AN ENFORCEMENT UPDATE: REMARKS ON DATA INTEGRITY

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U.S. Food and Drug Administration
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Geographically Aligned Organizational Model

ACRA
Associate Commissioner for Regulatory Affairs

ORA Regions
- Northeast Region (NER)
- Southeast Region (SER)
- Central Region (CER)
- Southwest Region (SWR)
- Pacific Region (PAR)

DACRA Deuty Associate Commissioner for Regulatory Affairs

Office of Communications and Quality Program Management (OCQPM)
- Quality Management Systems Staff (QMS)
- Project Coordination Staff (PCS)
- Division of Communication (DC)
- Food and Feed Policy Staff (FFPS)
- Medical Products and Tobacco Policy Staff (MPTPS)

Office of Policy and Risk Management (OPRM)
- Division of Planning, Evaluation and Management (DPEM)
- Risk Management Staff (RMS)
- Standards Implementation Staff (SIS)
- Contracts and Grants Staff (CGS)

Office of Partnerships (OP)

IT Staff Executive Secretariat Staff
Program Aligned Organizational Model

OFFICE OF THE ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS

OFFICE OF MANAGEMENT
OFFICE OF COMMUNICATIONS AND PROJECT MANAGEMENT
OFFICE OF CRIMINAL INVESTIGATIONS
OFFICE OF HUMAN AND ANIMAL FOOD OPERATIONS

OFFICE OF MEDICAL PRODUCTS AND TOBACCO OPERATIONS
OFFICE OF REGULATORY SCIENCE
OFFICE OF PARTNERSHIPS AND OPERATIONAL POLICY
OFFICE OF ENFORCEMENT AND IMPORT OPERATIONS

OFFICE OF TRAINING, EDUCATION AND DEVELOPMENT
Office of Enforcement and Import Operations

Doug Stearn, JD
Director, Office of Enforcement and Import Operations

Office of Enforcement and Import Operations

- Division of Enforcement
- Division of Food Defense Targeting
- Division of Import Operations Management
- Division of Import Program Development
  - Division of Southwest Imports
  - Division of Southeast Imports
  - Division of Northeast Imports
  - Division of Northern Border Imports
  - Division of West Coast Imports
Office of Enforcement and Import Operations

Import Program Divisions
- Division of Northeast Import (CT, DC, DE, MA, MD, ME, NY, NH, PA, RI, VA, VT, WV)
- Division of Northern Border Import (ID, IL, IN, ME, MI, MN, MT, NH, ND, NY, OH, SD, VT, WA, WI)
- Division of Southeast Import (AK, AL, AR, FL, GA, IN, KY, LA, MS, NC, PR, SC, TN)
- Division of Southwest Import (AZ, CO, IA, KS, MO, NE, NM, OK, TX, UT, WY)
- Division of West Coast Import (CA, HI, NV, OR, WA)

State Boundaries

Hawaii - West Coast Import Division

Alaska - Southeast Import Division

Puerto Rico - Southeast Import Division
Data Integrity

• Why does it matter?
  – Product data reliability
  – Facility data reliability

• Regulation foundations
Some History

• The Generic Drug Scandal
  – Numerous prosecutions
  – Legislation and policy approaches
    • Prosecutorial approaches
    • Looking at data integrity with CGMP
    • Application integrity policy
    • Debarment

• Data Integrity Issues Today and Tomorrow
New Variations, Old Problem

• Many examples

• What is new
  – Computerized data issues
  – More facilities across more jurisdictions involved in production

• What is not
Prosecution

• Criminal objectives: deterrence and retribution

• Common statutory approaches
  – General criminal statutes
    • False statements within FDA jurisdiction
    • Obstruction of agency proceeding
    • Mail and wire fraud
  – FDCA felonies: “intent to defraud or mislead” extends to FDA
Difficulties of Overseas Prosecutions

• Subpoena power in investigations
• Cooperation of foreign authorities
• Compulsory power at trial
• Evidentiary Issues
• Jurisdictional Issues
  – Extradition
  – The offense (FDASIA 718 (extraterritoriality))
Collateral Consequences

• Debarment
  – Stems from conviction
    • Clear focus on development work in ANDAs
    • Applies more broadly as well
  – Prevents services to applicants

• Medicare exclusion and corporate integrity agreements
CGMP Issues

• FDA view implicates data collection and recordkeeping
• Process leads to inaccurate or unreliable data
• Renders product adulterated
• Consequences
  – Warning letters and enforcement actions
  – Generally deemed material
  – Harder to investigate and to remedy
• § 211.68 (requiring “backup data are exact and complete,” and “secure from alteration, inadvertent erasures, or loss”)
• § 212.110(b) (requiring that data be “stored to prevent deterioration or loss”)
• §§ 211.100 and 211.160 (requiring that certain activities be “documented at the time of performance” and that laboratory controls be “scientifically sound”)
• § 211.180 (requiring records be retained as “original records,” “true copies,” or other “accurate reproductions”)
• §§ 211.188, 211.194, and 212.60(g) (requiring “complete information,” “complete data [] from all tests,” “complete record of all data,” and “complete records of all tests”).
Data Integrity Provisions in Decrees

• Analogous to other CGMP remedial requirements and application integrity
  – Investigation with third party
  – Remedial actions
  – FDA review and verification

• Unlike other provisions in investigating past application data
Accepting or Rejecting Data

• Implicit requirement of reliability
  – Not necessarily found fraudulent
  – Not necessarily found inaccurate

• FDA can reject data

• Application integrity policy – a subset
  – Applies to review (rather than rejection)
  – Applies to a pattern by applicant
Reasons Not To Be Sanguine

• Data integrity problems are
  – Not necessarily criminal
  – Not necessarily involving many people
  – Not necessarily easy to detect and often associated with rationalization, justification or denial
  – Not necessarily easy to fix

• Such problems can be extremely damaging
Good Industry Practices

• Reinforce rigor of procedures and unacceptability of short cuts

• Accountability in systems and procedures
  – Management knows who did what when
  – Accountability in electronic data is key

• Reference: Draft Guidance: Data Integrity and Compliance With CGMP
FDA Approaches

• To understand and probe integrity in digital records, not just those in “paper”
• To understand and link deviation patterns in practice to outcomes
• To stress proactive approach to industry to adopt good practices
“Unofficial” Systems

• Removal of defective units from the production line without documentation.

• Use of outside batches to blend and “create” batches meeting specification.

• Evidence of deletions or overrides in computer system.

• Raw data and results created outside of quality reporting systems (e.g., testing data solely on a flashdrive).
Questionable Documentation

• False documents
  – cover failure of documents to perform
  – job orders, preventative maintenance and equipment cleaning records

• Lab documents fail to note known facts (e.g., mold growth)

• Pre-recorded final batch quantities even before the batch had been weighed
Missing Data on Deviations

• Original results prior to retesting
  – Applied to analytical testing and specifications
  – Failures unreported and investigated

• Raw data thrown out or missing

• Evidence of deletions in computer system

• No evidence of failure ever

• Lack of documents to support activities actually took place
Lack of Safeguards

• No safeguards or audit trails to protect data
• Systems encourage testing into compliance
• Test records may not be reviewed and evaluated in making batch release decisions.