



HAL
open science

Computerized System Validation: Regulatory Compliance and Process Safety in the Pharmaceutical Industry

Yves Samson

► **To cite this version:**

Yves Samson. Computerized System Validation: Regulatory Compliance and Process Safety in the Pharmaceutical Industry. Conference ERTS'06, Jan 2006, Toulouse, France. <hal-02270463>

HAL Id: hal-02270463

<https://hal.science/hal-02270463v1>

Submitted on 25 Aug 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Computerized System Validation: Regulatory Compliance and Process Safety in the Pharmaceutical Industry

Yves Samson

Kereon AG, Mülhauserstrasse 113, CH-4056 Basel
www.kereon.ch

Abstract: One of the major concerns of the pharmaceutical industry is the importance of the regulations which have to be fulfilled. These establish various requirements for processes and associated systems without defining the ways to achieve the expected compliance. Such regulatory requirements concern also computerized systems used for manufacturing-, laboratory-, distribution- or clinical study-related activities.

After a short introduction to the pharmaceutical regulatory framework, this article will show the approach for achieving the regulatory compliance used within the industry, based on the recommendations promoted by the GAMP® Guide. Thereby, three key-topics will be presented: system life cycle, risk management and system testing.

Keywords: computerized system validation, regulatory compliance, system life cycle, risk management, testing, GAMP®

1. Introduction: “You’ll soon feel better! ...”

When we were sick as children, after being given some medicine, we often heard the sentence “You’ll soon feel better! ...”. Indeed, in highly developed countries, medicinal products extend the life of humans by 16 years on average. At the same time, due to side effects, medicinal products reduce the life of humans by 37 minutes on average. [1]

Unfortunately, in some third world countries, 10 to 50% of all drugs which patients receive are counterfeits. This signifies that some of them are without any active ingredients and/or with harmful other ingredients. [1]

The control of the market, with the help of regulations, inspections and testing in medicine control laboratories, makes the difference. The control of the market is as effective as it is focused on the risks associated with the products for the patients.

The challenge for the pharmaceutical industry is to fulfil regulatory requirements and at the same time maintain an economic efficiency.

2. Pharmaceutical Regulations

2.1 Regulatory Agencies

A regulatory agency is a national governmental authority which is responsible for the control of healthcare organizations regarding the correct consideration of national and, if appropriate, international standards.

The goal is to protect the citizen, i.e. the patient’s health.

Historically, the US Food and Drug Administration (US FDA) was the first to initiate the definition of the principles for software validation. Today, the major Agencies (incl. EMEA through the European Commission) establish such principles and related rules directly or via harmonisation working groups such as PIC/S.

2.2 Regulatory inspections

Regulatory agencies perform inspections of pharmaceutical organizations and their facilities on a regular basis. The inspection objectives are to control workflows, processes and systems in relation with a product.

For this reason, computerized systems are inspected based on their impact on the product quality and safety. In this way the inspection focus on computerized system could be more or less strong.

Since regulations define only requirements which have to be fulfilled by the pharmaceutical organizations without defining the ways to achieve the expected compliance, there is no absolute compliance standard.

2.3 Principles

The complex regulatory framework impacting pharmaceutical processes and equipment could be summarized in the following definition established by the US FDA in 1987:

“Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.” [2]

As consequence of this first definition, software validation is considered to be “*confirmation 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.*” [3]

2.4 Regulatory impact on computerized systems

The consequence of the above mentioned principles is that every system involved in product-related processes must be validated.

Various computerized systems are impacted by these requirements. There are for example:

- ◆ Laboratory equipment used for:
 - Product development
 - Product quality control
- ◆ Manufacturing equipment such as:
 - Automated production equipment
 - Infrastructure equipment (HVAC, water, ...)
- ◆ IT systems such as:
 - Clinical study applications
 - Document management systems
 - Manufacturing execution systems
 - Logistics systems

Especially in the area of process control and laboratory automation, the range of impacted automation systems is very wide. This covers for example:

- ◆ Process control systems
 - Distributed control systems (DCS)
 - Programmable logic controllers (PLC)
 - Supervisory, control, and data acquisition systems (SCADA)
- ◆ Automation devices
 - Sensors: measurement devices, etc.
 - Actuators: PID-controllers, motor controllers, etc.
- ◆ Laboratory systems
 - pH-meters
 - laboratory scales
 - Chromatography instruments (HPLC, HPGC)
 - DNA sequencers
 - PCR-based systems.

