An Executive Summary

# Five Essentials for Surviving Your Next Laboratory Inspection: A Quality Control Example (Part 1)


**Bob McDowall**
*Director*
RD McDowall Ltd

**Paul Smith**
*Global Compliance Specialist*
Agilent Technologies

**Josh Miller**
*OpenLab Software Marketing - eLearning Expert*
Agilent Technologies


## Good data integrity practices are essential to maintain compliance in a regulatory environment.

Data integrity (DI) is the ability of a laboratory to ensure that data are attributable, legible (and understandable), contemporaneous, contemporaneous, and accurate (ALCOA) as well as free from accidental or deliberate bias. DI has come under increasing scrutiny by FDA over the past 20 years, with the number of DI-related warning letters going up seven-fold since 2000 **Figure 1**. In 2005, FDA's initial focus on data integrity was triggered by a whistleblower at Able Laboratories, which had been using integration parameters, adjusted weighting factors, and even copying and pasting paper chromatograms to falsify batches (1). This prompted the agency to place more focus on e-records. In one case, a dissolution result of 29% was able to be forced to pass an 85% specification. At the center of the falsification was a well-designed chromatography data system (CDS) that had a non-optional, built-in audit trail. Using the audit trail, FDA was able to prove that fraud had taken place.

Needless to say, audit trails are now an essential part of demonstrating compliance, prompting inspectors to pay increased attention to the data created and stored in CDS. Concerns with issues such as unofficial testing, deletion of data, failure to protect electronic records, integration into compliance, and the selective invalidation of out of specification (OOS) results are under increased scrutiny. Since 2005, inspectors have increasingly moved away from looking at paper records and instead focused on electronic records and audit trail entries.

It is important to understand how DI will affect future inspections and to be able to answer questions succinctly, accurately, and completely. Of course, the work of having smooth and painless inspection starts well before then—with the management and analytical decisions that produce the data.

This article, the first in a two-part series, will discuss what can be done to ensure DI and as well as how to ensure a smooth inspection. Part two will address the data systems and technical controls that can be used to help guarantee regulatory compliance.

### The Data Integrity Model

While no two inspections are the same, there is often a common scope. The focus areas of a typical FDA inspection are presented graphically in **Figure 2**. Some foundational questions that inspectors try to answer are: 1) Does management support and encourage DI? 2) Is there a DI-focused culture here?


SPONSORED BY

Agilent

LC GC north america

**Figure 1:** FDA data integrity focus.

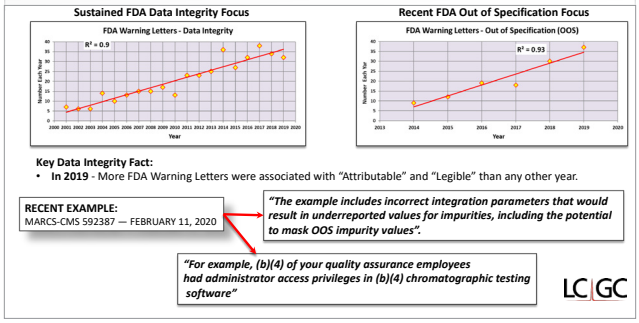
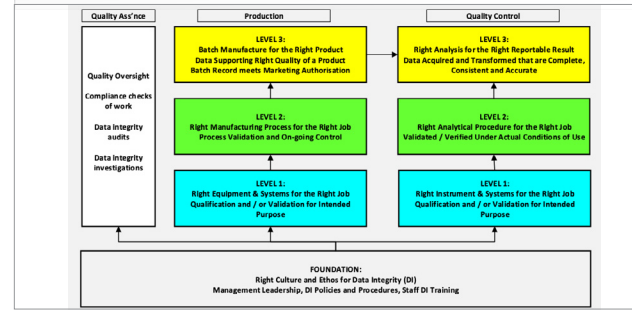



**Figure 2:** Pharmaceutical quality system.




Meeting these requirements calls for more than just the occasional email. A continuous demonstration of manager leadership is essential for passing inspections. Management leadership sets the tone for the quality culture and DI policies, procedures, and staff training.

This article primarily deals with questions in the right column of the figure, which relate to the quality control laboratory. The first level of that column has to do with the physical and technical equipment and instrumentation that is available at the laboratory, including the analytical instruments, their qualification and validation, as well as the information management system and its validation. All equipment must be kept in calibration against reference standards.

As a topical note at the time of this writing, many laboratories are currently shut down or operating in a reduced capacity during the COVID-19 response. When a laboratory is brought back into operation, the first task should be ensuring that equipment calibrations are current before any samples can be run.

Above the instrumentation are the procedures and methods they are used for. The right analytical procedure must be applied to the analysis. The methods must be validated and verified under their actual conditions of use. It is important to understand that pharmacopoeia methods simply provide overview that must be developed into a functional analytical procedure in-house.

