

## Data Integrity: Background and Practice

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## Overview

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### ■ Background

- Broader FDA context: why it matters
- Generic drug program and drug pricing
- FDARA and Concept of Operations
- India

### ■ Data Integrity Framework

- What is it and why it matters
- Regulations and FDA Guidance

### ■ Enforcement

- FDA approach
- Examples

## Commissioner Gottlieb and FDA's Drug Competition Action Plan

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- Generic drugs, pricing, and the 2018 and 2020 elections
- FDA is working to prohibit restrictions by brand companies on the drug samples that a generic company needs for drug development.
- FDA will limit perceived efforts of brand companies to block a generic approval by leveraging the requirement that brands and generics share a single shared REMS.
- FDA is considering modifying its Unapproved Drug Initiative, which calls for unapproved drugs to be removed from the market when a New Drug Application is approved.
- FDA is working with the Federal Trade Commission to determine whether there should be limits on “pay for delay” agreements and is referring anticompetitive behavior to the FTC.

## Commissioner Gottlieb and Generic Drugs

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- February 2018: 57 new product-specific guidances
- Gottlieb February 7, 2018 tweet: “Jan. ’18 had fewer generic approvals as companies work to implement new guidelines to protect patients from impurities like arsenic & lead in drugs. This is a temporary falloff in approvals. We should make up for the 1 month shortfall as the year advances.”
- We also broke records, with the highest number of generic drugs approved in a single month multiple times in 2017, and we recorded the highest annual total of generic drug approvals (1,027) in the agency’s history. We believe that, if current trends continue, we’ll exceed this record number of generic drug approvals in 2018.

## FDARA Context

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- Application of relevant GDUFA and PDUFA provisions to all drugs
- 10 month and 8 month timeframes
- Guidance on risk-based site selection model (GDUFA)
- Inform firm of NAI and VAI inspection results within 90 days of inspection (GDUFA)
- FDA annual public metrics (GDUFA)
  - Approval times
  - Median time from beginning of inspection to 483 issuance
  - Median time from 483 issuance to warning letter, import alert, and regulatory meeting
  - Median time from date of warning letter, import alert, and regulatory meeting to resolution of OAI status

## Organizational Changes

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- ORA Program Alignment: training and priorities
- CDER reorganization
- CDER “Concept of Operations”
  - Change in how to interact with FDA
  - Earlier exposure to subject matter experts
  - Change in decisionmaking authority
  - Time limits
    - 45 days for ORA to complete Establishment Inspection Report
    - 90 days for ORA to classify NAI and VAI inspections
    - 6 months for warning letters

## Organizational Changes and New Roles

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- Changes in training
  - Role of individual investigators
- Different authority distribution in CDER
  - Role of OPQ and Compliance and different authority figures
- Note the difference in slide presentations

## General Enforcement Priorities

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- Scott Gottlieb in 2011: “Instead of calling for targeted fixes of troubled plants, the agency has often required manufacturers to undertake costly, general upgrades to facilities. As a result, in 2010, product quality issues – and the subsequent regulatory actions taken by FDA to address these problems - were involved in 42% of the drug shortages.”
- CDER approach
  - More standards
  - More uniformity
  - Less of an “artisanal approach”
  - Patient first focus

## Enforcement Context: China and India

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- US-EU Mutual Recognition Agreement and China and India
- Official Action Indicated Rates (2016)
  - US: 5 percent
  - EU: 5 percent
  - India: 14 percent
  - China: 21 percent

## Enforcement Context: US Political Priorities

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- Congressional pressure and recent US Government Accountability Office report calling for increased oversight over foreign drug manufacturing
- Trump budget
- Trump Administration's trade policy
- 2016 Chinese FDA initiative
- Continued heparin oversight
- Data integrity and adverse events

## Data Integrity: Its Importance

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- Clinical trials and new drugs
- Manufacturing and labs
- Product safety, identity, strength, purity, quality
- FDA's treatment of its own data
  - Oversight
- U.S. Justice Department and data
  - Across industries
  - "Fraud"

