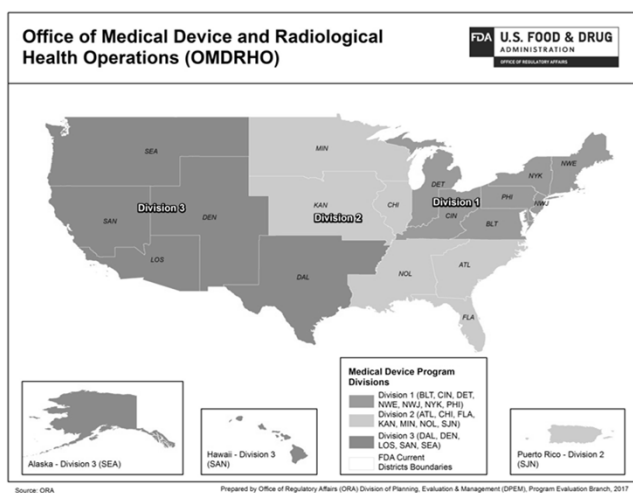
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Reorganization of Office of Regulatory Affairs (ORA) Boundary Map for OPQO



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Reorganization of Office of Regulatory Affairs (ORA) Boundary Map for OMDRHO



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Reorganization of Office of Regulatory Affairs (ORA) Fact Sheets

- Fact Sheets have been developed for each of the seven program areas. The OPQO example follows:

The Office of Pharmaceutical Quality Operations (OPQO), a program within the Office of Medical Products and Tobacco Operations in the Office of Regulatory Affairs (ORA), provides advice and counsel to ORA and FDA leaders regarding pharmaceutical products field operations and emergency response activities. OPQO collaborates with the agency's Center for Drug Evaluation and Research (CDER) and the Center for Veterinary Medicine (CVM) on all FDA-regulated pharmaceutical and biopharmaceutical products.



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Reorganization of Office of Regulatory Affairs (ORA) Fact Sheets

Alonza Cruse directs OPQO's day-to-day operations and coordination with CDER and CVM. The office structure includes a Division of Pharmaceutical Quality Programs, Division of Foreign Pharmaceutical Quality Inspections, and four Divisions of Pharmaceutical Quality Operations whose staff conduct investigations and manage compliance activities, recalls, and partnerships in ORA's 20 district offices.

ORA's program division directors, formerly district directors, are the most senior FDA officials in their geographic area and continue to be the point of contact for local staff, the public, and industry. FDA's local coordination with federal, state, local, tribal, and territorial regulatory and public health agency officials continues to be managed by district state liaisons.

Contact OPQO at [**engageORA@fda.hhs.gov**](mailto:engageORA@fda.hhs.gov)



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Reorganization of Office of Regulatory Affairs (ORA)

Recent Warning Letter Example

- The current versions of the Investigations Operations Manual (IOM) and the Regulatory Procedures Manual (RPM) do not specifically address how Program Alignment will affect the operations of ORA.
- Compliance Programs (e.g. CP7356.002 *Drug Product Inspections*) may also require revisions.
- Warning Letter recently issued to National Biological (manufacturer of medical device: UV phototherapy systems) has been posted to FDA Internet site.



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Reorganization of Office of Regulatory Affairs (ORA)

Recent Warning Letter Example

- Unique features of the Letter:
 - Manufacturer is located in Ohio. Inspection most likely performed by FDA personnel based in Ohio, although name(s) not mentioned.
 - Warning Letter was issued by MDRHO Division 1 (in Stoneham, MA, i.e. NWE-DO, New England District Office).
 - Compliance Officer (Gina Brackett) identified in Warning Letter is located in Ohio.
 - Acting Compliance Branch Director (Karen Archdeacon) and Program Division Director (Joseph Matrisciano, Jr.) are both located in Stoneham, MA.
 - Letter has been signed by Matrisciano.
 - Recipient is directed to send electronic reply to Archdeacon, but is also directed to reply within 15 business days in writing.



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FDA / EU Mutual Recognition Agreement

Response to the Global
Pharmaceutical Market

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FDA / EU Mutual Recognition Agreement

Main Points

- Mutual Recognition Agreement with EU pertains to pharmaceutical inspections.
 - Authorized under FDASIA (Food and Drug Safety and Innovation Act)
 - Medical Device Single Audit Program (MDSAP) is a separate project
- Goal of MRA is to be able to rely on each other's drug manufacturing inspections.
 - Vaccines and veterinary drugs are not covered
- EU and FDA still have to complete capability assessments of one another's regulatory authorities. FDA expects to recognize some EU authorities as "capable" by November 2017.



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FDA / EU Mutual Recognition Agreement

Main Points

- A “capable” inspectorate is one that:
 - Has the legal and regulatory authority to conduct inspections against a standard for GMP;
 - Manages conflicts of interest in an ethical manner;
 - Evaluates risks and mitigates them;
 - Maintains appropriate oversight of manufacturing facilities within its territory;
 - Receives adequate resources and uses them;
 - Employs trained and qualified inspectors with the skills and knowledge to identify manufacturing practices that may lead to patient harm; and
 - Possesses the tools necessary to take action to protect the public from harm due to poor quality drugs or medicinal products.

