Implementing Laboratory Computerized Systems in Pharmaceutical Industry: Regulatory Compliance

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Abstract:

The implementation of computerized systems in pharmaceutical industry must meet the compliance with regulatory requirements, assure high level of data integrity (DI) and product quality. This study reviews European legislation, the European and U.S. pharmacopoeias, and global guidelines, such as GAMP 5 and ALCOA++, to identify the necessary standards and best practices. Key directives of European and U.S legalisation emphasize the importance of system validation, quality risk management and secure data handling. The study highlights validation processes categorized by system complexity according to GAMP 5. Additionally, guidelines like ALCOA++ provide a robust framework for achieving DI throughout the data lifecycle. By adhering to these requirements, pharmaceutical manufacturers can ensure regulatory compliance, maintain high-quality standards and safeguard patient safety.

Keywords:
Compliance, computerized system, data integrity, GAMP 5, regulation, pharmacy, validation

1 Introduction

The pharmaceutical industry is a highly regulated environment where the implementation of a computerized system is a rather complex process. Any possible error that occurs in the process of drug manufacturing or drug testing can have a negative impact on patients who consume pharmaceutical products. Inadequate operation of a computerized system in pharmaceutical industry can lead to serious consequences. Therefore, it must be ensured that such a system is properly tested and fully validated before it is released to production. Validation must be approached strategically, with a clear goal of what is expected from the system. An important role in the validation process is played by the personnel responsible for system validation. Validation of the computerized system is usually carried out by experienced expert teams who have been working in a regulated pharmaceutical environment for a long time. It is specific knowledge that is difficult to acquire in formal education.

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The research question of this study is: Can we meet compliance with European and U.S. regulatory frameworks, Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP), and DI standards by following GAMP 5 and ALCOA++ guidelines?

This question emerges from the detailed exploration of various regulations and guidelines (EudraLex, European Pharmacopoeia, U.S. Pharmacopeia, GAMP 5, ALCOA++, etc.), their role in ensuring compliance, and their application in the validation, documentation, and operation of laboratory computerized systems in the pharmaceutical sector. It focuses on understanding how these guidelines and regulations contribute to achieving regulatory compliance, improving DI, and ensuring the proper functioning of systems impacting the quality of results and documentation. Overall, the goal is to provide a clear framework for the validation of laboratory computerized systems, ensuring compliance with regulatory standards and maintaining system integrity throughout its lifecycle.

2 Theoretical foundations

The implementation of laboratory computerized systems in pharmaceutical manufacturing must align with strict regulatory standards to en-

sure compliance, data integrity (DI), and product quality. In the European Union, directives such as 2001/83/EC and 2017/1572 mandate GMP adherence, equipment validation, and robust documentation. Complementary GLP directives, like 2004/10/EC, ensure laboratories maintain secure, validated systems with traceable data and proper maintenance records. These directives are consolidated in EudraLex Volume 4, particularly Annex 11, which details requirements for computerized systems. The European Pharmacopoeia and European Directorate for the Quality of Medicines & HealthCare (EDQM) guidelines further provide standards for laboratory equipment validation, categorized by system complexity, ensuring reliability through phases like installation qualification (IQ), Operational qualification (OQ), and performance qualification (PQ). Similarly, in the U.S., the CFR 21 enforces GMP and GLP via sections like Part 11, which governs electronic records, signatures, and audit trails to secure data authenticity. Guidelines such as GAMP 5 and the ALCOA++ principles offer a structured approach for managing system lifecycles and ensuring DI. GAMP 5 emphasizes risk-based validation and traceability, while ALCOA++ highlights essential attributes like data being attributable, legible, contemporaneous, and traceable. Together, these frameworks establish a comprehensive, globally recognized foundation for implementing and managing computerized systems in pharmaceutical environments

3 Methods

The implementation of the laboratory computerized system must be carried out in accordance with the legislation and pharmacopoeias that must be followed in order to produce pharmaceutical products. Using the compilation method, the literature on the requirements of European legislation, the European and American Pharmacopoeia, and relevant guidelines was reviewed. From the obtained information, it was determined whether adherence to the guidelines meets the regulatory requirements.

