REGULATORY HANDBOOK

# *DATA INTEGRITY: FDA AND GLOBAL REGULATORY GUIDANCE*

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# *INTRODUCTION*

Data integrity is a prerequisite for the regulated healthcare industry as decisions and assumptions on product quality and compliance with the applicable regulatory requirements are made based on data. Drug and medical device manufacturers or (service) providers, healthcare organizations, regulators and other government organizations, and users, i.e., patients and healthcare professionals, rely on data. Breaches in data integrity can have negative consequences and may lead to patient injury, or even death.

Whereas in the past data integrity was relatively easy to prove using forensic methods analyzing ink and paper, the advent of computerized systems has brought with it a different level of complexity. Identifying whether there could have been undocumented or even malicious changes to electronic data or records requires additional tools and expertise.

As it is much easier to change electronic data and records than it is to change a paper or other physical record, there is a much higher chance of such changes being effected. The regulatory authorities have put much emphasis on data integrity in recent years, not least because they have uncovered serious cases of data integrity breaches. This document provides references to the applicable regulations, guidance and reports on data integrity (breaches).

# DEFINITIONS

## Main Criteria for Data Integrity

[R.D. McDowall, Spectroscopy, Focus on Quality, December 2010]

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| **Accurate** | No errors or editing without documented amendments |
| **Attributable** | Who acquired the data or performed an action and when? |
| **Available** | For review and audit or inspection over the lifetime of the record |
| **Complete** | All data is present and available |
| **Consistent** | All elements of the record, such as the sequence of events, follow on and are dated or time stamped in expected sequence |
| **Contemporaneous** | Documented at the time of the activity |
| **Enduring** | On proven storage media (paper or electronic) |
| **Legible** | Can you read the data? |
| **Original/Reliable** | Written printout or observation or a certified copy thereof |
| **Trustworthy** | The data and the record have not been tampered with |

**Breaches of data integrity (BDI) are acts of "falsification, document adulteration, forgery and providing misleading information".**

[Carmelo Rosa ISPE FDA 3rd Annual GMP conference June 2014 Baltimore MD: Current Inspectional and Compliance Issues in Data Integrity (www.ispe.org)]

# MAJOR REGULATORY GUIDELINES

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| **US FDA** | • 21 CFR Parts 11, 211, 803 [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm]<br>• Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application, August 2003<br>• Carmelo Rosa ISPE FDA 3rd Annual GMP conference June 2014 Baltimore MD: Current Inspectional and Compliance Issues in Data Integrity (www.ispe.org) |
| **European Council** | • EudraLex Vol 4 Chapter 4 and Annex 11 [http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm]<br>• Directive 1999/93/EC of the European Parliament and of the Council of 13 December 1999 on a Community framework for electronic signatures [http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31999L0093&from=EN] |
| **ICH** | ICH Q7 [http://www.ich.org] |
| **MHRA**<br>**www.mhra.gov.uk** | • The MHRA is setting an expectation that pharmaceutical manufacturers, importers and contract laboratories, as part of their self-inspection program must review the effectiveness of their governance systems to ensure data integrity and traceability [http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/News/CON355490]<br>- This aspect has been covered during inspections since the start of 2014, when reviewing the adequacy of self inspection programs in accordance with Chapter 9 of EU GMP<br>- It is also expected that in addition to having their own governance systems, companies outsourcing activities should verify the adequacy of comparable systems at the contract acceptor<br>- The MHRA invites companies that identify data integrity issues to contact: GMPInspectorate@mhra.gsi.gov.uk<br>- GMP/GDP Consultative Committee, Note of Meeting; MHRA drew members' attention to the announcement on the website in relation to the Inspectorate's expectations in relation to self-inspection and data integrity [http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/News/CON355490]<br>- If companies identify issues, they are invited to contact the MHRA to discuss the issues and how to move forward<br>- MHRA is looking at how current inspection practice can be changed in order to build in data reliance checks early on in the inspection process. The result of the checks will then determine whether the remainder of the inspection process is carried out normally or if indeed a more forensic approach is taken<br>- In order to prepare for the process, industry can look at the way they design their systems, enabling the operators of those systems to comply. Easy checks that can be carried out during supplier audits or self-inspection include sample reconciliation and building in appropriate checks of audit trails and raw data. These are the types of things that will be initially looked for<br>- Additionally, a section on data falsification will be added to the Compilation of Community Procedures<br>• Falsification in the context of EU GMP – changes are being made to the definition of 'Critical' deficiency in EU GMP:<br>- Any wilful misstatement, misrepresentation, manipulation, adulteration, rewriting, hiding, replacing of quality related documents, materials, activities or buildings in order to give an item the appearance of GMP compliance when this is not the case – EU Compilation of Community Procedures. [Gerald W. Heddell at the ISPE/FDA conference Baltimore June 2014] |
| **WHO**<br>**www.who.int** | WHO Notices of Concern [http://apps.who.int/prequal/assessment_inspect/info_inspection.htm] |

