AXENDIA™

DATA INTEGRITY

The Foundation of Good Science

An Axendia eBook Presented by Dassault Systèmes

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Abstract

Healthcare is shifting to a Value Based model focused on improving the quality of patient outcomes, enhancing patient-centered care and adopting initiatives that control costs. The transition to Value Based Healthcare hinges on the availability of unbiased quality and outcomes data. Furthermore, the integrity of these decisions depends upon the accurate and objective analysis of these data to support patient care decisions.

Sound data is the foundation to good decisions and good science. In the Life-Science industry, patient outcomes, product quality, safety and efficacy all rely upon vast amounts of data that is generated throughout the product lifecycle. This means that patients and the equity and reputations of brand owners have the potential to suffer greatly without a strong Data Integrity foundation.

In recent years, regulators around the world have increasingly observed cGMP violations involving data during inspections. According to FDA's data, 14 of 23 warning letters issued by the Office of Manufacturing Quality referenced Data Integrity in the period from January 2015 to January 2016[1].

Data Integrity findings have led to warning letters, import alerts and consent decrees. One FDA warning letter specifically called out, "serious CGMP violations demonstrating that your quality system does not adequately ensure the accuracy and integrity of the data generated at your facility to ensure the safety, effectiveness, and quality of the drug products you manufacture[2]."

Examples of significant Data Integrity issues identified by the FDA[3] include:

- No raw data to support records
- Creating inaccurate and incomplete records
- Test results for one batch used to release other batches
- Backdating
- Fabricating data
- Discarding data

This is proof that the lack of Data Integrity has the potential to call into question an organization's entire quality system.

The Medicines and Healthcare products Regulatory Agency (MHRA) has also reported that Data Integrity has been a top priority for the Life Science industry in the UK. Published in March 2018, MHRA's Guidance on GxP Data Integrity[4] calls out fundamental failures identified by the agency and international regulatory partners during GxP inspections; many of which resulted in regulatory actions. Noteworthy is the often misconceived notion that acts of deliberate fraud are the root cause of Data Integrity issues. However, the MHRA Inspectorate has determined that bad practices, poor organizational behaviors and weak systems have created opportunities for data manipulation. To address these types of issues, companies should consider leading from the top and empowering from below, understanding the data lifecycle and giving special considerations to organizational and technical controls within the quality system leveraging the technologies available to the industry.

[1] http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm504306.pdf
[2] http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm432709.htm
[3] https://www.pda.org/docs/default-source/website-document-library/chapters/presentations/missouri-valley/data-integrity-issues-concerns.pdf?sfvrsn=4
[4] https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity

What Is Data Integrity?

FDA has defined Data integrity as the completeness, consistency and accuracy of data[5]. Complete, consistent and accurate data have the following attributes (using the acronym ALCOA):

A Attributable
data means knowing who put the data in, where, when and what system it came from

L Legible
data ensures whoever needs to read or interpret the data, can easily and clearly do so

C Contemporaneously
recorded data includes the time data was gathered, recorded and/or looked at

O Original,
first recording of data, raw or source data, or a certified true copy

A Accurate
data is correct including context/meaning (e.g., metadata) and edits

In a December 2018 press release[6], FDA Commissioner Scott Gottlieb, MD, announced the agency has updated the 2016 Guidance on Data Integrity with Data Integrity and Compliance With Drug CGMP: Questions and Answers, Guidance for Industry. Gottlieb also stated, "Companies need to create a quality culture where employees understand the seriousness of Data Integrity and promote Data Integrity as a core value. A work environment where employees are encouraged to promptly identify and properly report data issues is essential to product safety."

The guidance covers the design, operation, and monitoring of systems and controls to maintain Data Integrity. The agency revised the guidance in response to public comments requesting additional details on the agency's thinking on current best practices.

> "Companies need to create a quality culture where employees understand the seriousness of Data Integrity and promote Data Integrity as a core value."
>
> **Scott Gottlieb, MD,**
> Commissioner, US FDA

The revised recommendations are aimed at helping manufacturers address identified Data Integrity lapses, implement best practices to address gaps that can create risks to Data Integrity, and ensure consistent awareness and commitment to ensuring Data Integrity. It explicitly states: It is the role of management with executive responsibility to create a quality culture where employees understand that Data Integrity is an organizational core value and employees are encouraged to identify and promptly report Data Integrity issues. In the absence of management support of a quality culture, quality systems can break down and lead to CGMP noncompliance.

