Data Integrity Implementation Strategy for Pharma Industry

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***Abstract* —** *Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality as decisions on product quality are made based on the data. Electronic data and computerized systems have introduced new challenges to maintain data integrity; hence the data governance system should be integral to the pharmaceutical quality system as required by regulatory authorities as Food and Drug Administration (FDA) and Healthcare Products Regulatory Agency (MHRA). Data integrity requirements apply equally to manual (paper) and electronic data. The regulatory authorities have put much emphasis on data integrity in recent years because they uncovered serious cases of data integrity breaches. This project supports the pharma industry goal and success of operational excellence with zero FDA's alerts related to Data Integrity. This should also be a model to all plant sites within the same problem and avoid CGMP's violations or issues involving data integrity.*

Key Terms *— ALCOA, Data Integrity, ERES, GMP's.*

INTRODUCTION

Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality as decisions on product quality are made based on the data. Electronic data and computerized systems have introduced new challenges to maintain data integrity; hence the data governance system should be integral to the pharmaceutical quality system as required by regulatory authorities as Food and Drug Administration (FDA) and Healthcare Products Regulatory Agency (MHRA). The effort and resource assigned to data governance should be commensurate with the risk to product quality, and should also be balanced with other quality assurance resource demands. The manufacturers and analytical laboratories shall design and operate a system which provides an acceptable state of control based on the data integrity risk, and which is fully documented with supporting rationale.

Data integrity requirements apply equally to manual (paper) and electronic data. The regulatory authorities have put much emphasis on data integrity in recent years because they uncovered serious cases of data integrity breaches. It is always better to proactively prevent issues, such as data integrity failures to occur, then trying to remediate and resolve inspections findings. Compliances excellence makes good business sense.

This document provides the strategy to prevent the data integrity breaches by design, by procedural control and monitoring. Guidance of regulatory agencies and requirements to compliance with CGMP's.

RESEARCH OBJECTIVES

The main objective of this project is implement data integrity strategy for pharma industry to ensure high performance by complying with all regulations stipulated by regulatory authorities.

RESEARCH CONTRIBUTIONS

This project supports the pharma industry goal and success of operational excellence with zero FDA's alerts related to Data Integrity. This should also be a model to all plant sites within the same problem and avoid CGMP's violations or issues involving data integrity.

RESEARCH BACKGROUND & METHODOLOGY

In recent years, FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy and quality of drugs. These data integrity related CGMP violations have led to numerous regulatory actions, including warning letters, import alerts and consent decrees.

Data integrity is critical to regulatory compliance. USFDA has published the 21 CFR Part 11 and EU has published Annex 11 to spell out the requirement with respect to computerized system. 21 CFR Part 11 came into effect in 1997 and applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in Agency applies to all forms of computers part of a GMP regulated activities. A computerized system is a set of software and hardware components which together full fill certain functionalities. The application shall be validated, IT infrastructure shall be qualified [1]. Where a computerized system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process. Both FDA and MHRA use the acronym ALCOA to define its expectations of electronic data refer to figure 1 [2].

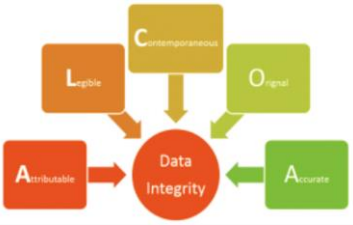


Figure 1
ALCOA

Attribute - The identity of the person creating a record should be documented. For paper records this is normally done by the individual signing and dating the record with their signature.

As the record, you may be signing may be legal document, you should clearly understand the implication of your signature.

A signature should be individual to a specific individual and the practice of signing someone else's name or initials is fraud and is taken very seriously.

Legible - A record that cannot be read or understood has no value and might as well no exist. All records should be composed so they conform to grammatical convention which should be consistent throughout.

It is best to avoid buzzwords, cliques and slang as these are prone to change with time and are often not understood outside a particular locality.

It is always good practice to have any record reviewed by a second person as this can often highlight any ambiguities.

Contemporaneous - All records must be made at the time an activity takes place. Delaying writing up, for example until the end of the day, will inevitably affect the accuracy of that record as details can be forgotten or miss-remembered.

Original - All records must be original; information must be recorded directly onto the document. This avoids the potential of introducing errors in transcribing information between documents.

If information from an instrument is printed out, by the instrument, that printout is the original record and should be signed, dated and attached to the record.