3.1 Overview of European legislation

For pharmaceutical companies operating in the territory of the European Union, it is first and foremost important that they comply with European legislation. In the chapters below, the content of the directives that directly or indirectly refer to the computerized system discussed in this work is described.

Directive 2001/83/EC establishes the Community code for medicinal products for human use. It mandates that all processes in the pharmaceutical industry be validated and that equipment used in manufacturing be detailed and validated. Equipment must also be accessible for inspection by authorized personnel. Manufacturers holding a license to produce drug products must adhere to GMP guidelines [1].

The GMP requires compliance with Commission Delegated Regulation (EU) No 1252/2014, which supplements Directive 2001/83/EC for active substances in medicinal products. Manufacturers must adhere to GMP principles, maintain Good Documentation Practice (GDP), and implement a quality risk management system. All production activities must be documented in real-time according to GDP, with proper batch records kept. Additionally, equipment must be properly designed and its use carefully planned [2].

Commission Directive (EU) 2017/1572 updates Directive 2001/83/EC on GMP for medicinal products for human use, replacing the outdated Directive 2003/94/EC. It applies to licensed manufacturers and importers, requiring member states to conduct regular inspections to ensure GMP compliance. The directive mandates proper planning and validation of premises and equipment to ensure product quality and minimize errors. A robust documentation system must be in place to guarantee DI, with data processing systems validated for proper storage and accessibility. Electronic data must be protected from unauthorized access, loss, or damage, with backup copies and an audit trail. Deviations from procedures and product issues must be documented and investigated. Additionally, any significant changes or new processes affecting production must be validated [3].

Directive 2004/9/EC requires EU member states to inspect laboratories for compliance with GLP as outlined in Directive 2004/10/EC. The goal of GLP is to ensure consistency across member states, allowing test results from one laboratory to be accepted by others. Inspections focus on ensuring proper record-keeping for equipment maintenance, calibration, and validation. Raw data from automated systems must be properly documented and archived, with any changes justified and signed by authorized personnel. Computer systems must be secure, accurate, and protected against unauthorized changes. Malfunctions must be investigated and documented. Study results should be complete and consistent with raw data. Access to archived data is restricted to authorized personnel, and all access is logged. Additionally, equipment must be properly calibrated, maintained, and serviced during inspections [4].

Directive 2004/10/EC aims to harmonize regulations related to GLP for non-clinical safety testing of various products. It emphasizes the use of validated computerized systems for data acquisition, storage, and environmental control, requiring these

systems to be properly designed, maintained, and calibrated. All data must be accurately recorded, signed, and dated by the responsible person. Proper documentation of equipment maintenance, calibration, and system validation is also required to ensure compliance with GLP standards [5].

In order to meet the requirements of the directives examined in the previous chapters, the European Commission prepared a collection of rules and regulations governing drug products in the European Union called EudraLex. EudraLex consists of ten parts, with Volume 4 being relevant to this case, as it contains the GMP Guidelines for medicinal products for human and veterinary use. Volume 4 includes several chapters that were studied in more detail:

- Chapter 3 – Premise and Equipment
- Chapter 4 - Documentation
- Annex 11 – Computerised Systems
- Annex 15 – Qualification and validation [6].

3.2 Overview of the European pharmacopoeia

The European Pharmacopoeia (Ph. Eur.) is a comprehensive document available online with the appropriate license. While reviewing the introductory pages, it was noted that the general working principles are described in individual regulatory guidelines, which are freely available on the EDQM website [7]. Therefore, during further research between the chapters in the Ph. Eur., no concrete regulations on computerized systems, the validation of computerized systems, or the qualification of laboratory equipment were detected. The research was then continued within the EDQM regulatory guidelines. The first relevant document discovered was entitled "Qualification of equipment - basic document." This document aims to harmonize the requirements of the ISO/IEC 17025 standard for testing and calibration laboratories within the network of official medicine control laboratories (OMCL). It consists of four brief chapters:

- Selection of instruments and suppliers
- Installation and release for use
- Periodic and motivated instrument checks
- In-use instrument checks [7].