[5] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf
[6] https://bit.ly/2QLTYFK

Is 160º Porridge Too Hot, Too Cold Or Just Right?

Answer: It depends on the context. A data value by itself is meaningless without additional information about the data. Metadata is often described as data about data. Metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data.

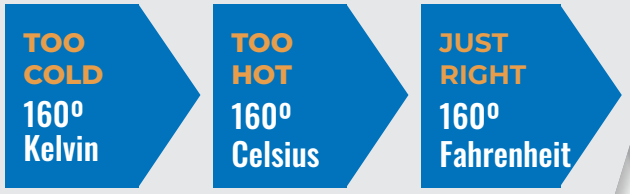
To determine whether the data is reliable, additional questions regarding the metadata must be considered (see the Infographic "What Goldilocks and Life-Sciences Companies Have in Common?")

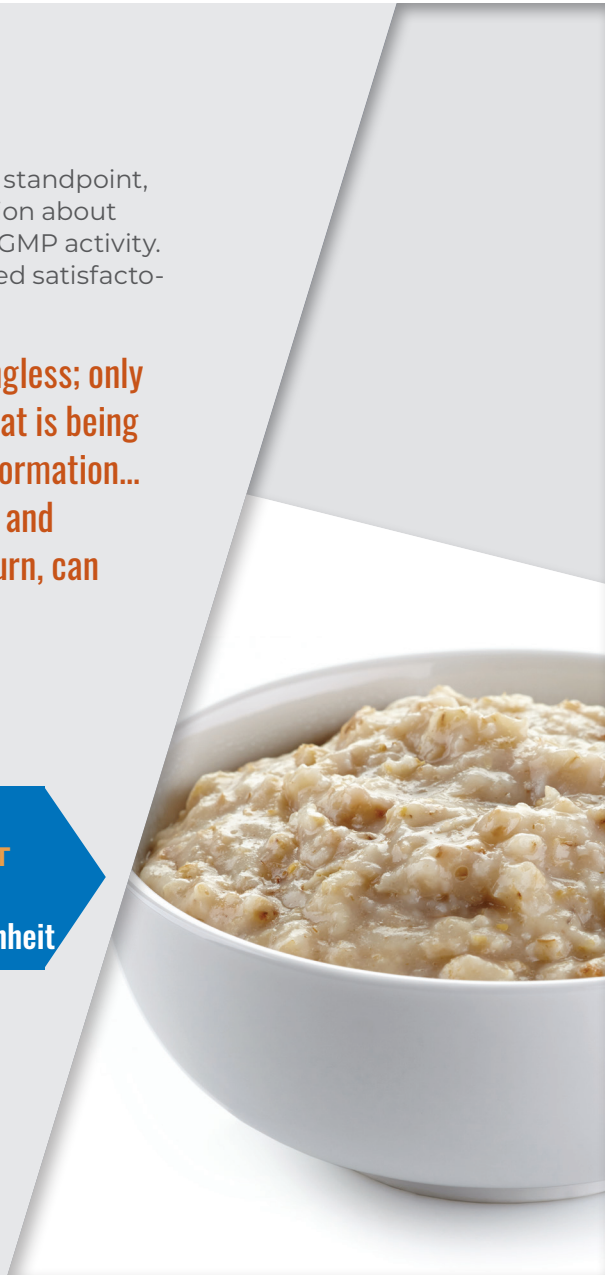
- When was the temperature taken and who took it?
- How was the data recorded? Is it legible?
- Was the temperature measured correctly?
- Was the right tool used to measure it?
- Was the thermometer properly calibrated?
- Was the calibration in effect when the measurement was taken?
- Was the temperature within specification?
- Were the right temperature units used?

Data by itself is not enough. From a GMP standpoint, metadata is all of the additional information about the data that is used to reconstruct the cGMP activity. Assuming all the questions were answered satisfactorily, Goldilocks would find that:

"By themselves they (data) are meaningless; only when we add critical context about what is being measured and how do they become information... That information can then be analyzed and combined to yield evidence, which in turn, can be used to guide decision-making[7]."