The challenge for the pharmaceutical organizations consists of achieving a consistent level of compliance based on the above mentioned principles for every impacted system.

3. Computerized System Validation

3.1 Validation in the daily business

“*Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.*” [2]

This principle can be illustrated based on the following scheme:

Predetermined specifications & quality attributes

- ◆ User requirements specification (URS)
- ◆ Functional specification (FS)
- ◆ Design specification (DS)
- ◆ etc.

Predetermined quality attributes

- ◆ Test specifications with expected results

Consistently

- ◆ Test specifications (against technical specifications, i.e. URS, FS, DS, ...):
 - Module & integration tests
 - Installation qualification (IQ)
 - Operational qualification (OQ)
 - Performance qualification (PQ)
 - Factory and site acceptance tests (FAT, SAT)
- ◆ Traceability matrix.

The main objective of the validation is to provide evidence that requirements are fulfilled and that the system (or the process) is fit for purpose.

3.2 How to fulfil regulatory requirements?

Complying with regulations implies satisfying, among others, requirements such as:

- ◆ To follow a prospective engineering approach
- ◆ To specify what is expected
- ◆ To define working processes
- ◆ To control that processes are followed correctly
- ◆ To test the system against the specifications
- ◆ To document consistently the different engineering phases
- ◆ To control changes
- ◆ To have a control organization:
 - Quality Assurance.

Although computerized system validation (CSV) impacts computer systems as well as users, procedural controls and the environment, the following part of this document will discuss only the aspects of:

- ◆ System life cycle
- ◆ Risk management
- ◆ System testing.

3.3 System Life Cycle

In order to work in a consistent manner, a well structured and formalized system life cycle (SLC) is necessary.

Often, the SLC is reduced by covering only the development activities: “*System Development Life Cycle*” (SDLC). Although the development phase is very important regarding system quality as well as security and safety, regulatory compliance requires that a system should be developed and operated according to current good practice.

3.3.1 System Development Life Cycle

Regulations as well as industry standards do not prescribe any life cycle model. Nevertheless, the usual reference model is the “V Model” (see Figure 1).

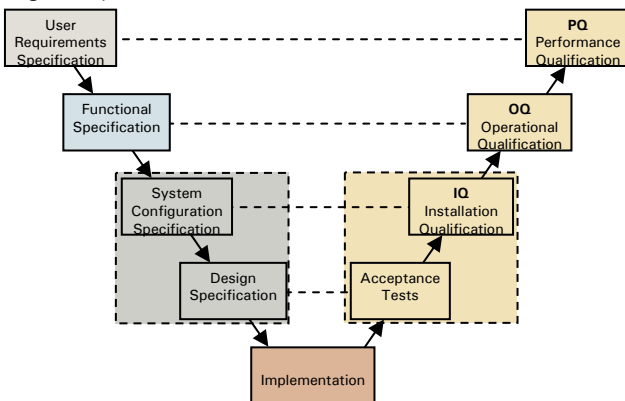


Figure 1: Reference “V Model”

One of the major benefits of this representation is to highlight the strong relationship between “*technical specifications*” (left branch) and the corresponding “*test specifications*” (right branch). Because regulations request evidence that the system meets the requirements, it is essential for performing validation activities that tests are systematically defined as well as that every requirement is tested in an appropriate manner.

Depending on the system complexity, the life cycle could be adapted and customized¹.

¹ Usually, the life cycle is binding and is defined in the system specific Validation Plan (or Qualification Plan).

- ◆ The SDLC of a specifically developed system should describe every activity with an appropriate granularity and depth. In this case, the design specifications should describe software design as well as each software module.
- ◆ By so called “*Commercial Off-The-Shelf*” systems (COTS), the SDLC includes little actual (software) implementation activities which are under the system owner’s direct responsibility.

Regardless of the chosen approach, it is the responsibility of the system owner to ensure that development activities are performed according to the current good practice. For COTS systems as well as for sub-contracted development work, supplier audits are an efficient way for demonstrating supplier maturity. In case of deficiencies, corrective (and supporting) measures based on the observed weaknesses should be put in place and controlled during the project.