The validation of computerized systems is essential to ensure DI and the proper functioning of systems impacting the quality of results, document control, and data storage. The validation guidelines categorize systems into exempted, simple, and complex systems, with different validation requirements for each. For all systems, manufacturers must maintain an inventory including system identification, purpose, validation status, storage location, and responsible person. Systems must be validated before use to ensure they meet the user's requirements (URS). The scope of validation depends on system complexity, with more complex systems requiring extensive testing. If a supplier is part of a verified program, OMCL may rely on their tests, reducing the validation scope to PQ. A Qualification Plan (QP) outlines the validation activities, including review of URS, test strategy, and performance criteria. The plan must be approved by relevant stakeholders before execution. If additional testing or revisions are required, the plan can be updated. The validation process includes several stages, such as Installation IQ, OQ, and PQ for complex systems, and culminates in a Qualification Report (QR) that confirms the system's suitability for use. Deviations during validation must be documented and assessed for their impact. Validated systems require periodic inspections to maintain their validated state. They must be protected against intrusions and physical damage (e.g., fire, power outages) and accessible only to authorized personnel with personalized login credentials. Audit Trails (AT) must record system events, such as user logins, data changes, and system activities, and cannot be disabled by users. For systems supporting electronic signatures, a declaration must confirm their equivalence to manual signatures. DI must be ensured, including regular backups, secure storage, and a clear recovery policy in case of system failure. Software versions should be archived, and change control procedures must be documented for system updates or modifications. Major changes, such as replacing hardware, require full re-validation. Finally, user training is mandatory, both for initial system use and for updates or changes, ensuring users are informed about relevant system changes and procedures [8].

3.3 Review of U.S. pharmacopeia

The American non-profit organization U.S. Pharmacopeia (USP) prescribes the use of the Code of Federal Regulations (CFR). The CFR is publicly available online, where the contents of all 50 titles covered by the Code can be accessed. Title 21, which pertains to the field of food and medicine, is relevant to their study. Title 21 includes over 1,400 parts of the code that prescribe requirements to be observed in the field of food and drugs. Several chapters are therefore relevant to this study. Related to GMP, the following addresses can be found:

- Part 210 - Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs
- Part 211 - Current good manufacturing practice for finished pharmaceuticals
- Part 58 - Good laboratory practice for nonclinical laboratory studies
- Part 11 - Electronic records; electronic signatures [9].

The review of Part 58 and Part 11 regulations focuses on adherence to GLP, excluding clinical laboratory studies. The regulations require that equipment must be clean, calibrated, validated, and well-maintained. Proper procedures for equipment use must be available, and personnel must be trained. Test data must be properly stored, with access limited to authorized personnel. Additionally, equipment used for data generation or environmental control must be appropriately designed and have sufficient capacity to function properly [10]. Part 11 regulates computerized systems, focusing on electronic records and electronic signatures. It is required by the FDA for all regulated processes. The regulations are divided into sections that cover:

Subpart B – Electronic records
- 11.10 Controls for closed systems (13 requirements)
- 11.30 Controls for open systems (1 requirement)
- 11.50 Signature manifestations (5 requirements)
- 11.70 Signature/record linking (1 requirements) [11].

Subpart C – Electronics signatures
- 11.100 General requirements (5 requirements)
- 11.200 Electronic signature components and controls (7 requirements)
- 11.300 Controls for identification codes/passwords (5 requirements) [12].

It is necessary to include these requirements in the URS document and thus require supplier to comply with 21 CFR Part 11.

3.4 Review of guidelines

In order to optimally integrate the findings from the previous chapter into consideration, the guidelines were also examined. The findings of the study should ensure compliance with regulatory requirements. Several different guidelines were studied. The focus of the study is on the GAMP 5 guidelines, which ensure the regulatory compliance of computerized systems, and the ALCOA++ guidelines, which ensure the achievement of the appropriate level of DI and GDP.

