

Data Integrity Déjà Vu

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Is data integrity your biggest compliance risk? Data integrity is a broad term. It can be the failure to maintain raw data to support a current Good Manufacturing Practices (CGMP) required record or in support of a marketing authorization application. It also can concern data security issues, such as shared passwords or, more significantly, the intentional destruction or falsification of data. While data integrity is most frequently associated with laboratory operations, it is by no means limited to the laboratory. Data integrity issues have been observed in the research and development, manufacturing, marketing and regulatory departments as well.

There has been a flurry of activity recently regarding data integrity issues from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). There have been numerous observations and/or regulatory actions involving data integrity issues, which can be found on regulatory body websites. This activity would seem to imply data integrity issues are a recent trend. History would indicate otherwise. In the late 1980s data integrity issues led to the criminal prosecution of a number of generic drug industry executives and the levying of large monetary fines against a number of generic drug firms.

This article outlines how companies can prepare for inspections covering data integrity, provides recent examples of data integrity violations and recaps some of the data integrity issues from the 1980s that led to what became widely known as the generic drug scandal.

Preparing for Data Integrity Inspections

How can a company prepare for inspections covering data integrity? First, verification of data should be a common daily practice. For example, where data are entered manually either on paper or into electronic systems, a second person should verify those entries. These verification checks should be made by supervisors, managers or members of the

quality unit. Second, the internal audit program should include data integrity. The procedures for the internal audit program should require a robust evaluation of data integrity in all appropriate departments.

In addition, the authors recommend using auditors from another site or contracting a third party specifically for these data integrity audits to increase their robustness and assure maximum auditor independence. Likewise, supplier qualification programs must have a data integrity element, i.e., the contracting company needs to evaluate the contractor's data integrity through robust audits.

Finally, employees should be rewarded for speaking up and identifying noncompliant issues including data integrity. This must not be confused with whistleblowing, which is still illegal in many jurisdictions; informing management of noncompliance with regulations is simply good business practice.

As data integrity may be new ground for many companies, use of a third party with proven experience to supplement the internal and external audit programs can be very cost effective in the long run. The failure to identify data integrity issues can be a huge business risk. Data integrity gaps can result in withholding approval of the pending application and extend to all marketed products eliminating access to chosen markets. With increased information sharing among regulatory authorities, other authorities may take similar actions preventing access to their markets.

All the recent data integrity issues lead to the obvious question, what new laws, regulations and/or guidance will regulatory agencies such as FDA look to implement to reduce the violations?

Recent Initiatives on Data Integrity

On 16 December 2013, MHRA announced pharmaceutical firms are expected to assess data integrity and traceability during their self-inspection programs and this now is being covered during MHRA inspections. This expectation for self-inspection for data integrity applies to outsourced activities as well.¹

On 18 December 2013, FDA and EMA announced the Generic Drug Applications Initiative to share inspection information and facilitate regulatory actions against noncompliant facilities.² The initiative followed a guilty plea by a pharmaceutical manufacturer charged with falsifying bioequivalence data for several generic drugs.³

Following are a few examples of common data integrity citations from FDA Warning Letters:

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

Your firm lacked accurate raw laboratory data records for API [active pharmaceutical ingredient] batches shipped by your firm. The inspection revealed that batch samples were retested until acceptable results were obtained. In addition, your quality control (QC) laboratory failed to include complete data on QC testing sheets. Failing or otherwise atypical results were not included in the official laboratory control records, not reported, and not investigated....

According to laboratory analysts interviewed during the inspection, the common practice was to complete the analysis and to record the sample preparation data only if the results were acceptable. If the results obtained were atypical, a fresh sample was to be prepared and analyzed. The original sample testing was not recorded....”

- “Failure to record activities at the time they are performed.
Specifically, your staff used ‘finished product reports review data’ worksheets to document critical laboratory information days after the actual testing was performed. The worksheets reported observations from your firm’s secondary reviewer, and next to each of these listed observations the analyst marked them as corrected....

The above examples raise serious concerns regarding the integrity, reliability and accuracy of the data generated and available at your facility. In your response to this letter, provide a comprehensive evaluation of the extent of the omission, deletion and destruction of records, a risk assessment regarding the potential impact on the quality of products, and a comprehensive corrective and preventive

action plan. Your response should include a summary of your investigation into missing, inaccurate or unreliable tests results with a description of the findings. Your investigation should assess the impact of these and any similar incidents on the quality of the drug products produced with your APIs [active pharmaceutical ingredients], and should describe the steps that will be taken to prevent these fundamental breaches of data integrity and management oversight in the future....”⁴

- “Failure to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards.

