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Role of Computer System Validation to Safeguard Data Integrity in Pharmaceutical Industry-A Review

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ABSTRACT : *In the pharmaceutical sector computer systems are integrated into the regular operations. The process or operation being controlled or monitored by the computer system, the procedural controls, process-related documentation, and the people. Computer systems performing regulated operations may control the quality of a product during its development, testing, manufacturing, and handling processes; manage information business operations; manage data used to prove the safety; efficacy and quality of the product and formulation.*

To provide the guidance to the industry on computer systems, 21 CFR PART 11 regulations are established in 1997 by the US FDA to elucidate the criteria under which USFDA considers electronic records and electronic signatures are trustworthy and reliable as equal as manual records and handwritten signatures.

The first most requirements for 21 CFR Part 11 electronic records is "11.10 (a): Validation of systems to ensure accuracy, reliability, consistent intended performance……" Here the word validation refers Computerized System Validation (CSV).

Though requirement of CSV is notified 21 CFR Part 11.10 (a) in 1997, discussion on CSV is enormous in the pharmaceutical industry in recent years due to lapse in data integrity. In recent times regulatory authorities, mainly US FDA issued increased number of warning letters/import alerts for several pharmaceutical companies including major established organizations for decades

The aims of this study to emphasize the role of computer system validation to ensure data integrity, compliance on computer systems being used in the pharmaceutical industry.

KEY WORDS:-*21 CFR PART 11,Computerized System Validation (CSV),US FDA, System Validation.*

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I. INTRODUCTION

This document explains the importance of data integrity in pharmaceutical industry and consequences of data integrity breaches. Also explains the role of GAMP computer system validation approach to establish, verify and maintain the system and procedural controls as established in US FDA 21 CFR Part 11 regulations.

Data integrity:Data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.

21 CFR Part 11: Title 21 CFR Part 11 is the part of Title 21 of the Code of Federal Regulations that establishes the United States Food and Drug Administration (FDA) regulations on electronic records and electronic signatures (ERES).

GAMP:Good automated manufacturing practice (GAMP) is both a technical subcommittee of the International Society for Pharmaceutical Engineering (ISPE) and a set of guidelines for manufacturers and users of automated systems in the pharmaceutical industry.

Computer system validation:It is process ofconfirmation by examination and provision of objective evidence that computer system specifications conform to user needs and intended uses, and that all requirements can be consistently fulfilled

II. DISCUSSION

3.1 21 CFR Part 11

Automation and electronic records have some significant advantages over paper records: cost effective, lower space and easier retrieval are just a few of those advantages. In the late 1980's considering futuristic need of regulation on electronic records and electronic signatures United States Food and Drug Administration (FDA) issued criteria for acceptance of electronic records and signatures i.e.21 CFR Part 11 regulations.

After the release of 21 CFR Part 11 regulations, industry had some confusion on scope of part 11 with respect to the records required to be maintained under predicate rules or submitted to the FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply.

To clarify industry confusion and to elaborate the scope of part 11, US FDA released "Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application" in 2003 and it indicates "Records that are required to be maintained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities". These records can be called as GxP records.

The most important requirement for Part 11 are mentioned below

✔ System Validation - 11.10(a)
✔ Limited Access - 11.10(d)
✔ Audit Trails - 11.10(e)
✔ Enforcement of Permitted Sequencing - 11.10(f)
✔ Use of Authority Checks - 11.10(g)
✔ People Qualification - 11.10(i)
✔ Individual Accountability - 11.10(j)
✔ Controls Over System Documentation -11.10(k)

If a computerized system fully complies with 21 CFR Part 11 requirements data integrity laps can be controlled efficiently. Computer system validation is an important tool to evaluate the computerized system, whether meeting 21 CFR Part 11 regulations.

3.2 21 CFR Part 211.68

These requirements are established prior to 21 CFR Part 11 and describe the requirements of computer or related systems briefly. Important requirements of Part 211.68 are given below

-Validation
- Backup, retention and security
- Controls on access, changes and inadvertent erasures, or loss

Part 11 enhances Section 211.68 by providing additional requirements associated with computer systems performing operations covered by the US FDA

Most of the observations on computerized systems by US FDA are cited against 21 CFR part 211 resembling "Appropriate controls are not exercised over computers or related systems...Specifically…" In fact those observations can be cited against 21 CFR Part 11.