3.4.1 GAMP 5

GAMP 5 guidelines provide best practices for managing computerized systems throughout their lifecycle, which is divided into four phases: concept, project, operation, and retirement. In the concept phase, companies evaluate automation opportunities, assess benefits and drawbacks, and decide whether to proceed with purchasing the system. A Initial Risk Assessment (IRA) is required before moving to the project phase, which includes planning, preparing technical specifications, configuring the system, and creating test documentation. After successful validation, the system is confirmed for regular use. The guidelines emphasize risk reduction, and traceability of activities, particularly for more complex systems. Roles and responsibilities of both the buyer and supplier are also clearly defined throughout the lifecycle [13].

GAMP 5 categorizes computerised systems into 4 categories that differ from each other in configurability and customization (the higher the category, the higher level of configurability and customization the computerised system achieves). GAMP 5 thus describes 4 different categories of computerised systems:

- Category 1 - Infrastructure Software
- Category 3 – Standard system components
- Category 4 – Configurable components
- Category 5 – Applications and components that are custom made [13].

Individual systems can consist of one or more GAMP 5 categories. Companies usually categorize the system according to the component that achieves the highest level [13]. *Figure 1* shows an example of a computerised system that contains all 4 categories and would thus be categorized as GAMP category 5.

Before using computerized equipment, appropriate verification must be carried out depending on the category. For categories 4 and 5 components, it is crucial to thoroughly evaluate the supplier. The V-model (see *Figure 2*) outlines the steps and val-

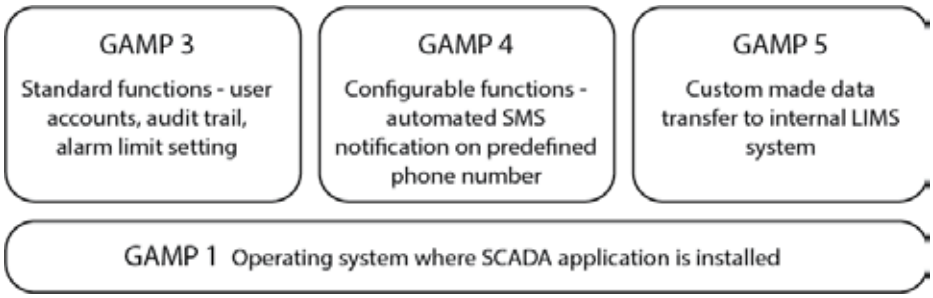

Figure 1 : *Example of a computerised system categorization into category 5 [13]*