At the top level of the model is the analysis of the sample. The correct analysis must be applied to obtain the relevant result. Documentation, procedures, and training of the personnel all come into play at this point. The documentation must demonstrate that the method was performed appropriately, that system suitability was assured, and that the analysis of the data was performed in a consistent and accurate manner.

A failure at any level in this model invalidates the level(s) above it. The right analysis cannot be done if the right analytical procedure has not been established, and neither the analysis nor the procedure can be performed if the instrumentation is not validated and in calibration. Lastly, none of the above is possible if the management and leadership are not committed to maintaining DI. A similar hierarchical structure applies to the manufacturing side, but is outside the scope of this article.

## Analytical Instrumental Qualification

Instruments such as liquid chromatographs should only be used within the range of operation that has been qualified. For instance, if a pump has only been qualified at 1.0 mL/min, that is the only rate it should be used at. You are allowed to interpolate, but not extrapolate. If methods use the range of 1–2 mL/min, qualifying the pump between 0.5 mL/min and 2.0 mL/min is acceptable, although there is little cost in extending that range to accommodate unusual uses that may arise. Additionally, documents and logs of qualification should be easily accessible; this will both speed inspections and make it easy for technicians to verify that they are operating within the qualified range.

It is important to note that the manufacturer's instrument specification is not equivalent to a user qualification. The specifications are not necessarily created under the conditions of use, and thus cannot be directly translated into the laboratory environment, which is often more variable than the conditions in which the specifications on an instrument were set. It is also common for an instrument to drift out of specification over time, therefore regular re-qualifications are necessary.

In the event that an instrument is used outside of its qualified range (e.g., a new method with an unusual wavelength or flow rate), the system can be qualified for the extension. using additional tests with certified reference standards or calibrated test equipment will be required.

## Configuration of the CDS Application

Laboratory personnel's ability to view, edit, and sign data should be limited to what is needed for their roles. Any conflicts of interest where a single person can both generate and approve data should be avoided. The configuration of the CDS and its permissions should be completely documented in a standard operating procedure. Having the data system configured to protect against tampering and enabled audit trails also

helps ensure DI. In-software electronic signatures for approvals are a mature technology and are more secure than referring to an external paper report that can be misplaced or altered.

## During the Inspection

Inspectors ask a lot of questions. The general advice is to not volunteer information that has not been asked for. However, being deliberately literal and obstinate will also antagonize the inspector and prolong the inspection. For example, if asked, "Do you have an inventory of chromatography instruments in this laboratory?" the most concise answer is a simple "Yes."

However, you will most likely be asked to present the documentation. As a rule, if asked something that has verifying documentation to support the answer, it is best to anticipate the need to present that documentation. This will make the process go much more smoothly and prevent antagonizing the inspector or raising suspicions that you have something to hide or are deliberately delaying the inspection.

As an example, let's look at a quality assurance laboratory operating under GMP and analyzing active pharmaceutical ingredients and finished products. It is currently undergoing a preapproval inspection (PAI). Chromatography is the primary analytical technique and their CDS is a networked, validated system. It has secure central storage of backups to the database. Printouts and transcription errors are avoided because all the calculations take place within the chromatography system. Final reports have electronic signatures. All these represent a strong foundation to ensure DI. During the inspection, you can expect to be asked about training as well. Come into an inspection prepared to be able to demonstrate adequate training procedures as well as testing and verification. There should be questionnaires to confirm that employees understand the DI procedures, and they should be required to retake the training if they cannot demonstrate adequate understanding of DI procedures.

DI is more than just numbers; it includes the culture and attitude toward the handling of data. All processes and practices related to data handling are involved. The role of management is essential. They have the power to set the metrics and dictate the culture. When creating incentives for productivity, consider the unintended behaviors they might encourage. For example, awarding a bonus to the most samples run creates a disincentive for reporting errors that might invalidate a run.

## Conclusion

Staying in compliance with regulatory requirements requires close attention to DI, which can only be achieved with commitment from management to create a quality-focused culture within the organization. In the laboratory, consistency and appropriateness are the order of the day. A given analysis should be performed with the appropriate instrumentation, and those instruments should be validated and qualified for the purpose to which they are applied. The validations should be under conditions consistent with use, and the method should be appropriate to provide the reportable result needed. All processing, transporting, and transformations that lead from the initial measurements to the final report in the database need to be consistent and accurate.

The vast majority of the work associated with a smooth and painless inspection happens when the inspector is not in the laboratory. Training, combined with testing and documentation, are essential parts of a successful inspection. When asked if you are ready for an inspection, the answer should be "yes" on any given day.

## Reference

1. FDA, "Able Laboratories, Inc., Cranberry, NJ, FDA 483 Inspectional Observations, dated 05/02-07/01/2005," https://www.fda.gov/media/70711/download

Stanislav_uvarov/stock.adobe.com