3.3 GAMP 5

GAMP 5 guide offers A Risk-Based Approach to Compliant GxP Computerized Systems. It is set of guidelines designed by industry experts to help companies understand and meet cGMP regulation for computerized systems. This guide gives enough information on validation and compliance of computerized system throughout the life cycle. Most systems have components of varying complexity, such as an operating system, un-configured components, and Configured or custom components. Effort should be concentrated as follows:

Custom > Configured > Non-Configured > Infrastructure

As per GAMP 5 systems are categorized based on the risk associated to commercial availability, configuration and customization. There are four different categories as per GAMP 5 based on system risk explained below

Category	**Description**
1. Infrastructure Software	• Layered software (i.e., upon which applications are built) • Software used to manage the operating environment
3. Non-Configured	Run-time parameters may be entered and stored, but the software cannot be configured to suit the business process
4.Configured	Software, often very complex, that can be configured by the user to meet the specific needs of the user's business process. Software code is not altered
5. Custom	Software custom designed and coded to suit the business process

(Category 2 - This Category is no longer used in GAMP 5).

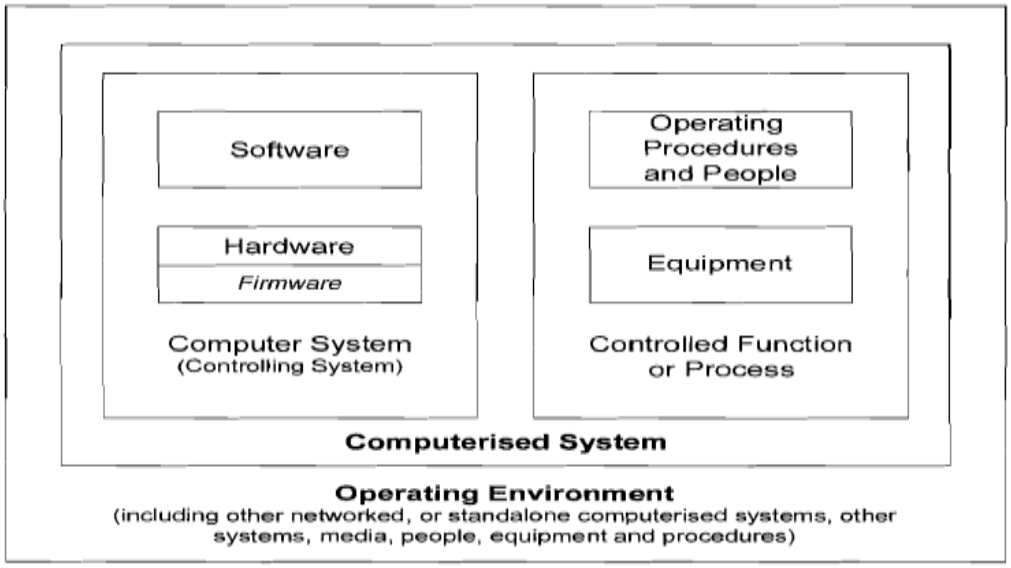
The guide clearly inculcates that there is no necessity of keeping equal validation efforts for all GxP computerized systems. The framework aims to safeguard patient safety, product quality, and data integrity. Risk based approach of GAMP 5 clearly indicates systematic process for the assessment, control, communication, and review of risks to patient safety, product quality, and data integrity.

3.3 GxP Regulated Computerized System:

GxP regulation refers the fundamental international pharmaceutical requirements, such as those set forth in the US FD&C Act, US PHs Act, FDA regulations, EU Directives, Japanese regulations, or other applicable national legislation or regulations under which a company operates. GxP indicates (but are not limited to) GMP, GCP, GLP, GDP etc.