Robert M. Califf, M.D.,
Former FDA Commissioner stated,





[7] Source: http://blogs.fda.gov/fdavoice/index.php/2015/12/what-we-mean-when-we-talk-about-data/?source=govdelivery-&utm_medium=email&utm_source=govdelivery

How Does Data Integrity Enable Good Decision Making?

Data Integrity is a foundational requirement for a strong and reliable quality system that enables sound decisions based on scientific facts. This applies equally to manual (paper) or electronic systems — regardless of where the data came from. The pursuit of Data Integrity promotes a quality culture within an organization. It requires participation and commitment by all staff levels as well as supplier networks and distributors – from suppliers of raw materials to the end user.

Finally, Data Integrity enables senior management to assess Data Integrity risks for mitigation and communication in accordance with the principles of quality risk management. Data Integrity starts with senior management commitment but permeates throughout the entire value chain.

Who Is Responsible For Data Integrity?

Data Integrity is ultimately the responsibility of Senior Management[8]. There needs to be a master data management system that supports governance around data in order to support its integrity. However, for the system to have value, participation and commitment by staff at all levels (both internal and external resources) is necessary. The tools to support Data Integrity include management commitment, policies and procedures, education and technical controls.

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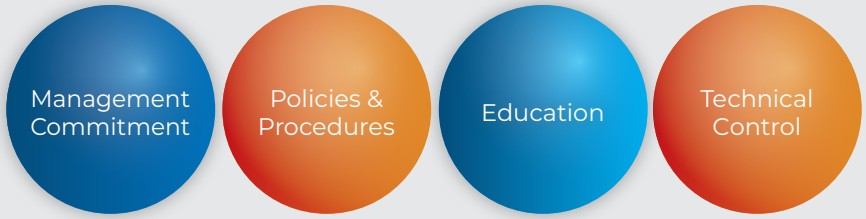
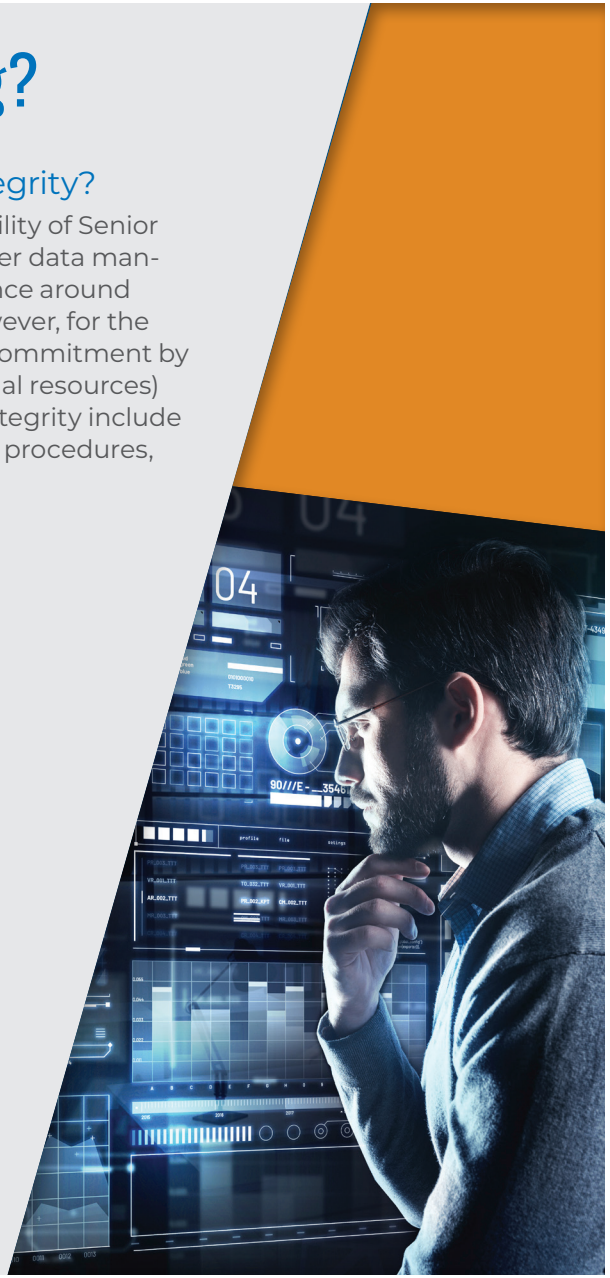
Tools to Support Data Integrity Include





