SHIMADZU
Excellence in Science

Technical Report

Data Integrity Compliance Using the LabSolutions Report Set

Mamoru Kikumoto[1]

Abstract:

A recent topic related to analytical data is the lack of data integrity due to data modification and replacement. Whether caused intentionally or accidentally, such problems are often the result of incorrect operating procedures. Accordingly, the question of how to ensure data integrity has become a pressing issue for analysis laboratories.
In addition to the sophisticated security functions provided in the previous version, LabSolutions DB/CS version 6.50 includes a new Report Set function that enables the visibility of software operations. Therefore, not only can it help ensure the reliability of the analysis data required by analysis laboratories but, it can also cut decrease the amount of time needed to check analysis results to a half of or a third of that previously required.

Keywords: data integrity, Report Set

1. Data Modification

A recent topic related to analytical data is the lack of data integrity due to data modification and replacement. Whether caused intentionally or accidentally, such problems are often the result of incorrect operating procedures. Accordingly, the question of how to ensure data integrity has become a pressing issue for analysis laboratories.

2. Actual Pharmaceutical Company Case

The FDA (the U.S. Food and Drug Administration) currently issues a large number of warning letters and Form FDA 483s related to data integrity. These notifications have reportedly been triggered by a case of fraud committed by a generic drug manufacturer based in the state of New Jersey in the United States. An FDA audit of an actual pharmaceutical company in 2005 revealed inconsistencies between paper-based and electronic data at the analysis laboratory and revealed that non-conforming test results were never investigated. Consequently, the company halted shipments, recalled all products, and stopped manufacturing. Furthermore, they withdrew seven generic drug applications. Then, after filing bankruptcy in October 2005, they were purchased later that year by a different pharmaceutical company. The chairman and CEO resigned and four responsible persons were accused of criminal activity.[1,2,3]

3. Form FDA 483

The FDA issued Form FDA 483 to Able Laboratories and posted it on the FDA website.[1]

In that form, the following was included as "OBSERVATION 1."

OBSERVATION 1

"... The Quality Unit failed to: review electronic data as part of batch release, review computer audit trails in the Waters Empower Data Acquisition System and provide adequate training to analytical chemists. ..."

This indicates that the chromatography data system is being called into question.

The form also included the following.

• OOS results were substituted with passing results by Analysts and Supervisors.

• Changed chromatogram headers by cutting and pasting, so during review all sample injections would appear to be in sequence. ..."

This indicates that:

• Non-conforming test results were replaced with passing results and

• Chromatogram headers were modified by cutting and pasting.

4. FDA Response

According to the GMP News[5] report from the ECA[4], the FDA responded to the above case as follows.

Triggered by the cases of fraud at Able Laboratories in 2005, the requirements for audits of data integrity during FDA Pre-Approval inspections have been set in the Compliance Programme Guide (CPG) 7346.832. Moreover, FDA's inspectors have been explicitly trained on computer systems and the data they contain.

Table 1 Categories and Remedies for Issues Raised by the FDA

Category	Description	Examples of Issues	Remedies
1	Problems with inadequate recognition	• Paper-based test results did not contain all analytical data.	• Regulatory requirements should be interpreted correctly.
2	Functional deficiencies, inadequate settings, and usage issues	• There were no audit trail functions. • Login IDs and passwords were being shared. • Data deletion was not restricted using user rights.	• Systems should be updated to enable compliance with regulations. • System settings should be specified appropriately.
3	Testing process reliability issues	• Tests were repeated until acceptable results were obtained. • Out-of-specification (OOS) data was neither investigated nor reported.	• Operations should be checked for any improper actions.

5. Categories and Remedies for Issues Raised by the FDA

There are multiple data integrity issues that have been raised by the FDA, however, they can generally be categorized as indicated in Table 1. Category 1 includes issues that result from a fundamental lack of recognition, which requires properly interpreting regulatory requirements. Category 2 includes issues related to functional deficiencies, setting inadequacies, or usage factors. These issues require updating systems to be able to comply with regulations or specifying proper settings. Category 3 includes issues related to the reliability of the testing processes. These issues require verification to confirm that no invalid operations are being performed. Because FDA investigations are currently focused on data integrity, importance has shifted toward providing evidence that no improper operations were performed with respect to analytical results. This approach of the investigators based on suspicion, which is a major departure from the approach used in previous investigations.[6]