Accurate - The record must reflect what actually happened. Any changes made to a record should be signed by the person making the change and dated to show when it was made and a written explanation should also be provided. Any changes should be made without obscuring or obliterating the original information, the use of whiteout or correction fluid is prohibited.

Remember, the record may be needed after you have left the company and cannot be contacted for clarification [3].

Generic Drug Scandal - In 1989, a major scandal erupted involving the procedures used by the FDA to approve generic drugs for sale to the public. Charges of corruption in generic drug approval first emerged in 1988, in the course of an extensive congressional investigation into the FDA. Investigation discovered that several manufacturers had falsified data submitted in seeking FDA authorization to market certain generic drugs. In April 1989, the FDA investigated 13 manufacturers for irregularities; and Dozens of drugs were eventually suspended or recalled by manufacturers [4].

At the outset of the generic drug scandal uncovered in the late 1980's FDA developed an administrative Application Integrity Policy. At or about the same time, legislation (the Generic Drug Enforcement Act [GDEA] of 1992), provided for debarment of individuals convicted of certain misdemeanor or felony offenses. This meant that an individual that was convicted could be debarred permanently from providing directly or indirectly any services in any capacity to a firm in the pharmaceutical industry. This is interpreted to include any service (including cutting the grass) if employed by a pharmaceutical company.

During the generic drug scandal, there were 22 criminal convictions of drug companies and 70 convictions of industry and FDA personnel as well as $50 million in fines levied against these organizations and individuals. Eventually there were some 70 individual debarment actions relating to the shenanigans that occurred but to date no firm has been debarred under the provisions of the GDEA. Following are the number of debarments looked like over the last few years. Refer to table 1.

Table 1
Debarments

Year	Numbers of Debarments
2013	4
2012	13
2011	18

Most of the debarments seen now are either for clinical investigators that have falsified study records, individuals that have engaged in the distribution of unapproved drugs or those that have perpetrated mail fraud or some other type of fraud. One must remember that debarment can be permanent or permissive (with a defined period of time usually from 5-10 years).

So even after the lessons of the past, there are some that continue try to beat the system, perform illegal activities or fraudulently create data for their own gain or the gain of others. The saying that history has a tendency to repeat itself appears to be true when speaking of issues that could result in debarment. We need to learn from the past before it is forgotten.

Review of Warning letters issued by FDA related to data integrity - During inspections, the FDA verifies that a firm's procedures and processes are in compliance with FDA GxP regulations such as Good Laboratory Practices, Good Clinical Practices, and Good Manufacturing Practices. If the FDA inspections identify deviations from the regulations, they will issue inspectional observations using 483 forms, also referred to as "483s" or inspectional observations. Depending on the severity of the deviations, instances of repeat observations, and a firm's response to the 483, the FDA may issue a formal letter listing some or all deviations of the 483, called an FDA Warning Letter.

One of the top global issues reported in the pharmaceutical media over the past 2 years has been data integrity. Regulatory actions resulting from data integrity failures have led to the withdrawal of supply across multiple markets, product recall, and serious reputational damage for those companies concerned. However, this hot topic is not a new requirement, as basic data integrity principles are already described in international good manufacturing practice guidance [5].

Author reviewed the FDA web site and identified that total 59 Warning Letters were issued worldwide to the pharmaceutical industries from

Jan-2012 to Jun-2014. These are further categorized as below. Refer to Table 2.

Table 2
Warning Letters

Categorized	Warning Letters
API Manufacturing	12
Finished Pharmaceuticals	46
Testing Laboratories	1

The observations related to laboratory control are sub-classified as depicted in the Fig 2. Most of the observations are pertaining to breach of data integrity in the laboratory e.g. unauthorized changes in electronic data, falsification of data, false data recording, lack of computer system control, incoming material testing etc.

The observations related to laboratory control are sub-classified as depicted in the Fig 3. Most of the observations are pertaining to breach of data integrity in the manufacturing e.g. Torn GMP documents found in the waste bin, microbial contamination, lack of computer system control etc. Most of the companies who found engaged in the data integrity issues, FDA has issued them import alert notification means these companies cannot further export the products to US market till the issues are resolved to the satisfaction of USFDA.