[8] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section16

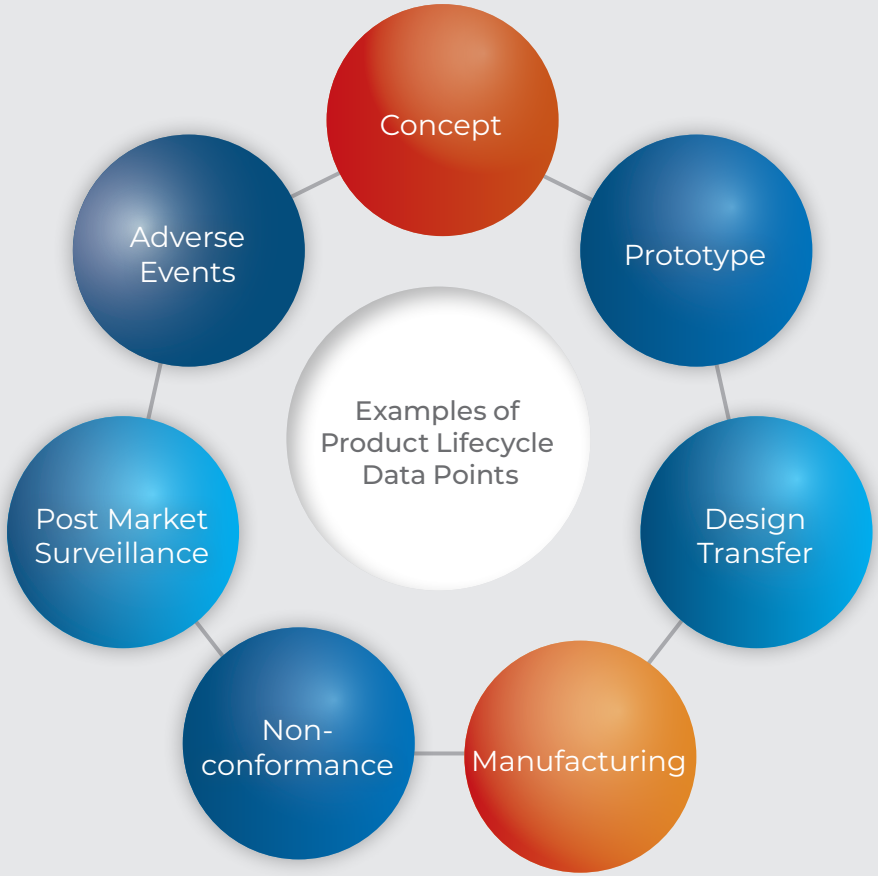
So Much Data, So Little Intelligence

Companies regulated by the FDA are obsessed with collecting data, retaining and hoarding it to meet statutory and regulatory requirements. Unfortunately, most companies do not harness this data to produce better quality products. As a result, companies are data rich but Intelligence poor.

An example of data points typically collected throughout a product's lifecycle include: concept, prototype, design transfer, manufacturing, non-conformances, post market surveillance, adverse events.

Vast amounts of data are generated by a multitude of systems, but unfortunately very little Intelligence is available regarding how this information can be harnessed to produce a better quality product. The integrity of this data is vital to showing FDA a company's commitment to compliance. However, compliance and quality are not the same!

Life Science companies are in business to make high quality, life-sustaining products, not documents.



FDA Is Shifting Focus

There are new FDA initiatives being promulgated to industry such as the *Case for Quality* to consider compliance as a baseline and quality as an investment. Collecting documented evidence of compliance with regulatory requirements is an overhead cost – it does not add value. Being in business to be compliant is different from being in the compliance business. Life Science companies are in business to make high quality, life-sustaining products, not documents.

With the implementation of FDASIA Title VII Section 706[9], the FDA is shifting its focus to requesting information in advance of, or in lieu of, an inspection in either electronic or physical form. This shift to e-Inspections of drug manufacturers requires massive amounts of data and information that can only be as good as the quality of available data and analytic tools used.

FDA's Quality Metrics program is a key step in the Agency's objective to encourage industry to implement state-of-the-art, innovative quality management systems that drive industry to focus on improving product quality, rather than simply ensuring compliance to regulatory requirements.