Computerized systems that are subject to GxP regulations areGxP Regulated Computerized System. The regulated company must ensure that such systems comply with the appropriate regulations

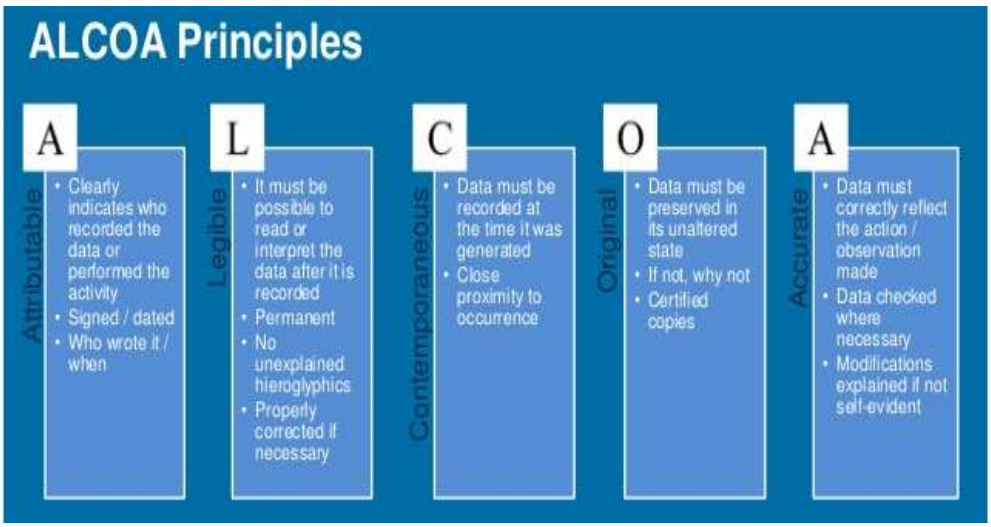
Computerized system:



Computerized system-From GAMP 5 guidance document

3.4 Data integrity:

Plenty of paper or electronic data involves during manufacturing and testing of drugs to assure the quality. Integrity of data plays a key role to represent the product quality. There are some characteristics (ALCOA) to ensuring data integrity and are addressed throughout the CGMP regulations for drugs. These are explained below



3.4.1 Trend of data integrity related warning letters

In recent times few of pharmaceutical firms including familiar firms struggling due to data integrity breaches. Data integrity issues show huge impact on business and brand value. Apart from this there are other consequences due to data integrity non-compliance and those are briefed below

- ✔ Warning letters (WL)
- ✔ Import alerts
- ✔ Product recalls
- ✔ Penalties
- ✔ Damage to company reputation
- ✔ Loss of sale/jobs/share value

Currently, pharmaceutical industry facing challenges to control data integrity breaches. Considering industry observations on data integrity compliance, US FDA predominantly focused on similar observations from the year 2013 and data integrity related warning letters are gradually increased till the year 2016. In recent times industry more attentive to control those breaches to ensure data integrity through awareness programs, system and procedural controls. Due to this efforts data integrity related warning letters are coming down in present times.

The given table shows trend of warning letters due to data integrity breaches

	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018
Total WLs	**38**	**22**	**19**	**46**	**69**	**95**
U.S. WL Sites with Data Integrity	**0 of 13** (0%)	**0 of 4** (0%)	**1 of 3** (33%)	**8 of 11** (73%)	**12 of 20** (60%)	**10 of 22** (45%)
OUS Sites with Data Integrity	**10 of 25** (40%)	**12 of 18** (67%)	**13 of 16** (81%)	**29 of 35** (81%)	**33 of 49** (67%)	**44 of 73** (60%)
Total Number of Warning Letters Citing Data Integrity	**10** (26%)	**12** (55%)	**14** (74%)	**37 of 46** (79%)	**45 of 69** (65%)	**54 of 95** (57%)

*U.S.-United States; OUS- Out of United States

3.4.2 Data integrity potential breaches

As per the industry trend, most of the data integrity allied warning letters are due to following potential breaches

- ✔ Backdating
- ✔ Fabricating data
- ✔ Discarding data
- ✔ Changing integration parameters of chromatographic data to obtain passing results
- ✔ Deletion/manipulation of electronic records
- ✔ Inadequate controls for access privileges
- ✔ Turning off audit trail
- ✔ Sharing password
- ✔ Inadequate/incomplete computer validation

3.4.3 Assuring data integrity controls through computer system validation

Above mentioned breaches can be controlled during computer system validation if it is performed per GAMP 5 guideline and in agreement to 21 CFR Part 11 regulations.

There are many deliverables are established for each category of software in GAMP 5 guide to prove its intended purpose. Few of them are very critical deliverables to ensure data integrity controls, i.e.