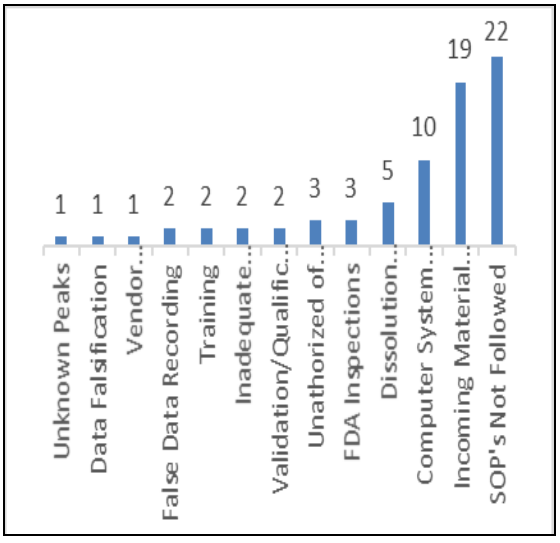


Figure 2
Warning Letters Laboratory Control

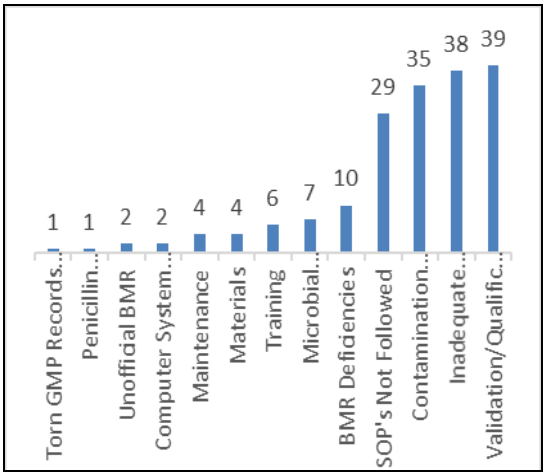


Figure 3
Warning Letters Manufacturing Control and Quality System

Data integrity issues may result into warning letters, import alerts and penalties to the organization. To the individuals who are involvement in the wrong doings, it can be debarment and imprisonment.

RESULTS & DISCUSSION

The methodology followed was the implementation of strategies to avoid Data Integrity. Following are the recommendations to avoid any data integrity issues and avoid any regulatory impact during the audits.

Defining (limiting) Scope - Defining what must be in scope for the strategy is one of the most important elements to get right to ensure A) time and effort is invested correctly by your organization, and B) a quality, consistent approach to all data integrity controls are in place. The scope can be defined by identifying which systems and within which areas are subject to both 21 CFR Part 11 requirements, and also EU GMP Annex 11 requirements. This can be done via the aid of a decisions tree as the one shown in Figure 4 [6].

What is equally important is being clear about what should not be in scope to avoid any ambiguity. One must look at their respective data generating processes (both laboratory and production) and avoid being distracted by administrative IT systems. This is essential as the

focus must be on critical systems handling product quality or patient safety relevant GMP-data.

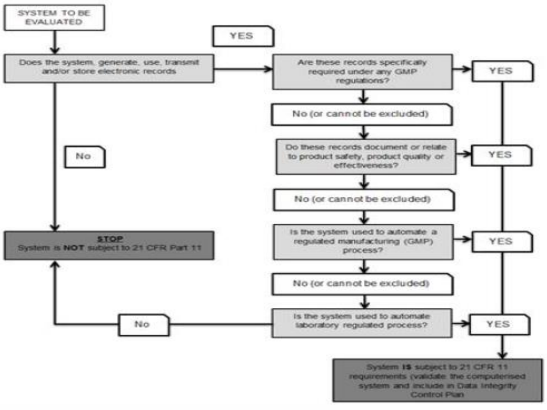


Figure 4
System Evaluation Decision Tree

Building and Sustaining the Quality culture in the organization - There is a general misconception that data integrity failures only result from acts of deliberate fraud. The majority of issues relate to bad practice, poor organizational behavior and weak systems, which create opportunities for data to be manipulated. However, there is a way for companies to navigate the troubled waters of data integrity deficiencies by taking some basic behavioral, procedural and technical steps to significantly improve their systems.