For example,

- a. Your firm is missing the fundamental raw data and information necessary to document your analyses....
- b. Your firm frequently performs ‘unofficial testing’ of samples, disregards the results, and reports results from additional tests. For example, during stability testing, your firm tested a batch sample six times and subsequently deleted this data....

Your Senior QC Officer confirmed that QC laboratory employees had frequently practiced the use of ‘trial’ injections at your facility. Significantly, in addition to the example above, our inspection found 5,301 deleted chromatograms on a computer used to operate two HPLC [high-performance liquid chromatography] instruments in your QC laboratory. Many of these files were ‘trial’ injections of batches.

- c. Similar unacceptable data handling practices were observed in your laboratory’s conduct of gas chromatography (GC) analyses.

In addition, the inspection revealed numerous examples of deleted GC electronic raw data files on the computer controlling the GC instruments that were replaced with identical ‘official’ chromatogram file names. The identically named GC data files that were deleted had been created at different times and contained disparate data. Also, it appeared that data was not consistently archived to the central server....

Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21.CFR §211.68(b))....

The destruction of CGMP records produced by your firm’s manufacturing facility is a serious deficiency that raises concerns about the integrity of all records generated by your firm. There was a lack of basic oversight by operations, quality unit, and site managers, as rewriting and destruction of original CGMP records was allowed to persist over a significant period without implementation of systems and controls to prevent data manipulation....”⁵

- “Failure to maintain complete data derived from all testing and to ensure compliance with established specifications and standards pertaining to data retention and management.

Your firm did not retain complete raw data from testing performed to ensure the quality of your APIs. Specifically, your firm deleted all electronic raw data supporting your high-performance liquid chromatography (HPLC) testing of all API products released to the US market. In addition, your firm failed to retain basic chromatographic information such as injection sequence, instrument method or integration method for the tests. Your firm’s lack of data control causes us to question the reliability of your data.

In addition, your laboratory management was unaware of, and therefore did not follow, the written procedure detailing the review of analytical data. Furthermore, your management confirmed that the review of analytical data did not include evaluating the system suitability parameters to ensure proper column performance....”

- “Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

Your firm did not have proper controls in place to prevent the unauthorized manipulation of your laboratory’s raw electronic data. Specifically, your laboratory

systems did not have access controls to prevent deletion or alteration of raw data. The inspection noted that all laboratory employees were granted full privileges to the computer systems.

In addition, prior to January 7, 2014, HPLC and gas chromatograph (GC) computer software lacked active audit trail functions to record changes to data, including information on original results, the identity of the person making the change, and the date of the change....”⁶

Déjà Vu All Over Again?

Data integrity issues were at the heart of the generic drug scandal of the late 1980s. A number of generic drug companies were found to have submitted false data in their applications to FDA. The authors were employees in the FDA New York District Office and conducted investigations involving generic drug companies. Some of the issues uncovered during those agency investigations were the same or similar to those encountered today.

In one investigation, FDA received numerous complaints of stinging or burning of the eyes related to an ophthalmic product manufactured by Pharmafair. The investigation found the original laboratory data showed stability samples failing pH. However, in communications to FDA, the pH data were reported as meeting specifications. The investigation focused on three employees most likely to have been responsible for the false data reporting. Interviews led to one employee admitting the former company president threatened his job if he did not falsify the data.

In another investigation, Vitarine Pharmaceuticals submitted false batch records and bioequivalence data. During the investigation, raw material receiving records showed insufficient raw materials to manufacture the number and size of development batches. Management informed FDA the R&D laboratory had been locked up and the suspect employees placed on administrative leave. FDA investigators dumped the R&D waste receptacles onto the floor and found original handwritten batch records that had been torn into small pieces. In addition, Vitarine falsified bioequivalence test samples, as brand-name products were disguised to match the description of its generic product.

In another example from the 1980s, one of the authors conducted an inspection of American Therapeutics to follow up on complaints of tablets disintegrating. Retained samples were examined by the investigator and all appeared intact. It was later revealed the retained samples shown to the investigator were false. The retained samples were being opened and the disintegrated tablets replaced with new tablets.