## FDA on Data Integrity's Importance

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- Breaches conceal patient risk
- Data integrity breach breaks confidence between regulator and regulated
- FDA “relies on firms to do the right thing when [it is] not there”
- Enhances and sustains brand
- Provides basis for management oversight of systems and processes
- Without reliable and accurate data, building efficient and robust systems is difficult or impossible
- Reduced risk of enforcement action
- Competitive advantage for firms

## Data Integrity: Definition

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- Requirement that data are complete, consistent, and accurate
- “ALCOA”
  - Attributable – e-signature
  - Legible – no overwriting
  - Contemporaneous – time stamp
  - Original/true copy – audit trail
  - Accurate - validation

## Regulations from Paper Era

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- 211.100, 211.160: certain activities must be documented at the time of performance and laboratory controls must be sound
- 211.68: backup data must be secure and complete and secure from alteration, erasures, and loss
- 211.80: requires true copies or other accurate reproductions of the original records
- 211.188, 211.194, 212.60(g): require complete information, complete data derived from tests, complete records of all tests performed.
- 212.110(b): data must be stored to prevent deterioration or loss

## 2016 Data Integrity Draft Guidance

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- Effort to systematize FDA approaches to DI
- Note January 2018 US Department of Justice limitations on the use of guidances:
  - <https://www.akingump.com/en/news-insights/doj-limits-use-of-guidance-documents-in-affirmative-civil.html>

## Metadata

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- Contextual information required to understand data
- Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the GMP activity
- Examples of metadata
  - date/time stamps
  - user ID
  - instrument ID used to acquire data, audit trails

## Audit Trail

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- Secure, computer-generated, time-stamped electronic record that allows for reconstruction of events relating to the creation, modification, or deletion of an electronic record
- Who, what, when, and sometimes why of a record
- Example: audit trail for an HPLC run could include user name, date/time of run, integration parameters used, details of a reprocessing
- GMP compliant record-keeping practices prevent data from being lost or destroyed
- Audit trails capture: overwriting, aborting runs, “testing into compliance,” deleting, backdating, altering data

## “Backup” Data

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- True copy of original data that is maintained securely throughout the records retention period.
- Should include associated metadata
- Different from files temporarily maintained in case of computer crashes. These file do not satisfy the requirements of 211.68(b) to maintain a backup.

## Exclusion of GMP Data from Decisionmaking

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- Any data (including metadata) must be evaluated by the quality unit as part of release criteria and maintained.
- Any exclusion of data from the release criteria decisionmaking process must be scientifically justified (See FDA's OOS Guidance)
- Bottom line: be very careful.

## Restricting Computer System Access

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- Must ensure that any changes to records be made only by authorized personnel
- FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means (e.g. limiting permissions)
- System administrator should be different from those with substantive responsibility
- Shared login accounts are problematic.

## FDA-Provided Example of Administrator Privilege Problem

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- Warning letter: Systemic data manipulation across the facility, including actions taken by multiple analysts and on multiple pieces of testing equipment.
- “Specifically, your Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events.”

## Review of Audit Trails

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- FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record.
- Audit trails subject to regular review should include changes to:
  - history of unfinished product test results
  - sample run sequences
  - sample identification
  - critical process parameters
- FDA recommends routine scheduled audit trial review based on complexity of the system and its intended use
- Personnel responsible for record review should review audit trails that capture changes to critical data as they review the rest of the record

## FDA-Provided Example of Audit Trail Problem

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- Raw data were being deleted or altered on IR spectrometer
- No access controls
- No active audit trails on IR
- File names altered to make it appear tests supports additional lots of API
- Warning letter stresses lack of audit trails for lab instruments and turning off audit trails

## Control of Blank Forms

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- Blank forms (e.g. worksheets, laboratory notebooks) should be controlled by the quality unit or by another document control method
- Numbered sets of blank forms may be issued and should be reconciled upon completion of the activity,
- Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement.