Culture is symbolic communication. Some of its symbols include a group's skills, knowledge, attitudes, values, and motives. The meanings of the symbols are learned and deliberately perpetuated in a society through its institutions. A quality focused culture:

- Creates a healthy work environment
- Develops people
- Enables managers to guide effectively
- Staff feels that their efforts are worthwhile
- Leads to satisfied customers

Follow a software development lifecycle- A Software Development lifecycle methodology helps oversee that quality related tasks are performed to address pertinent lifecycle phases from software development, software testing, integration and installation to ongoing system maintenance. All computer systems should be appropriately developed, qualified, tested and assessed on a regular basis. Refer to Figure 5 [7].

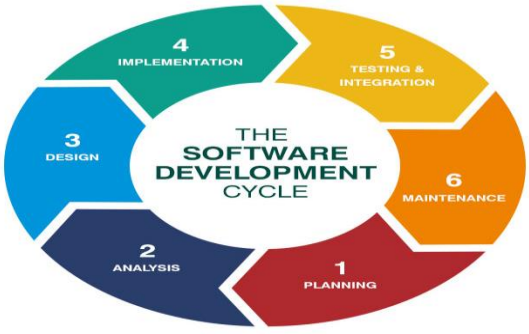


Figure 5
Software Development Life Cycle

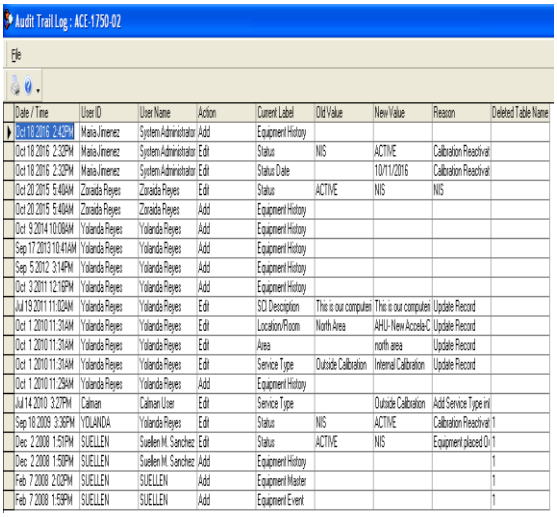
Validate your computer systems - Software Validation provides documented evidence to deliver assurance that a specific process consistently produces a product that meets its pre-determined specifications and quality attributes. To ensure your system can be validated, it is key to work with vendors that provide validation. Refer to Figure 6.

Figure 6
Computer System Validation

Implement audit trails – Audit trial is a security-relevant chronological record, set of records, and/or destination and source of records that provide documentary evidence of the sequence of activities that have affected at any time a specific operation, procedure, or event.

A secure, computer-generated, time-stamped audit trail records the identity, date and time of data entries, changes, and deletions. Audit trails ensure the trustworthiness of the electronic record, demonstrate necessary data ownership and assure

records have not been modified or deleted. Refer to Figure 7.


Audit Trail Log : ACE-1750-02

File

Date / Time	User ID	User Name	Action	Current Label	Old Value	New Value	Reason	Deleted Table Name
Oct 18 2016 2:42PM	Maira.Jimenez	System Administrator	Add	Equipment History				
Oct 18 2016 2:32PM	Maira.Jimenez	System Administrator	Edit	Status	NIS	ACTIVE	Calibration Reactivat	
Oct 18 2016 2:32PM	Maira.Jimenez	System Administrator	Edit	Status Date		10/11/2016	Calibration Reactivat	
Oct 20 2015 5:40AM	Zoraida Reyes	Zoraida Reyes	Edit	Status	ACTIVE	NIS	NIS	
Oct 20 2015 5:40AM	Zoraida Reyes	Zoraida Reyes	Add	Equipment History				
Oct 9 2014 10:08AM	Yolanda Reyes	Yolanda Reyes	Add	Equipment History				
Sep 17 2013 10:41AM	Yolanda Reyes	Yolanda Reyes	Add	Equipment History				
Sep 5 2012 3:14PM	Yolanda Reyes	Yolanda Reyes	Add	Equipment History				
Oct 3 2011 12:16PM	Yolanda Reyes	Yolanda Reyes	Add	Equipment History				
Jul 19 2011 11:02AM	Yolanda Reyes	Yolanda Reyes	Edit	SCI Description	This is our computeri	This is our computeri	Update Record	
Oct 1 2010 11:31AM	Yolanda Reyes	Yolanda Reyes	Edit	Location/Room	North Area	AHU-New Access C	Update Record	
Oct 1 2010 11:31AM	Yolanda Reyes	Yolanda Reyes	Edit	Area		north area	Update Record	
Oct 1 2010 11:31AM	Yolanda Reyes	Yolanda Reyes	Edit	Service Type	Outside Calibration	Internal Calibration	Update Record	
Oct 1 2010 11:29AM	Yolanda Reyes	Yolanda Reyes	Add	Equipment History				
Jul 14 2010 3:27PM	Calman	Calman User	Edit	Service Type		Outside Calibration	Add Service Type inf	
Sep 16 2009 3:36PM	YOLANDA	Yolanda Reyes	Edit	Status	NIS	ACTIVE	Calibration Reactivat	1
Dec 2 2008 1:51PM	SUELLEN	Suellen M. Sanchez	Edit	Status	ACTIVE	NIS	Equipment placed O	1
Dec 2 2008 1:50PM	SUELLEN	Suellen M. Sanchez	Add	Equipment History				1
Feb 7 2008 2:02PM	SUELLEN	SUELLEN	Add	Equipment Master				1
Feb 7 2008 1:59PM	SUELLEN	SUELLEN	Add	Equipment Event				1