6. Relationship Between Inputs and Outputs

Using HPLC analysis as an example, consider what is lacking in current practices, in terms of data integrity. Based on the prerequisites indicated in Fig. 1, it appears that current practices are acceptable as long as security settings, such as login IDs, audit trail settings, and user rights for deleting data, are configured in compliance with established regulations. Normally, only the printed chromatograms are checked, the instrument conditions (instrument parameters) used for the analysis, the data analysis conditions (data processing parameters), the batch analysis conditions, or other factors. However, reliability can be ensured only by checking all these factors in addition to the chromatogram report.[7]

It is easier to understand this as a relationship between the input and output processes. Fig. 2 shows that, even if stronger security measures are implemented for outputs (analysis data), they are meaningless without proper inputs (such as acquisition and data analysis conditions). While computers can apply security measures, they cannot judge the malicious intent of humans.
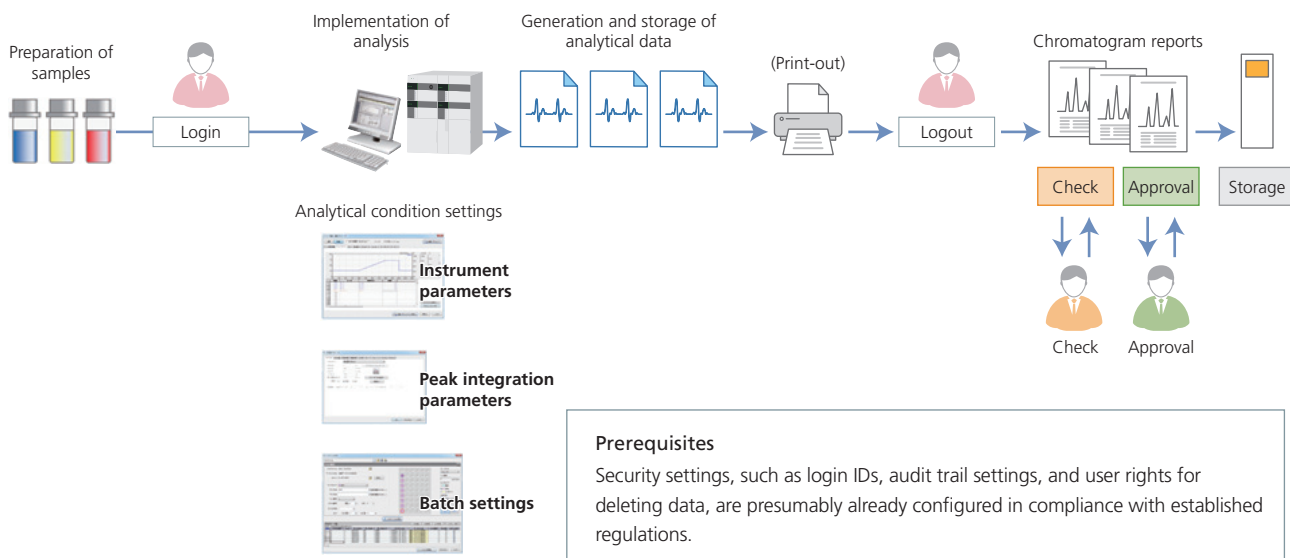

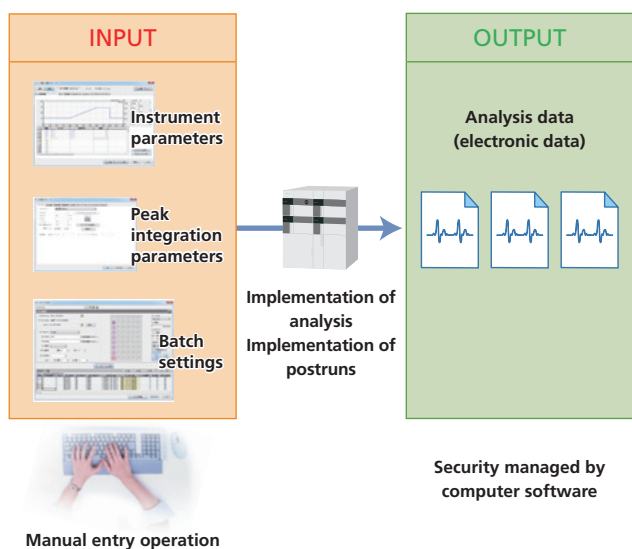Fig. 1 HPLC Analysis Process Flowchart

Fig. 2 Relationship Between Inputs and Outputs for HPLC Analysis

Therefore, even if security is strengthened in the computer, it is difficult to prevent improper operations for processes that require human intervention (such as specifying analytical conditions or analyzing analysis data).

