

ISPE-FDA 3<sup>rd</sup> Annual CGMP Conference  
2 – 4 June 2014  
Baltimore, MD



ISPE-FDA Third Annual  
CGMP Conference

Legal Aspects of Data Integrity

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Agenda

- I. Basic Legal Framework for Data Integrity
- II. Real-Life Examples and How Addressed
- III. Practical Legal Considerations

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Broader Meaning for “Data Integrity”

- The concept of data integrity encompasses more than just the “fraud and untrue statements of material facts” addressed under FDA’s Application Integrity Policy (AIP).
- Data integrity can also refer to FDA’s ability to rely on the data submitted to it or found in the files of a sponsor or manufacturer.
- Mistakes and omissions can lead to data integrity issues.

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I. Basic Legal Framework for Data Integrity Requirements

- A. Federal Food Drug and Cosmetic Act (FDCA or Title 21 of the U.S.C.)
- B. FDA regulations in Title 21 of the Code of Federal Regulations (C.F.R.)
- C. Federal Criminal Code in Title 18 of the United States Code (U.S.C.)
- D. FDA's Application Integrity Policy (AIP) announced in 56 Federal Register 46,191 (Sept. 10, 1991)

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The Statute Requires Creation and Submission of Data to FDA

- An “*applicant shall establish and maintain such records, and make such reports*” to FDA of “*data or information, received or otherwise obtained by such applicant*” if FDA decides through regulation “*that such records and reports are necessary*” under FDCA § 505.
- “*The failure to establish or maintain any record, or make any report, required*” is a “*prohibited act*” under FDCA § 301(e).

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FDA Regulations Require Data to be Created, Retained, and/or Submitted

- Numerous regulations for drug development, manufacturing, and marketing require the generation of records and/or submission of records to FDA.
- If the records in an applicant's files or submitted by it to FDA contain untrue or incomplete information, FDA could contend that the applicant has “*fail[ed] to establish or maintain any record, or make any report, required*” in violation of the FDCA.

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### FDA's GMP Regulations Require Generation of Numerous Records

- “[P]roduction and process control functions shall be documented at the time of performance. Any deviation . . . shall be recorded and justified.” 21 C.F.R. § 211.100(b)
- “[L]aboratory control mechanisms . . . shall be documented at the time of performance. Any deviation . . . shall be recorded and justified.” 21 C.F.R. § 211.160(a)
- “Laboratory records shall include complete data derived from all tests.” 21 C.F.R. § 211.194(a)

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### FDA's FAR Regulation Requires Submission of Reports to FDA

- Application holders are required to submit Field Alert Reports (FARs) to FDA's district offices within three business days of obtaining certain reportable information about distributed drug products relating to misbranding, counterfeiting, bacteriological contamination, significant changes or deterioration, and failures to meet specifications. 21 C.F.R. § 314.81(b)(1)

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### FDA's Adverse Event Reporting Regulation Requires Reports to FDA

- “The applicant shall report to FDA adverse drug experience information,” including 15-day alert reports, follow-up reports, and periodic reports. 21 C.F.R. § 314.80
- In addition to data integrity remedies, “FDA may withdraw approval of the application . . . if an applicant fails to establish and maintain records and make reports required” under the adverse event reporting regulation.

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### FDA's Regulations for Marketing Applications Require Data Submission

- Applications are “required to contain the technical sections” with “data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application,” including CMC, stability, and reports of clinical and animal testing (NDAs) or bioequivalence information (ANDAs).

21 C.F.R. §§ 314.50 & 314.94

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### US Criminal Code Makes Providing False Information to FDA a Crime

- “Whoever, in any matter within the jurisdiction of . . . the Government of the United States, knowingly and willfully—(1) falsifies, conceals, or covers up . . . a material fact; (2) makes any materially false . . . statement or representation; or (3) makes or uses any false writing or document” may be prosecuted under the “false statements” rule in 18 U.S.C. § 1001.
- Often the Government’s preferred method for addressing data integrity issues.

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### Application Integrity Policy (AIP)

- Applies only to “the integrity of data and information in applications submitted for Agency review and approval.”
- Is not binding law, but rather a statement of FDA policy that the agency adapts to the specific factual situation before it.
- Typically used in instances of widespread fraud where FDA has little confidence in the information it is asked to review.

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## II. Real-Life Examples

- A. Adverse Event Reporting
- B. Drug Development Data
- C. Stability Testing
- D. Contract Laboratory

*\*\* Actual facts and circumstances changed for sharing \*\**

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### Example – AE Reporting

- Hypothetical: Company discovers that its AE staff and contracted medical affairs personnel lacked sufficient qualifications and had been inadvertently mischaracterizing and underreporting adverse events for years.
- Response: (1) targeted sampling followed by comprehensive audit; (2) submission of corrected AEs accompanied by disclosure communication to FDA; and (3) adoption of interim controls for AE process.

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### Example – Drug Development Data

- Hypothetical: Company discovers that researcher has generated some BE data for tests he never ran and the data were included in a pending ANDA.
- Response: (1) flag and review all data provided by that researcher; (2) re-run analyses in ANDA to confirm no impact; and (3) submit amendment to pending ANDA to retract previous data and submit new data, accompanied by FDA communication.

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### Example – Stability Testing

- Hypothetical: Company discovers that two analysts in its QC laboratory had pulled samples and performed stability testing on dates different than what was recorded in laboratory records.
- Response: (1) consult audit trails to determine dates of actual testing; (2) provide only legitimate stability data and note issues in next annual report; and (3) revise personnel policies.

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### Example – Contract Laboratory

- Hypothetical: Company learns from FDA that data integrity issues had been discovered at its contract laboratory through the discovery and report of another customer.
- Response: (1) immediate, for-cause audit to determine scope of problems; (2) testing of retain samples where necessary; (3) selection and qualification of new laboratory; and (4) inclusion of new language in Quality Agreement.

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### III. Practical Legal Considerations

- Defining and limiting the scope of the problem
  - Designing an appropriate investigation plan
  - Promptly executing on the plan
- Deciding whether and how to disclose to FDA
- Identifying CAPAs
  - Need for new or revised contractual language?
  - Additional or different focus for audits?
  - New or revised policies or procedures?
  - Changing procedural controls? (e.g., Part 11)

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### What FDA Needs to Know If a Disclosure Communication is Made

- The company takes the issue as seriously as FDA does.
- The company has addressed the specific data integrity issue and put measures in place to ensure it will not recur (CAPAs).
- If there is ever a problem that requires reporting, the company is going to be transparent, and FDA will know about the situation.

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### Questions?

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