Figure 7
Audit Trial

Maintain backup and recovery procedures - A Quality Management System with Standard Operating Procedures builds quality into the process by systematically controlling the process. It is essential to write and follow good effective procedures to ensure clear accountability.

Control By procedure - Remember that procedural controls are needed in the pharmaceutical organization. The following are title of the SOPs that can be available with clear objective, defined responsibility and instructions to the users:

- System Maintenance
- Incident Management
- Operational Change Management
- Periodic Review
- Data Backup, Archiving and Restore
- Disaster Recovery
- Security Management
- Business Continuity Planning
- Security Management
- System Administration
- Archiving and Retrieval

Risk Management - Risk management should be applied throughout the lifecycle of the computerized system taking into account patient safety, data integrity and product quality. Decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerized system. Refer to Table 3 [8].

Table 3
FEMA Risk Assessment

	Pre-mitigation						Post-mitigation					
	Severity						Severity					
Functions	Q	C	B	S	O	D	RF	Q	C	B	S	O	D	RF
Operational Functions														
Wavelength accuracy	H	H	H	H	M	H	H	H	H	H	H	L	L	L
Wavelength reproducibility	H	H	H	H	M	H	H	H	H	H	H	L	L	L
Spectral resolution	H	H	H	H	M	H	H	H	H	H	H	L	L	L
Stray light	H	H	H	H	M	H	H	H	H	H	H	L	L	L
Photometric stability	H	H	H	H	H	H	H	H	H	H	H	L	L	L
Photometric noise	H	H	H	H	H	H	H	H	H	H	H	L	L	L
Spectral base line flatness	H	H	H	H	H	H	H	H	H	H	H	L	L	L
Photometric accuracy	H	H	H	H	H	H	H	H	H	H	H	L	L	L
Quality and Data Integrity Functions														
Access Controls	H	H	H	H	L	L	L	H	H	H	H	L	L	L
Electronic Signatures	H	H	H	H	L	L	L	H	H	H	H	L	L	L
Password Controls	H	H	H	H	L	L	L	H	H	H	H	L	L	L
Data Security	H	H	H	H	L	L	L	H	H	H	H	L	L	L
Audit Trail	H	H	H	H	L	L	L	H	H	H	H	L	L	L
Time Stamps	H	H	H	H	L	L	L	H	H	H	H	L	L	L

H = High, M = Medium, L = Low
Q = Quality, C = Compliance, B = Business, S = Severity, O = probability of Occurrence,
D = Non-Detectability, RF = Risk Factor

CONCLUSIONS

Both FDA and MHRA use the acronym ALCOA to define its expectations on data integrity. Electronic data and computerized systems have introduced new challenges to maintain data integrity; hence the data governance system should be integral to the pharmaceutical quality system as required by regulatory authorities as Food and Drug Administration (FDA) and Healthcare Products Regulatory Agency (MHRA). Data integrity requirements apply equally to manual (paper) and electronic data. The regulatory authorities have put much emphasis on data integrity in recent years because they uncovered serious cases of data integrity breaches. This project supports the pharma industry goal and success of operational excellence with zero FDA's alerts related to Data Integrity. This should also be a model to all plant sites within the same problem and avoid CGMP's violations or issues involving data integrity.

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