To support this effort, the agency has released a guidance document on the Submission of Quality Metrics Data[10]. These include:

- Lot Acceptance Rate (LAR)
- Product Quality Complaint Rate (PQCR)
- Invalidated Out-of-Specification (OOS) Rate (IOOSR)

In a Q&A with the Agency[11], we asked how the FDA intends to use Quality Metrics data to benefit the Agency, Industry, Providers and ultimately the patient? FDA answered with, "Quality Metrics data reporting is the first step in enabling a new approach – a potential step-change – in regulatory oversight of pharmaceutical products. Additional quantitative and objective insight into the state of quality for the product and facility will allow FDA to reduce other types of oversight, such as the frequency of on-site surveillance inspections. This insight will also enable us to improve the effectiveness of inspections when they are conducted and help to identify factors leading to supply chain disruption. Improving overall product quality and potentially identifying the potential for drug shortage early will benefit patients. Long term success of the Quality Metrics Program will largely be driven by the extent of participation, since a large body of data is needed to draw the most meaningful conclusions about the quality of a site or product."

> "Quality metrics data reporting is the first step in enabling a new approach — a potential step-change — in regulatory oversight of pharmaceutical products."
>
> Source: FDA response to Axendia inquiry, August 1, 2018

Quality is the initiative that drives improvements, to streamline processes resulting in operational efficiencies and reduced waste. Therefore, investing in improving product quality can actually lower costs and improve profitability. To support this transition from compliance to quality, it is necessary to transform data into truth.

In a presentation titled "Data Integrity Issues and Concerns," the FDA pointed out that Data Integrity issues break trust and that the agency relies on firms 'to do the right thing' when the FDA is not present.[12]

[9] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section16
[10] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm455957.pdf
[11] http://axendia.com/blog/2018/08/22/do-you-want-less-fda-inspections-here-is-fdas-rx/
[12] https://www.pda.org/docs/default-source/website-document-library/chapters/presentations/missouri-valley/data-integrity-issues-concerns.pdf?sfvrsn=4c

Why Should You Focus On Data Integrity?

The problem is not that we don't have enough systems but that there we have too many systems. As a result, managing data across multiple systems – seeking a single source of truth – becomes a challenge. Having a platform that allows you to ensure Data Integrity, connect the dots and turning that data into knowledge, is critical to support this process.

To achieve Data Integrity, companies need to have controls (whether electronic or paper) over the system, validation and supporting evidence. Technical Controls include access control / passwords, audit trails, metadata and supporting evidence.

Digital transformation and continuity – the ability to transform processes – should not be confused with digitalization. Simply digitizing poor data does not improve it or achieve the integrity needed. In fact, it exacerbates it by producing more substandard output more quickly.

In "Innovation Through Digital Continuity" we discuss how most people today, consume data as static documents. These documents, however, often represent dynamic processes where data can be managed and parameters can be defined.

The first step towards transformation is information efficiency and transitioning from the old paradigm of managing static documents to the new paradigm where documents are the graphical representation of the data... not the end in and of themselves. In the new paradigm, one can use the integrated systems to interpret data, get ranges, tolerances and other metrics in a context that is relevant to the decision being made.

Data and data models can be managed to support digital continuity and promote visibility to support continuous improvement across the product lifecycle. A connected system is a dynamic system providing digital continuity to allow people to *follow the drug, not the documents,* permitting full traceability downstream or upstream (i.e. raw materials to patient to outcome). It can also be used to support Regulatory changes to enable more efficient adoption of innovative technologies, regulatory evaluation, both in review and inspection, and over the product lifecycle.

Data Integrity is the foundation that supports good science.

A connected system is a dynamic system providing digital continuity to allow people to follow the drug, not the documents, permitting full traceability.