User requirement specification(URS): It should be more elaborate in terms of operational, 21 CFR part 11 and data integrity requirements

Functional risk assessment: All data integrity related risk and its mitigations must be discussed in this document

Assignment of access privileges: Privileges must be designed appropriately based on actual need of individual roles (operator, supervisor, administrator, service etc..)

Qualification (IQ/OQ/PQ): All data integrity, 21 CFR Part 11 requirements must be verified with appropriate evidence during execution of these protocols.
21 CFR Part 11compliance assessment: This document should explain how the system complying with 21 CFR Part 11 provisions.
Traceability matrix (TM): This document should explain how the user requirements (including Part11 and data integrity requirements) are achieved.

Examples for assuring data integrity controls through computer system validation

Observation	Regulation expectations	Controls ensuring through computer system validation
Backdating Altering data Discarding data Changing integration parameters of chromatographic data to obtain passing results Deletion/manipulation of electronic records Inadequate controls for access privileges	21 CFR Part 11.10 (d):Limiting system access to authorized individuals - Limited access can be ensured through physical and/or logical security mechanisms. Privileges can be defined based on roles (operator, supervisor, administrator and service). 21 CFR Part 211.68 (b): Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Computer systems must have adequate controls to prevent unauthorized access or changes to data, inadvertent erasures, or loss	Requirements related to these controls must be documented in URS and achievement of requirements should be discussed in the traceability matrix CSV qualification protocols should have verification tests to ensure following controls - Date and time restrictions to user - Data alteration/deletion privilege restriction to user - Restriction of integration parameter change - Verification of access privileges against privilege matrix duly approved by Quality unit Written procedures shall be placed to hold the administrative privileges including any rights to alter files and settings with personnel independent from those responsible for the record content Related controls should be documented in 21 CFR Part 11compliance assessments in detail. Both procedural and system controls must be documented in 21 CFR part 11 compliance assessment in detail
Inadequate controls for access privileges	21 CFR Part 11.10 (d):Limiting system access to authorized individuals - Limited access can be ensured through physical and/or logical security mechanisms. Privileges can be defined based roles operator, supervisor, administrator and service. 21 CFR Part 211.68 (b): Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel	Privileges required to be defining in the URS and duly approving by quality unit. Accordingly privileges can be configured and those must be verified during qualification with appropriate evidence. Written procedures shall be placed to maintain validation state throughout system life cycle Both procedural and system controls must be documented in 21 CFR part 11 compliance assessment in detail.
Turning off audit trail	21 CFR Part 11.10 (e):Procedures should be available to use secure, computer generated, time stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. 21 CFR Part 211.68 (b): Appropriate controls shall be exercised over computer or related systems	Requirements related to audit trail and its configuration must be documented in URS and achievement of requirements should be discussed in the traceability matrix CSV qualification protocols required to have audit trail verification - Audit trail verification and restriction of audit trail settings to user Written procedures shall be placed to maintain validation state throughout the system life cycle Related controls should be documented in 21 CFR Part 11compliance assessments in detail.

Sharing password	21 CFR Part 11.10 (d):Limiting system access to authorized individuals -Develop procedures for limited system access to authorized individuals. This should include a password policy. 21 CFR Part 11.10 (j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification 21 CFR Part 211.68 (b): Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel	Procedures related to password policies shall be placed and those are required to be verified as part of the qualification. Related procedural controls should be documented in 21 CFR Part 11 compliance assessments in detail.
Inadequate/incomplete computer validation	21 CFR Part 11(a) Validation of systems to ensure accuracy, reliability, consistent intended performance 21 CFR Part 211.68 (b): Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system	The Site Validation Master Plan shall be describe the computer system validation approach in line to GAMP 5 Related procedural controls should be documented in 21 CFR Part 11 compliance assessments in detail

III. CONCLUSION:

Successful regulatory inspections are more crucial for survival of any pharmaceutical company. Success of inspections purely depends on quality and integrity of data provided to auditors during inspections. Data integrity is essential tool to offer adequate confidence to regulatory bodies on data associated to manufacturing and testing process at each pharmaceutical firm. Computer system validation is an important tool to establish and maintain data integrity controls though out the data life cycle. Computer system validation approach of pharmaceutical manufacture should be implemented in line with GAMP 5 guideline to confirm 21 CFR Part 11and other major regulatory compliance.

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