Even if the V Model is widely used as the reference model for the development activities it does not assume that a sequential waterfall model has to be followed. An iterative approach of the development tasks is also acceptable. In such cases, each iteration should follow the V Model (specify, implement, test, report) and the entire development corresponds to a succession of several “Vs”.

It is worth mentioning here that the approach recommended by the (IBM Rational) Unified Process satisfies both the requirements for a well formalized prospective workflow as well as an iterative methodology facilitating good progress control and risk management based on prototyping.

3.3.2 Integral System Life Cycle

At the end of the development, as soon as the system becomes operational and until its retirement, it is necessary to take into account the corresponding regulatory requirements.

For this reason, a binding formalization of activities is indispensable. It concerns the following topics:

- ◆ System access control
 - Physical and logical access control
- ◆ Data management [9]
 - Backup and restore
 - Archiving and retrieval
- ◆ Disaster recovery and business continuity
- ◆ Change control and maintenance.

At the time the system must be retired, it is also necessary to decommission the system with sufficient control:

- ◆ To prove that the system worked correctly until the end

- ◆ To ensure the integrity of records which must be kept at least for regulatory purpose after the system is turned off.

This Integral System Life Cycle is also called the “Spoon Model” due to its representation which is similar to a spoon (see Figure 2).

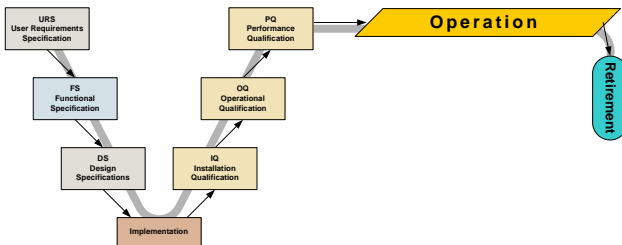


Figure 2: Spoon Model

3.3.3 Life Cycle Requirements

Regardless of the kind of specific life cycle activity, the following requirements must be fulfilled:

- ◆ The activity must be achieved prospectively
 - Pre-defined operational procedures (SOP)
 - Pre-defined task schedule, if appropriate
 - Pre-defined controls and acceptance criteria
 - Pre-defined of behaviour in case of deviation
- ◆ Activity as well as documentation must stay under change control based on formalized procedures
- ◆ Procedures (SOP) must be exercised (especially SOPs which are rarely used, e.g. disaster recovery).

Because process documentation is vital to demonstrate that the process and systems run accordingly to the specifications, data and especially record management are critical tasks. One objective of the CSV is to ensure the integrity of data and records. (See also [4], [5], [6] and further [7])

In addition to the regulatory agencies, which perform inspection to control healthcare organizations, controls, releases and audits are executed internally by the quality assurance (QA) department. Every SOP, every URS, every validation plan and report as well as every change request must be approved by QA.

3.4 Risk management

Since it is not possible and not cost-effective to test all functionality (and especially in combination with each other), it is necessary to follow a more pragmatic approach based on the identification of critical functions and process steps. The validation (incl. test) effort will be focused on the functionality identified as critical.

3.4.1 Which risks?

The criticality and finally the risk assessment should consider the following aspects and impacts:

- ◆ Safety and security
 - Risk for people (safety)
 - Environmental risk (ecology)
 - Risk for plant and equipment (security)
- ◆ Product related risks
 - Insufficient quality: the product does not meet the pre-defined quality attributes
- ◆ Regulatory risks
 - Regulatory and/or legal requirements are not fulfilled correctly
- ◆ Operational and business risk
 - Corporate reliability and reputation, ...

3.4.2 Risk assessment

Even regulatory agencies have endorsed a validation approach based on risk evaluation for a number of year, they do not prescribe or recommend any particular methodology regarding risk assessment and risk management.

For this reason, the GAMP® Forum proposed in [8] a basic approach which can be easily enhanced with the help of more intensive methods like HAZOPS, HACCP, FMEA, or based on ISO/EN 14971:2002.

After identification of the risk scenarios, the risk evaluation must consider for each scenario the following aspects (see also [8], Appendix M3):

- ◆ Risk likelihood
- ◆ Business impact
- ◆ Probability of failure detection

The business impact should be understood widely (covering safety, security, product quality and operational aspects incl. regulatory compliance).