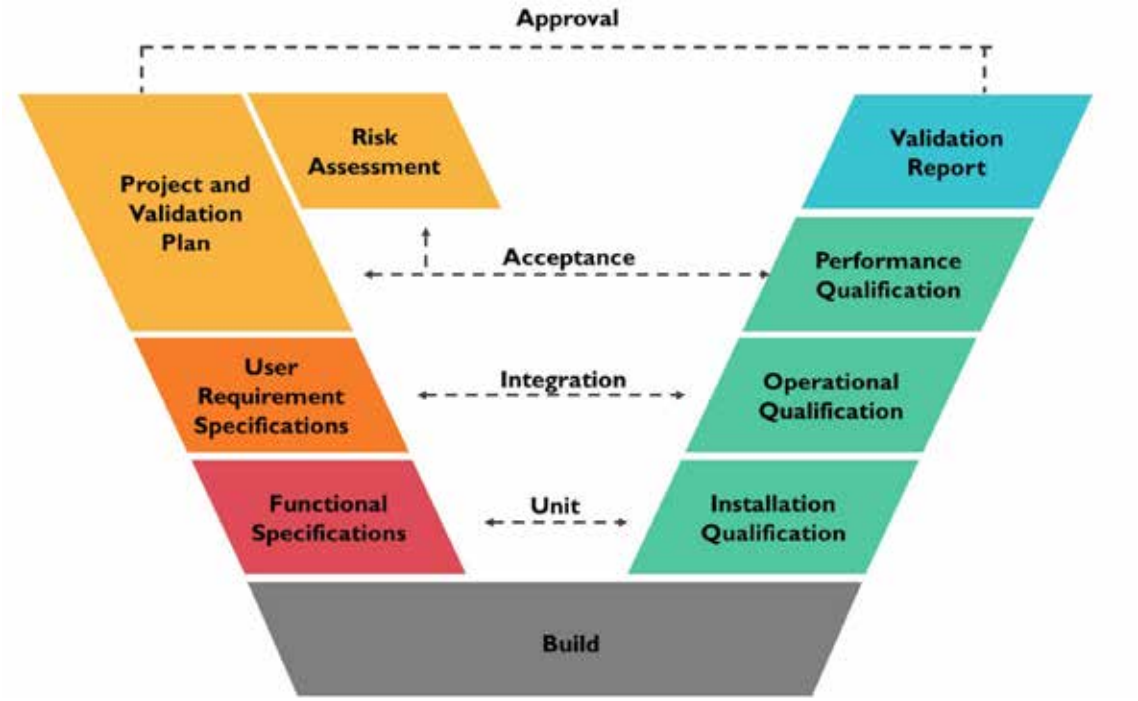

Figure 2 : *GAMP 5 V-model [14]*

idation results required for a successful validation strategy. It defines the necessary specifications and tests for each phase, ensuring the creation of appropriate documentation. The model also includes the involvement of both the supplier and the customer throughout the process [14].

One of the first authors to mention the validation of computer systems as early as 1979 is Boehm R., who is the author of the work "Guidelines for Verifying and Validating Software Requirements and Design Specifications." In the aforementioned work, he presents the so-called V-model, which can be found in the GAMP 5 guidelines as a basis today [15].

The release of the system into use is approved by the regulated company when the adequacy of the system is confirmed by the successfully implemented and completed planned testing phases. Before handing over the system to the user, the project team must prepare instructions for working with the system, instructions for maintenance and the process of maintaining the validated state of the system. The guidelines also describe in detail the phase of operation and retirement, which are not yet relevant to their topic. A special chapter of the GAMP 5 guidelines is dedicated to suppliers and developers of computerised systems, with useful guidelines and instructions on what expectations regulated companies have of them.

3.4.2 ALCOA++

High level of DI is the basis for manufacturing pharmaceutical companies, as in this way to guarantee the veracity of data, identity, product safety, efficiency and a high level of quality [16]. The acronym ALCOA was first introduced by the FDA in the 1990s with the aim of directing regulated industries to achieve compliance with the FDA's DI requirements. ALCOA's guidelines cover electronic, written and hybrid data and are critical to the provision of GDP [17]. The acronym consists of the initials of the principles:

- **A**ttributable
- **L**egible
- **C**ontemporaneous
- **O**riginal
- **A**ccurate [18].

In 2010, 4 more principles called CCEA were added to the ALCOA guidelines. This is how the abbreviation ALCOA-CCEA was born, which was later renamed to ALCOA+. The abbreviation CCEA is a composite of the initials of principles [17]:

- **C**omplete
- **C**onsistent
- **E**nduring
- **A**vailable when needed [18].

Not long ago, on September 10, 2023, the European Medicines Agency (EMA) added a tenth principle to the ALCOA+ abbreviation in its guidelines for computerized systems and electronic data in clinical studies. This principle was denoted by an additional '+' in the abbreviation, resulting in ALCOA++ [18]. The tenth principle of the guidelines stands for:

- Traceable

Data must be traceable throughout the data lifecycle. All changes to data, metadata must be traceable, must not obscure the original information and must be explained if necessary. Changes should be documented as part of metadata (e.g. audit trail) [18]. The regulation does not mention compliance with the ALCOA++ principles, but the requirements according to individual principles are still found.

4 Results

The implementation of computerized systems in pharmaceutical manufacturing must align with stringent regulations to ensure compliance, product quality, and DI. A comprehensive review of European legislation, pharmacopoeias, and global guidelines reveals the essential requirements and best practices for achieving regulatory compliance. For pharmaceutical companies operating within the European Union, compliance with Directive 2001/83/EC is paramount. It mandates validated processes and equipment, adherence to GMP, and detailed documentation for inspection. Supplementing this, Commission Regulation (EU) No 1252/2014 and Directive (EU) 2017/1572 require manufacturers to implement quality risk management systems and validate computerized systems to protect electronic data from unauthorized access or damage. Directives 2004/9/EC and 2004/10/EC extend these requirements to laboratories, emphasizing Good Laboratory Practice (GLP) through secure data storage, audit trails, and system validation. EudraLex Volume 4, particularly Annex 11, provides specific guidelines for computerized systems. These include requirements for system validation, DI, regular inspections, and data protection measures such as access controls and backup systems. Deviations and changes in the system must be documented and thoroughly investigated to ensure consistent compliance.