7. Achieving Visibility for Computer Operations

Consequently, what techniques should be used to provide evidence that no improper operations were performed with regards to analysis results?

This can be accomplished by ensuring that computer operations are easily visible.

The visibility of computer operations refers to retaining the results of operations that require human intervention, such as setting analytical conditions or analyzing data, and presenting them in a form that is easily visible. Visibility makes it possible to provide evidence that no improper operations were performed, such as modifying or replacing data.

8. LabSolutions DB/CS Report Set

Fig. 3 shows such computer operations presented in a visible form using the Report Set function in LabSolutions DB/CS version 6.50. The Report Set function converts a set of reports, such as batch analysis reports, operation log reports, and chromatogram reports, to PDF format and then digitally consolidates the reports into a single PDF file. This report set, which includes the results of operations involving human intervention, provides visibility of the software operations, and makes it easy to provide evidence that no improper operations were performed, such as modifying or replacing data.

The following are three key features of the report sets.

《Feature 1》
Visibility of the Series of Analysis Operations Reduces the Work Involved in Checking Results and Ensures Reliability

The newly included Report Set function digitally converts batch analysis reports, operation log reports, chromatogram reports, and other reports into a single PDF file. In this case, batch analysis reports do not refer to the batch analysis schedule but rather to an analysis ledger that summarizes (lists) the actual series of analyses and the corresponding postrun analyses performed. The operation log report consists of an analysis (and postrun analysis) computer operation log that records all analysis operations (and a postrun analysis) performed between the start and finish of the analysis processes.
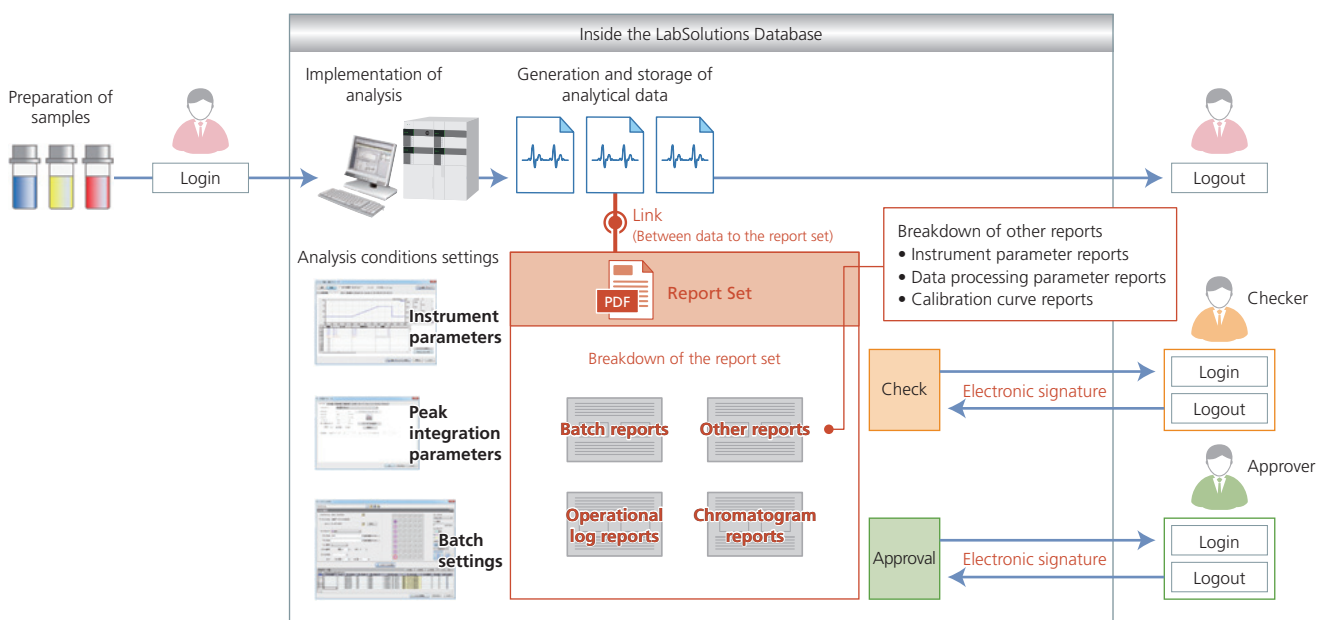

Fig. 3 Data Integrity Compliance Using LabSolutions DB/CS Report Set

Report sets consolidate all the necessary information in a single PDF file, so that the entire series of operations involved in the analysis (and post-run analysis) are easily visible. With the same feel as an electronic book, you can check the details while turning the pages. As a result, it is not necessary to switch between a number of windows or tabs to check operations and settings as in the past. In this way, the Report Set function reduces the work involved in checking results and ensures reliability.