Changes to Assure Data Integrity

Historically, the reaction to significant industry noncompliance issues has been the promulgation of new laws, regulations, policies and/or guidance. The generic drug scandal resulted in several such changes focused on assuring data integrity. These included the FDA Application Integrity Policy (AIP), *Compliance Policy Guide Sec. 120.100, Compliance Program Guidance Manual (CPGM), Preapproval Inspections 7346.832* and the *Generic Drug Enforcement Act (GDEA)*.

The AIP entitled, “Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities; Final Policy” (*Federal Register*, 56 FR 46191) was published 10 September 1991. An AIP list is available on the FDA website showing which companies have had their application reviews and/or are withdrawing an approved application for reasons of fraud, untrue statements of material fact, etc.⁷

Compliance Policy Guide Sec. 120.100, “Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities,” was issued in July 1991. The guide states: “Actions on the part of an applicant to subvert the integrity of an FDA review process through acts such as submitting fraudulent applications, making untrue statements of material facts, or giving or promising bribes or illegal gratuities, may call into question the integrity of some or all of the applicant’s submissions to the agency. In such cases, FDA will conduct an investigation to identify all instances of wrongful acts and to determine the extent to which the wrongful acts may have affected approved or pending applications.”⁸

The FDA preapproval program (CPGM 7346.832) was updated and states in the background section: “Generic drug applications also represent an important agency goal

in providing greater availability of medicines to the American public. As a result of the generic drug manufacturing history and the *Generic Drug Enforcement Act (GDEA)* of 1989, this inspectional program was significantly revised to include more emphasis on data integrity. More than 30 individuals and nine companies admitted or were found guilty of various fraud and corruption offenses involving generic drugs.” This program also lists three objectives: readiness for commercial manufacturing, conformance to application and data integrity audit.⁹

Provisions in the *GDEA* include: Debarment of Corporations and Individuals, Authority to Deny or Withdraw Product Approval, Suspend Product Distribution, Agency Hearings, Judicial Review of *GDEA* Decisions, Civil Penalties, Certifications and Effect on Other Laws.¹⁰

Return to Focus on Data Integrity

While the requirement for assessing data integrity has been in the preapproval inspection program since the 1990s, recent Warning Letters, Form FDA 483 inspectional observations and FDA presentations have highlighted the agency’s return to a focus on data integrity. Specific focus on analytical instrument software such as that for HPLC allows the agency’s investigators to see whether additional injections to those reported were made. If these injections are not explained in the analytical method or chromatography standard operating procedure (SOP), FDA may wonder whether the company may have taken the opportunity to substitute passing data for failing data. Even when the results of “trial injections” are not quantified, companies have not successfully defended this practice to FDA investigators.

Also, skilled investigators know today’s laboratory equipment has sophisticated security features to prevent the analyst from acquiring and potentially manipulating data. These features always should be used and administrative rights to software and electronic data carefully controlled.

The authors also have seen observations of failing to maintain sample custody and failure to physically inventory physical quantities of Quality Control samples in the laboratory. This is not specifically required by 21 *CFR* Part 211, but is intended to show gaps that provide an opportunity for improper data manipulation.

These issues are not limited to the laboratory. Production equipment frequently has software to capture processing parameters. There is a risk this information is not captured for review during final batch record review. Also, if data are not downloaded to other permanent media, they can be overwritten and lost.

FDA may place a company on an Import Alert preventing importation of any products into the US. The burden of proof for initiating import alerts is low, allowing FDA to expeditiously take action as a result of finding data integrity gaps. The trend is expected to continue. In the last few years, several companies have had FDA Warning Letters or Untitled Letters issued and been placed on an Import Alert with the letter strongly recommending the company conduct a global assessment of its operations with the assistance of a qualified third party.

Conclusion

Assessing data integrity is a clear priority identified by regulatory agencies and will continue to receive significant coverage during inspections. In addition, the information sharing among regulatory authorities will continue to increase resulting in more efficient and broader regulatory actions when serious data integrity issues are found. A robust data integrity program accomplished through daily checks by supervisors, managers or members of the quality unit and the internal audit program is essential. The procedures for the internal audit program should include a robust evaluation of data integrity in all appropriate departments. The use of external or third-party auditors should be considered to enhance the data integrity program further.

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