# DISCUSSION TOPICS

## REGULATORY AGENCY INSPECTION OBSERVATIONS

Companies are encouraged to review published inspection observations regarding data integrity. These are a valuable source of information, however, these merely list the symptoms, not the underlying root causes. We have grouped the observations to make them more useful for root cause analysis. All of this information is publicly available free of charge on the following websites:

- http://www.fda.gov/ICECI/EnforcementActions/default.htm
- http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do

An analysis of the observations in the above resources shows that there are three key areas of concern:

- Lack of adequate controls
- Lack of staff competence
- Lack of adequate root cause analysis

Without doubt, such issues can occur in any company anywhere in the world. Thus, it is prudent to pay particular attention to these aspects when addressing data integrity.

## LITERATURE ARTICLES

These often provide summary overviews of data integrity issues, combined with an analysis of the underlying issues and potential root causes. In addition, they often discuss solutions and industry best practices. Not all literature sources are free of charge. The following are a selection of pertinent article excerpts from several sources widely used in industry.

- Data integrity problems continue to bedevil pharmaceutical manufacturers, if recent warning letters issued by FDA are any indication
- Of the five drug GMP warning letters issued December 2009–February 2010, three showed data integrity lapses. [Data Integrity Problems Continued to Surface in Recent Warning Letters, The Gold Sheet February 2010]
- FDA inspectors using a new forensic approach to inspections in responding to a rash of data integrity

problems found in pharmaceutical manufacturing facilities. Attorneys advise firms to pay careful attention to their adverse event reports and field alert reports as data integrity breaches can be found there too

FDA and the pharmaceutical industry are recommending a forensic approach to inspections and internal audits to combat growing data integrity problems: Digging through trash cans and drawers is not considered out of bounds in the current environment. [FDA Aggressively Looking for Data Integrity Problems in Inspections, The Gold Sheet June 2014]

# *DATA INTEGRITY ISSUES EVERYWHERE?*

**Excerpt from "Data Integrity, Pharmaceutical Technology Europe, Volume 38, Issue 7, pp. 82, July 2014. www.pharmtech.com**

**Q: "Data integrity issues" have been making headlines recently, in response to foreign inspections by the Food and Drug Administration or European regulatory agencies. Based on these reports, it appears that the issues centre largely on manufacturing companies in Asia. Should we conclude that this only concerns firms already struggling to comply with basic good practices in this part of the world?**

**A:** In general, media tend to report on the most serious violations uncovered by regulators. Oftentimes when companies find similar issues through their own internal investigations, they remain confidential and unreported. Therefore, it would be presumptuous to assume violations reported on by the press are representative of the industry as a whole.

However, what inspections have triggered is increased attention toward potential data integrity issues lurking across the industry. Few companies would have data integrity verification activities integrated into their quality oversight programs before these examples of serious violations of healthcare regulations became public knowledge in the form of warning letters, consent decrees or reports in the European EudraGMDP database.

Conscientious companies have taken these potential data integrity issues seriously by starting internal investigations, incorporating data integrity assessments into their quality assurance oversight programs, and in some cases, establishing a special data integrity office. Companies - even those in good standing with regulators - have initiated such activities regardless of existing or anticipated compliance concerns.