《Feature 2》
The Series of Analysis Results Is Automatically Protected Against Modification
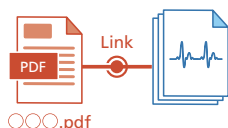
Once a digital link is created between the series of analysis results (electronic data) and the report set for which visibility is being provided, editing is automatically disabled (locked). This will help prevent any data modification, such as replacing or deleting the analysis results.

The digital link created between the data not only ensures a unique relationship between the report set the analysis results (electronic data), but it also enables analysis results (electronic data) to be searched and checked quickly.

《Feature 3》
Enhanced Productivity Thanks to Digitization of the Confirmation Process for the Analysis Results Report
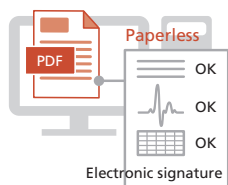
The Report Confirmation function can be used to retain evidence that the content of the chromatogram report included in the PDF file was reviewed. This evidence can be left anywhere in the chromatogram report in the same way as with printouts. A confirmation assistant function is included to ensure content reliability by emitting an error to provide notification of unchecked items.
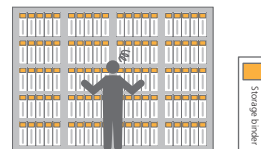
Problem 1 Associated with Printouts
The significant amount of time needed for analysis report printing, summarization, checking, and storage tasks can interfere with daily operations.

Problem 2 Associated with Printouts
The increasing number of binders required to store printouts can cause storage space problems.

Problem 3 Associated with Printouts
Analysis results might be replaced or discarded.
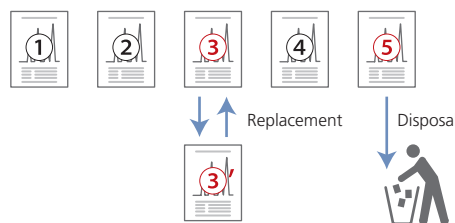
Replacement   Disposal

Fig. 4   Problems Associated with Printouts

Electronic signatures can be used for report set review and approval processes, with the original source electronic data (analysis results data) also being reviewed and approved at the same time. Using electronic signatures means electronically signed reports do not necessarily need to be printed out and signed by hand. Consequently, migrating to a paperless work flow can solve the problems associated with printouts (see Fig. 4) and reduce the time required to check various results by one half to a third of that previously required.

The Report Set function is included in LabSolutions, which increases CSV efficiency because a separate validation process is not necessary.

References

1) ORA FOIA Electronic Reading Room. July 6, 2005.
   http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm061813.htm, (accessed March 7, 2016).
2) R. D. McDowall. *Quality Assurance Journal*. 2006. Volume 10, Issue 1, pp. 15–20, doi:10.1002/qaj.357. http://onlinelibrary.wiley.com/doi/10.1002/qaj.357/pdf, (accessed March 7, 2016).
3) FDA. U.S. Department of Justice Press Release. March 8, 2007. http://www.fda.gov/ICECI/CriminalInvestigations/ucm258236.htm, (accessed March 7, 2016).
4) http://www.gmp-compliance.org/eca_index.html (Note: The ECA (European Compliance Academy) is a non-profit organization established in the EU in 1999 that provides GMP training and conferences for the pharmaceutical industry. About 4000 members of it are from over 60 countries, mainly in Europe.)
5) ECA. "Data Integrity: New Inspection Focus of the FDA". GMP News. February 25, 2015.
   http://www.gmp-compliance.org/enews_04704_Data-Integrity-New-Inspection-Focus-of-the-FDA.html, (accessed March 7, 2016).
6) Paul Smith. "Data Integrity in the Analytical Laboratory". *Pharmaceutical Technology*. May 2, 2014.
   http://www.pharmtech.com/data-integrity-analytical-laboratory?pageID=1, (accessed March 7, 2016).
7) Keiko Bansho. Chapter 5 Operations and Management for Paper-Based and Electronic Data for Compliance with Regulations by the Three Authorities. *Recording and Managing Data and Migration to Digitization at Laboratories Based on the Issues Raised by the Three Authorities*. Science & Technology, May 15, 2015, pp. 127–146

SHIMADZU

Shimadzu Corporation
www.shimadzu.com/an/