## FDA-Provided Example of Misuse of Blank Forms

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- “Our investigator observed many copies of uncontrolled blank and partially-completed CGMP forms ... without any accountability or oversight of your quality unit.”
- “[A] supervisor said he photocopied a blank OOS form and transcribed the information because he had made mistakes in the original document.” FDA rejects firm’s argument that OOS form was not an “official document” until it was placed in the QA system. Firm did not follow firm’s SOPs.
- ”Your quality unit is responsible for reviewing and approving these critical production records to ensure that, if an error occurred, a comprehensive investigation is conducted. Uncontrolled destruction of CGMP records also raises concerns, because retention of CGMP records must follow established procedures approved by your quality unit.”

## Electronic copies and paper records

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- Electronic copies can be used as true copies of paper or electronic records, provided that copies preserve the content and meaning of the original data, which includes associated metadata and the static or dynamic nature of the original records
- Paper printouts/static records may be retained instead of original electronic records if they are a complete copy of the original record.
  - For example, pH meters and balances may create a paper printout or static image during data acquisition as the original record.
  - Electronic records from certain types of instruments are dynamic records and a printout is insufficient.

## Electronic signatures

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- Electronic signatures can be used instead of handwritten signatures for master production/control records.
- Part of the intent of the full signature requirement is to be able to clearly identify the individual signing the record.
- Firms using electronic signatures should document the controls used to ensure that they are able to identify the specific person who signed the records electronically.
- FDA's own experience with electronic signatures

## Definition of GMP record

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- All data generated to satisfy a GMP requirement becomes a GMP record.
- Firms must document or save the data at time of performance
- Processes must ensure that maintained data cannot be modified.
- Not acceptable to store data in temporary memory or on pieces of paper that will be discarded after the data are transcribed to a lab notebook
- Computer systems, such as LIMS or Electronic Batch Record systems, can be designed automatically save after each separate entry

## FDA-Provided Example of Deficient Recordkeeping

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- Firm used “mock” sheets to capture important manufacturing data
- Batch production records were completed and backdated days after operations ended.
- FDA detected discrepancies between the “mock” sheets and the complete batch records
- No evidence that batch records were accurate
- “Batch production records must be generated contemporaneously and include complete and accurate information on the production and control of each batch. The practice of using unbound, uncontrolled loose paper, in conjunction with backdating records, raises additional concerns about the integrity, authenticity, and reliability of all your data, and the quality of your API.”

## Use of Actual Samples During “System Suitability” Runs

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- FDA prohibits “testing into compliance” -- sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result
- If an actual sample is used for system suitability
  - It should be a properly characterized secondary standard
  - Written procedures should be established and followed
  - Samples should be from a different batch than the samples being tested
- All data should be included in records retained and subject to review unless there is documented scientific justification for its exclusion.
- An FDA warning letter favorite

## Discarding Final Results

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- It is not acceptable to only save the final results from reprocessed lab chromatography
- If chromatography is reprocessed, written procedures must be established and followed and each result retained for review

## Handling Internal Tips

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- Firms must investigate internal tips.
- “Suspected or known falsification or alteration of records required under parts 210, 211, and 212 must be fully investigated under the CGMP quality system to determine the effect of the event on patient safety, product quality, and data reliability; to determine the root cause; and to ensure the necessary corrective actions are taken (see 211.22(a), 211.125(c), 211.192, 211.198, 211.204, and 212.100)”
- “FDA invites individuals to report suspected data integrity issues that may affect the safety, identity, strength, quality, or purity of drug products at [DrugInfo@fda.hhs.gov](mailto:DrugInfo@fda.hhs.gov)”
- Application Integrity Policy

## Whistleblowers

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- FDA will examine whether firms support whistleblowers and have systems in place to handle complaints
- Whistleblowers occasionally reach out to FDA and the media.

## Training

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- “Training personnel to detect data integrity issues is consistent with the personnel requirements under 211.25 and 212.10, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.”
- Ensure that training is up to date, as FDA issues new guidances and warning letters.
- If problems are detected in one facility, consider whether CAPA requires training across the enterprise.