The question now is, what have these internal investigations uncovered, if anything? The answer, surprisingly, is that they have uncovered a significant amount. Once you start studying analytical data, root cause analyses, logbooks and any other data source, gaps are repeatedly found in data traceability and trustworthiness. A few data-related issues include: uncertainty where the data originated from and who created it - e.g. where several analysts use the same user ID and password on a set of similar instruments; which raw information produced the reported data - e.g. where a summary table reports stability data results, but all raw data on the chromatography instrument have since been deleted, and whether these are the original data - e.g. where there is no audit trail on the analytical instrument. These issues are not necessarily the result of wilful malpractice, but are often caused by insufficiently controlled processes, poor documentation practices, suboptimal quality oversight and, often enough, professional ignorance.

Occasionally people do intentionally falsify data. This is unfortunate but, thankfully, still a rarity.

## Here are some steps you should take to ensure data integrity:

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| Embed data integrity verification activities into internal audit processes | Train your internal auditors to understand what to look for when detecting data integrity deficiencies |
| Create awareness among staff so they can assist with this endeavor, and report concerns before they become full-fledged issues | Seek external support to assure completely unbiased, third-party investigations and/or to enhance your internal investigation program |

It should come as no surprise that companies already struggling to meet basic compliance standards are at a disadvantage when it comes to data integrity. However, making data integrity a key element of your compliance approach will give you a competitive advantage. It is always better to proactively prevent issues, such as data integrity failures to occur, than trying to remediate and resolve inspection findings. Compliance excellence makes good business sense.

- The need to ensure data integrity through the life cycle of a clinical trial and across all the systems involved is of paramount importance as inconsistent, incorrect or corrupted data could endanger the safety of patients, adversely affect the outcome of the trial and increase the risk of a failure during the submission procedure. Therefore, this aspect has increasingly become the focus of regulatory oversight. One of the main drivers for this has been that the industry has embraced individual or strategic outsourcing of clinical trial activities to Contract Research Organizations (CROs) and sponsors as well as CROs also adopting Software as a Service (SaaS) offerings especially in the area of Electronic Data Capture (EDC) or Interactive Voice Response Systems/ Interactive Web Response Systems (IVRS/IWRS). Often this leads to a chain of partners with an increasing risk of losing direct control for the sponsor. Even when strategically partnered with a CRO, the responsibility to address these risks resides with the Sponsor and cannot be delegated. This requires extensive and increasing efforts for oversight, which must be considered when addressing the risks with regard to data integrity. [Validation and Data Integrity in eClinical Platforms June 2014, http://blog.ispe.org/?p=1526]

# CONFERENCES AND TRAINING COURSES

As yet only a limited number of events have been organized on the subject of data integrity. Even fewer have had regulatory agency speakers presenting. The specific advantage of these events is the direct access to regulators and the opportunity to share expertise and experiences with industry peers. PAREXEL subject matter experts regularly attend, present and are members of the organizing committees for such conferences.

In 2014, speakers from FDA presented on the topic of data integrity at events in the U.S. and overseas (e.g., ISPE FDA Annual Conference in Baltimore, MD; DIA FDA EDQM Data Integrity Workshop in Bangalore, India). The presentations from the regulatory agency speakers are usually made available via the agencies' websites; other presentations may only be available to the attendees.

# CONCLUSION

**Given the increased scrutiny for data integrity, companies are well advised to establish internal competency, assessment and monitoring programs, and assure data integrity is an integral part of the internal audit/self-inspection program. Relevant information on data integrity can be gleaned from a multitude of sources; and if in doubt, specialist consultants can provide invaluable assistance with all aspects of compliance.**

## AUTHOR BIOGRAPHY


Siegfried Schmitt, Principal Consultant, joined PAREXEL Consulting in 2007. He provides consulting services to the medical device and pharmaceutical industry on all aspects of regulatory compliance, particularly the design and implementation of Quality Management Systems and Competitive Compliance. He is the PAREXEL practice lead for Quality by Design.

Dr. Schmitt's areas of expertise include all aspects of quality and compliance for systems, processes, facilities and operations for drug substances and drug products, for all types of formulations.

He has previously held positions in industry as Senior Production Chemist with Roche and global Quality Director with GE Healthcare and as Validation Manager with Raytheon and Senior Lead Consultant with ABB.

He is an active member of various industry associations, including DIA, PDA, RAPS and ISPE, conference presenter and organizer of international events. He is also an accomplished author and editor, and member or chairman of several boards of editors.

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