Source: Frequently Asked Questions / The Mutual Recognition Agreement March 2, 2017
(Email Inquiries: FDA-MRA@fda.hhs.gov)



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Responsible Corporate Officer Doctrine

The Crime of Doing
Nothing (Strict Liability)

POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

Background

- The Food Drug and Cosmetic Act is a “strict liability” statute.
- This means that individuals, usually high level executives, can be held responsible for violations that occur at facilities under their control
- This is true even if the executives did not know of the violations and did not intend for them to happen
- FDA has relied on two Supreme Court cases to uphold this concept
- Result: Individual executives are liable for the acts of subordinates and can be named as criminal or civil defendants in addition to the company



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POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

Dotterweich Supreme Court Decision (1943)

- U.S. v. Buffalo Pharmacal, Inc. and Joseph H. Dotterweich, President and General Manager
- US Supreme Court ruling in 1943 – before the GMP requirement was in the law
- Interstate shipment of misbranded drug products
- Mr. Dotterweich tried to avoid personal responsibility on several grounds
 - He was unaware of the problems
 - The corporation was the responsible party
- He lost at the Supreme Court, 5-4 (split decision)



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POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

Dotterweich Supreme Court Decision (1943)

U.S. Supreme Court [320 U.S. 277, 284 (1943)]

“The prosecution to which Dotterweich was subjected is based on a now familiar type of legislation whereby penalties serve as effective means of regulation. Such legislation dispenses with the conventional requirement for criminal conduct: Awareness of some wrongdoing. In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger.”

“The Act makes any person who violates (it) guilty of a misdemeanor. It specifically defines ‘person’ to include ‘corporation’. But the only way a corporation can act is through the individuals who act on its behalf.”



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POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

Dotterweich Supreme Court Decision (1943)

- Addressing the question of whether strict liability is a fair standard:

“Hardship there doubtless may be under a statute which thus penalizes the transaction though consciousness of wrong-doing be totally wanting. Balancing relative hardships, Congress has preferred to place it upon those who have at least the opportunity of informing themselves of the existence of conditions imposed for the protection of consumers before sharing in illicit commerce, rather than to throw the hazard on the innocent public who are wholly helpless.”



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POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

Park Supreme Court Decision (1975)

- 1975 Supreme Court Case, U.S. v. Acme Markets, Inc., and John R. Park, President
- Filthy food warehouse in Baltimore, MD
- Track record of continuing violations despite repeated warnings
- Park's primary excuses:
 - It wasn't me; I delegated responsibility
 - My subordinates were "dependable"; I had "great confidence in them"
 - The jury was not properly instructed in how to apply strict liability
- He lost at the Supreme Court, 6-3



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POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

Park Supreme Court Decision (1975)

U.S. v. Park, 1975

"The Act imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will ensure that violations will not occur."

"The requirements of foresight and vigilance imposed on responsible corporate agents are beyond question demanding and even onerous, but they are no more stringent than the public has the right to expect...We are satisfied that the Act imposes the highest standard of care and permits conviction of responsible corporate officials, who in light of this standard of care, have the power to prevent or correct violations"



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POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

DeCoster (2017) Supreme Court Lets Misdemeanor Conviction Stand

- Petition for Writ of Certiorari denied by Supreme Court
 - Interstate shipment of adulterated food (*Salmonella* contaminated eggs)
- Eighth Circuit Appellate Court split decision (July 2016) stands. Three month prison sentences and \$100,000 fines.
 - The three judges of the Circuit Court wrote separate decisions

Despite separate decisions, the three judges appeared unanimous in finding that a penalty of imprisonment for a misdemeanor violation of the FDC Act *would* violate principles of due process if the offense is merely one of “vicarious liability,” defined as liability “for the actionable conduct of a subordinate . . . based on the relationship between the two parties.”

However one judge concluded that a demonstration of “mens rea” (i.e. guilty mind or intent) would be required for imprisonment.



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POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

Points to Consider

- Under the Park Doctrine, strictly liability for unintentional violations of the FDCA extends to corporate officers whose companies engage in unlawful activities.
- Misdemeanor convictions (1 year / \$100,000) can result – **even if the corporate official was unaware of the violation** – so long as the official was in a position of authority to prevent or correct the violation and did not do so.

Pleading guilty under the Park (RCO) doctrine (supervisory liability) without admitting knowledge or negligence does not eliminate the potential for a sentence to be imposed based on the inspectional evidence. Debarment can also be imposed.

Continued aggressive prosecution and sentencing of strict liability cases cannot be ruled out.



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POTENTIAL CRIMINAL LIABILITY OF EXECUTIVES

Points to Consider

- Recommending Park Doctrine prosecutions (see FDA's Regulatory Procedures Manual). Factors to consider include:
 - Whether the violation involves actual or potential harm to the public;
 - Whether the violation is obvious;
 - Whether the violation reflects a pattern of illegal behavior and/or failure to heed prior warnings;
 - Whether the violation is widespread;
 - Whether the violation is serious;
 - The quality of the legal and factual support for the proposed prosecution;
 - Whether the proposed prosecution is a prudent use of agency resources.



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Questions?

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For further information, please contact

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