## FDA Access to Electronic Records

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- FDA: “All records required under CGMP are subject to FDA inspection. You must allow authorized inspection, review, and copying of records, which includes copying of electronic data.”
- GMP records vs other records
- FDA will consider an Import Alert if it deems that a denial of access interferes with an inspection.
  - FDASIA Section 707
  - FDA Guidance on Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection

## Enforcement: FDA List of Significant Issues

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- Repeated tests, trial runs, sample runs (testing into compliance)
- Changing integration parameters of chromatographic data to obtain passing results
- Deletion/manipulation of electronic records
- Altered data
- Turning off audit trail
- Sharing password
- Inadequate controls for access privileges
- Inadequate/incomplete computer validation

## Enforcement: FDA List of Significant Issues (2)

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- Inadequate investigations
- Inaccurate reporting of microbial sterility, or endotoxin data results
- Loss of data during changes to the system
- Activities not recorded contemporaneously
- Records falsely indicating that an employee completed a manufacturing step

## Import Alert?

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- Violation could cause drug quality defect with potential adverse patient health consequences
- Repeat violations
- FDASIA Section 707
- Significant data integrity violations
  - Negligence or fraud
  - How widespread
  - Firm's reputation
  - Firm management's attitude
  - Responsiveness to agency

## Warning Letter Language

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- January 2018:
- 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. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following.
  - A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting.
  - B. 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.
  - C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan.

## Warning Letter Language (2)

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- January 2017
- 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. We strongly recommend that you retain a qualified consultant to assist in your remediation.
- In response to this letter, provide the following:

## Warning Letter (2)

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- A. 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 manufacturing and laboratory 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.

## Warning Letter (2)

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- B. 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.

## Warning Letter (2)

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- C. 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.

## Warning Letter (2)

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- 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.

## General Response to Data Integrity Violation

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- Comprehensive evaluation
- Risk assessment
- Remediation and management strategy

## Comprehensive Evaluation

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- SOPs
- Nature of management involvement
  - Neglect
  - Active steps to discourage data integrity problems
- Principles established in FDA's Contract Manufacturing Guidance
  - Has the firm tried to contract away its compliance responsibilities?
- Personnel actions
- Did the firm detect the problem because its system was working?

## Comprehensive Evaluation (2)

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- Comprehensive, thorough, and complete evaluation
  - Detailed description of how evaluation was conducted
- List of records and documents that have been or will be examined
- Interview critical personnel
- Examine systems involved in the breach as well as other systems that could have the same problem (depends on the nature of the breach and how widespread it is)
  - Raw materials, components, ingredients
  - Testing records
  - Production and process records
  - Equipment

## Risk Assessment

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- Part of “Patient First” philosophy
- Examine:
  - OOS
  - Recalls
  - FARs
  - Adverse Drug Events

## Remediation & Management

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### ■ CAPA

- Analysis of findings
- Consultant's recommendations
  - It is *your* responsibility and *your* decisions
- Corrective actions taken
- Time table
  - Better right than early
  - OK to modify
- Identify responsible persons
- Procedures for monitoring the plan
- Always included training
  - If there is an SOP issue, almost always firmwide

## What to expect

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- Aside from working on one site (warning letter/import alert/OAI), you will likely see additional inspections at other sites
- Inspections at other sites will look for similar issues
- Highly damaging if problem keeps recurring
- Make sure FDA is aware of timetable at future inspections
- Other regulators will be aware of your 483 or warning letter or import alert
- Be sure you are ready before requesting reinspection
  - A poor reinspection is a major setback

## “Zero tolerance”

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- Does FDA have a “zero tolerance” policy for data integrity?
- Depends on the definition of data integrity and severity
- Try to avoid the label, if possible
- If 483 mentioning data integrity issue is incorrect, consider seeking a correction:
  - <https://www.akingump.com/images/content/6/1/v2/61908/AkinGumpNov3article.pdf>

## “Zero Tolerance”: The Case of Cetero

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- 1900 instances of absent technicians recorded as conducting studies
- Some studies required reanalysis; some required a data integrity audit
- Untitled Letter
- FDA receives criticism for going too far and not far enough
- Cetero shuts down
- Effect on patients