The Ph. Eur., though not directly focused on computerized systems, is complemented by the EDQM's Qualification of Equipment document, which harmonizes ISO/IEC 17025 standards. It defines validation requirements based on system complexity, categorizing systems into exempted, simple, and complex. Validation processes include IQ, OQ, and PQ, supported by documentation like QP, QR. These ensure that systems meet regulatory and operational expectations, with periodic inspections to maintain compliance. USP and CFR 21 provide a detailed framework for computerized system compliance. Part 58 mandates validated, well-maintained systems for GLP adherence, while Part 11 focuses on electronic records and electronic signatures. It requires secure user authentication, comprehensive audit trails, and validated electronic record-keeping systems to meet DI standards. These regulations ensure data accuracy, traceability, and accessibility, with stringent controls for system updates and modifications. GAMP 5 guidelines offers best practices for managing computerized systems across their lifecycle, emphasizing risk-based validation, clear role definitions, and traceability. Systems are categorized by their level of configurability, with the validation process following the V-model. This structured approach ensures compliance at every phase, from system concept and project development to operation and retirement. On the other hand ALCOA++ provides DI principles essential for regulatory compliance and quality assurance. Initially encompassing Attributable, Legible, Contemporaneous, Original, and Accurate, the guidelines have expanded to include Complete, Consistent, Enduring, Available, and Traceable. These principles emphasize metadata integrity, audit trails, and the importance of maintaining a complete data history. The recent addition of traceability further highlights the need for robust documentation throughout the data lifecycle.

5 Conclusion

Through a review of legislation, pharmacopoeias, and relevant guidelines, we identified the necessary steps and documentation for introducing a computerized system into a pharmaceutical laboratory. Our analysis revealed that European and US regulations, such as Annex 11 in EudraLex and 21 CFR Part 11, mandate comprehensive validation for computerized systems in both GLP and GMP environments.

The implementation of computerized systems in pharmaceutical industry must adhere to a complex network of regulations and guidelines. European legislation, complemented by global guidelines like GAMP 5 and ALCOA++, provides a comprehensive approach to system validation, data protection, and quality assurance. By following guidelines EDQM, GAMP 5 and ALCOA++, manufacturers can ensure DI, maintain regulatory compliance, and safeguard the quality and safety of pharmaceutical products. Proper validation, robust documentation, and periodic system reviews are critical components in achieving these objectives.

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Regulativna skladnost ob implementaciji laboratorijskih računalniških sistemov v farmacevtski industriji

Povzetek:
Implementacija računalniških sistemov v farmacevtski industriji mora zagotavljati skladnost z regulativnimi zahtevami, visok nivo integritete podatkov ter kakovost izdelkov. Študija pregleduje evropsko zakonodajo, evropsko in ameriško farmakopejo ter globalne smernice, kot sta GAMP 5 in ALCOA++, da bi opredelila potrebne standarde in najboljše prakse. Ključne direktive evropske in ameriške zakonodaje poudarjajo pomen validacije sistemov, upravljanja tveganj kakovosti in varnega ravnanja s podatki. Študija izpostavlja procese validacije, razvrščene glede na kompleksnost sistema v skladu z GAMP 5. Poleg tega smernice, kot so ALCOA++, zagotavljajo trden okvir za doseganje integritete podatkov skozi njihov celotni življenjski cikel. S študijo želimo ugotoviti, ali lahko ob upoštevanju smernic farmacevtski proizvajalci zagotovijo regulatorno skladnost, vzdržujejo visoke standarde kakovosti in zagotavljajo varnost pacientov.

Ključne besede:
skladnost, računalniški sistem, integriteta podatkov, GAMP 5, regulativa, farmacija, validacija