Based on the assessed criticality, risk mitigation measures should be defined, implemented and tested. Depending on the criticality, good engineering practices and, if needed, more intensive qualification work should be specified in order to ensure that the mitigation measures are correctly implemented, without producing additional (and un-assessed) risks. (See also [10])

Finally, whatever the chosen risk evaluation method is, the risk management process must be formalized and the results have to be documented accurately.

3.5 System testing

3.5.1 Objective

The first and major objective of testing is:

- ◆ To provide evidence that a system is fit for purpose, meeting user and business requirements.

For this reason, every specification item, identified as critical regarding the validation state, needs to be tested formerly.

3.5.2 When to test?

According to the reference life cycle model, several test phases, achieving different goals, should be executed:

- ◆ Acceptance tests
 - Software module tests & software module integration tests
 - Factory acceptance tests (FAT)
 - Site acceptance tests (SAT)
- ◆ Qualification
 - Installation qualification (IQ)
 - Operational qualification (OQ)
 - Performance qualification (PQ).

During the initial acceptance tests, the system design fitness should be demonstrated.

During the qualification, the IQ should prove the correct installation of the system. Afterwards, OQ and PQ should demonstrate the fitness for purpose of the system. The PQ should support the final user acceptance of the system.

3.5.3 How to test?

Tests must occur based on formal test scripts. These have to be approved prior to beginning the testing.

The test scripts are structured based on test cases. For each test case, it must be defined, amongst others:

Test identification number (Test-ID)

- ◆ Cross-reference to the related specification
 - e.g. Requirement or specification-ID
- ◆ Test pre-requisites
- ◆ Test method (& test data)
- ◆ Expected test result
- ◆ Test result
- ◆ Test record
- ◆ Test fulfilment statement
 - Passed/Failed

- ◆ Date & signature of the tester

- (Note: only for tests performed manually. For automated testing, a different formalism could be agreed).

The test results must be consistently reproducible and the test records must be reviewed and approved. The basic principle is that tests must be performed and test records must be approved prior to the beginning of the next test phase unless a different procedure is agreed in the validation plan.

Although the required test formalism could seem to be a little heavy, the regulations expect such formalism.

Test consistency and reproducibility are the keys for providing *“objective evidence that computer system specifications conform to user needs and intended uses, and that all requirements can be consistently fulfilled.”* [3]

4. Industry Standards

Because regulations do not give any recommendation about the way to achieve compliance, regulated users² need support regarding the possible and appropriate ways to achieve regulatory compliance and to maintain the computerized systems in a validated state.

Already in the second half of the eighties, the pharmaceutical companies started to work together within the PMA CSVC on the elaboration of a guideline related to the Computer System Validation.

At the beginning of the nineties, after several difficult inspections (so called “pivotal inspections”), several people, mostly coming from the industry, started the “GAMP[®] initiative”, initially to provide guidance for the suppliers of the pharmaceutical industry.

After several years and versions, the GAMP[®] Guide ([8]) is a recognized document within the healthcare sector for users, suppliers as well as regulators.

The Guide is not binding and it is neither a regulation nor a norm. However the recommendations proposed by the GAMP[®] Forum represent a reasonable and well accepted way to meet regulatory requirements, even if other approaches are possible.

Today, several “Good Practice Guides” develop specifically the concepts promoted in GAMP 4 ([8]) needing a particular focus, e.g.:

- ◆ Validation of Process Control Systems
- ◆ Validation of Laboratory Computerized Systems

² ‘users’ (owners of the good practice computerised systems being inspected) are collectively referred to as ‘regulated users’ [7]

- ◆ IT Infrastructure Control and Compliance
- ◆ Electronic Records and Signatures.

The GAMP® Forum is now a technical subcommittee of ISPE.

On the regulator's side, international working groups have developed guidance for the inspectors. The guide PI 011-2 [7] edited by PIC/S is one of the major documents concerning computerized systems validation.

5. Conclusion

Compared to the situation 15 years ago, industry and regulators now have available valuable and mature guides and recommendations for achieving regulatory compliance.

Although the formalism regarding processes and the documentation of activities is strong, the pharmaceutical industry has wide freedom to define the most appropriate approach to achieve compliance.

Based on a few fundamental concepts and on a prospective approach to project management and engineering activities, the regulated user is able to choose the way how to fulfil regulatory requirements for its particular system.

This is only possible if the life cycle for the development and operational phases are correctly formalized – based on an established quality management system – and if the existing risks are assessed consistently.