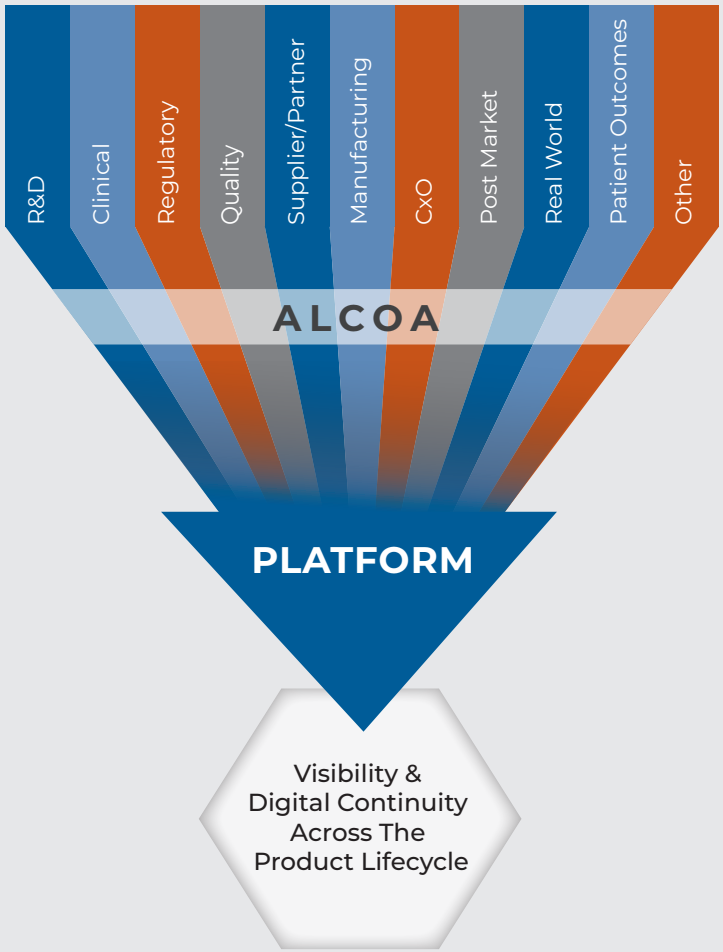
What Are The Components Of An Optimal Solution?

According the Paula Katz, Director of Manufacturing Quality Guidance and Policy Staff at CDER Office of Compliance, "Data Integrity problems are not always intentional; sometimes they result from poorly controlled systems[13]."

As a result, the optimal solution will include a Data Integrity strategy. Data Integrity needs to be consistent across the entire domain and throughout the product lifecycle from research and development to quality and manufacturing.

A platform approach allows a company to integrate data applications, processes and people across the organization as well as external organizations. Data sources can be integrated with data consuming applications from the business, manufacturing, laboratory and quality areas. This will allow users across the value chain to access, organize, analyze and share scientific, quality and process data with full confidence of their integrity.

At the same time, the solution should have the capabilities for enterprise quality and data management, laboratory informatics and data analytics. This approach supports digital continuity – the ability to maintain the digital information of a creator in such a way that the information will be available, as needed and where needed. It focuses on making sure that information is unaltered, complete, available and therefore usable.



"...Data Integrity problems are not always intentional; sometimes they result from poorly controlled systems."

Paula Katz
Director of Manufacturing Quality Guidance and Policy Staff
CDER Office of Compliance

[13] http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm504306.pdf

Conclusion

The transition to Value Based Healthcare hinges on the availability of unbiased quality and outcomes data. Furthermore, the integrity of these decisions depends upon the accurate and objective analysis of these data to support patient care decisions.

For sound data to be the foundation for good decisions and good science, there can be no questions with regards to its integrity. Patient outcomes, product quality, safety and efficacy of products rely upon vast amounts of data that are generated throughout the product lifecycle. Much of this data is often produced by a multitude of disconnected stand-alone or redundant systems that were generally implemented by functional areas to address specific needs. This disconnect can result in a lack of Data Integrity and consistency. Therefore patients, brand equity and reputations have the potential to suffer without a strong foundation for Data Integrity. By taking a platform approach, companies can integrate data consuming applications that support business, manufacturing, laboratory and quality areas.

As regulators encourage industry to implement state-of-the-art, innovative quality management systems shifting from documents to Quality Metrics, Data Integrity becomes critical to support decision making and show regulatory agencies your commitment to quality.

Data Integrity is ultimately the responsibility of executive management. These teams must be committed to ensuring that a master data management system supports governance around data in order to support its integrity. However, for the system to have value, participation and commitment by staff at all levels (both internal and external resources) is necessary in order to support a single source of truth.

Is your company doing good science? Without Data Integrity, the results of that science can be in question.

Acknowledgments

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