Finally, nothing is possible without the presence of a QA organization which controls the application of the defined working approach and its conformity (compliance) with the organization QMS and applicable regulatory requirements

6. Acknowledgement

The author acknowledges especially

- ◆ Philip A. Burgess for the review of this paper and the members of the GAMP steering committee as well as various speakers at ISPE conferences, in particular:
 - ◆ Chris Clark
 - ◆ Anthony J. Margetts
 - ◆ David W. Selby
 - ◆ Guy A.S. Wingate
 - ◆ Siôn Wyn.

7. References

- [1] Dr. Joerg Neuhaus: "Global GMP regulatory conference", ISPE, Prague, Czech Republic, September 2005.
- [2] FDA Guidelines on: "General Principles of Process Validation", May 1987
- [3] FDA "Glossary of Computerized System and Software Development Terminology"
- [4] European Commission: Annex 11 "Computerized Systems" to the EU Guidelines of Good Manufacturing Practice for Medicinal Products
- [5] FDA, 21 CFR Part 11: "Electronic Records; Electronic Signatures", valid as of 1997-08-20.
- [6] FDA, "Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application", 2003-09-03
- [7] PIC/S, PI011-2: "Good Practices for computerized systems in regulated 'GxP' Environments", 2004-07-01.
- [8] ISPE/GAMP, "GAMP 4: Validation of automated systems", December 2001
- [9] Yves Samson: "White Paper: Introduction to Good Process Record Management (GxP)", 2005-10-27 (www.kereon.ch/wp)
- [10] Yves Samson: "Risiko-orientiert Reinräume zeit- und kosteneffizient qualifizieren und validieren", Pharma + Food, 3/2004, Hüthig Verlag, June 2004 (www.kereon.ch/pub)

8. Glossary

COTS	Commercial Off-The-Shelf
CSV	Computerized System Validation
CSVC	Computer System Validation Committee (part of PMA)
DCS	Distributed Control System
DNA	Deoxyribo Nucleic Acid
DS	Design Specification
EMEA	European Agency for the Evaluation of Medicinal Products
FAT	Factory Acceptance Test
FMEA	Failure Mode Effect Analysis
FS	Functional Specification
GAMP	Good Automated Manufacturing Practice
GxP	Generic expression covering Good Clinical, Distribution, Laboratory and Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Points Study
HAZOPS	Hazard Operability Study
HPGC	High Performance Gas Chromatograph

<i>HPLC</i>	High Performance Liquid Chromatograph
<i>HVAC</i>	Heating Ventilation Air Conditioning
<i>IQ</i>	Installation Qualification
<i>ISPE</i>	International Society of Pharmaceutical Engineering
<i>OQ</i>	Operational Qualification
<i>PCR</i>	Polymerase Chain Reaction
<i>PIC/S</i>	Pharmaceutical Inspection Cooperation Scheme
<i>PLC</i>	Programmable Logic Controller
<i>PMA</i>	Pharmaceutical Manufacturers Association
<i>PQ</i>	Performance Qualification
<i>QA</i>	Quality Assurance
<i>QMS</i>	Quality Management System
<i>SAT</i>	Site Acceptance Test
<i>SCADA</i>	Supervisory, Control, and Data Acquisition system
<i>SDLC</i>	System Development Life Cycle
<i>SLC</i>	System Life Cycle
<i>SOP</i>	Standard Operating Procedure
<i>URS</i>	User Requirements Specification
<i>US FDA</i>	US Food and Drug Administration: Regulatory Agency in the USA (US government)

10. Contact

Kereon AG
Mülhauserstrasse 113
CH-4056 Basel
Phone: +41:61:383 04 55
e-Mail: csv@kereon.ch
www.kereon.ch

9. Useful links

- ◆ A white paper based on this document is available at the following address:
 - www.kereon.ch/wp
- ◆ ISPE: Engineering Pharmaceutical Innovation
 - www.ispe.org
- ◆ GAMP® Forum
 - www.ispe.org/gamp
- ◆ PIC/S: Pharmaceutical Inspection Cooperation Scheme
 - www.picscheme.org
- ◆ EMEA: European Agency for the Evaluation of Medicinal Products
 - www.emea.eu.int
- ◆ European Commission
 - pharmacos.eudra.org
- ◆ FDA: Food and Drug Administration
 - www.fda.gov
 - www.fda.gov/cder