Computer System Validation Basics

By Praxis Life Sciences
Computer System Validation Basics

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Your Praxis Facilitator

• Debra Bartel, MBA, CQA, PMP

• Principal, Praxis Life Sciences

• 25+ years experience specializing in software quality assurance, validation and regulatory compliance, Information Systems project management, and process design.

• Prior to joining Praxis, held management positions in the pharmaceutical industry in both Quality Assurance and Information Systems organizations

• Active member of American Society for Quality (ASQ), Northeastern Illinois Section, Software Division
How We Help

- Consulting
- Audit Services
- Training
- Library

Target Audience

**Industries**
- Pharmaceutical & Biologics
- Medical Device
- Clinical Studies
- Blood Products

**Regions**
- Operating in the US
- Selling to the US Market

**Personnel**
- IT Personnel and Managers
- Quality Personnel and Managers
- Auditors and Audit Managers
Webinar Outline

1. CSV Regulatory Requirements
2. CSV Purpose & Benefits
3. CSV Methodology
4. CSV Scope
5. CSV Failure Consequences
6. CSV Program Implementation

CSV Regulatory Requirements
Part 1
CSV Regulatory Requirements

Computer System Validation is require for companies that …

<table>
<thead>
<tr>
<th>Activities</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design, Develop</td>
<td>Pharmaceuticals</td>
</tr>
<tr>
<td>Conduct clinical trials</td>
<td>Biologics</td>
</tr>
<tr>
<td>Manufacture, Package</td>
<td>Medical Devices</td>
</tr>
<tr>
<td>Label, Store, Distribute</td>
<td>Blood and Blood Components</td>
</tr>
<tr>
<td>Install, Service</td>
<td>Human Cell and Tissue Products</td>
</tr>
</tbody>
</table>

**USA**

**FDA 21 CFR 11 Electronic Record; Electronic Signatures**

Subpart B—Electronic Records, Sec. 11.10

Controls for closed systems. Such procedures and controls **shall include** the following: (a) **Validation of systems** to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

**21 CFR 820 Quality System Regulation**

Subpart C Design Controls, Sec. 820.30(g)

Design validation **shall include software validation** and risk analysis, where appropriate.

Subpart G Production and Process Controls, Sec. 820.70(i)

When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall **validate computer software for its intended use** according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.
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**USA**

**FDA 21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceuticals**

Subpart D—Equipment, Sec. 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.*

21 CFR 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products

Subpart D Current Good Tissue Practice, Sec. 1271.160(d)

*You must validate the performance of computer software for the intended use,* and the performance of any changes to that software for the intended use, if you rely upon the software to comply with core CGTP requirements and if the software either is custom software or is commercially available software that has been customized or programmed (including software programmed to perform a user defined calculation or table) to perform a function related to core CGTP requirements.

**European Union**

**EC COUNCIL DIRECTIVE 93/42/EEC**

**ANNEX I ESSENTIAL REQUIREMENTS**

12.1a For devices which incorporate software or which are medical software in themselves, the software must be validated according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification.

**EudraLex Volume 4 Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use**

**Annex 11 Computerised Systems**

*The application should be validated; IT infrastructure should be qualified.*
Brazil

Brazilian ANVS Good Practices of Medicament Manufacturing

TITLE VIII. GOOD PHYTOTHERAPIC MEDICAMENTS MANUFACTURE PRACTICES, CHAPTER IV
VALIDATION, Art. 18.

Any aspect of operation, including significant changes in the facilities, location, computer systems, equipment or processes that can affect product quality, directly or indirectly, must be qualified and/or validated.

TITLE VII, COMPUTER INFORMATION SYSTEMS, Art. 573.

Validation shall be considered part of the computer system’s life cycle, which includes the planning, specification, scheduling, test, documentation, operation, monitoring, maintenance and change stages.

Japan

Japan’s Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-drugs

The purpose of this guideline is ... to ensure proper enforcement of the “Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices” ... and the “Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs” ... by specifying the necessary matters during development of computerized systems, the validation items to verify such systems, ... in order to ensure such systems function as intended.
ICH Q7A, Good Manufacturing Practice for Active Pharmaceutical Ingredients

GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.

ICH E6 Good Clinical Practice

When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:
Ensure and document that the electronic data processing system(s) conforms to the sponsor’s established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation)
**PIC/S**

**PIC/S PE 005-3 GMP Guide for Blood Establishments**

9.8 The hardware and software of the computers should be checked regularly to ensure reliability. The software (program) should be validated before use.

**PIC/S PE 009-11 Guide to Good Manufacturing Practices for Medicinal Products**

5.40 GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.

**PIC/S PE 011-1 Guide to Good Distribution Practice for Medicinal Products**

Before a computerised system is brought into use, it should be demonstrated, through appropriate validation or verification studies, that the system is capable of achieving the desired results accurately, consistently and reproducibly.

**PIC/S PI 011 Good Practices for Computerised Systems Used in Regulated “GXP” Environments**

- 4.9 The regulated user should be able to demonstrate through the validation evidence that they have a high level of confidence in the integrity of both the processes executed within the controlling computer system and in those processes controlled by the computer system.
- 14.1 Regulated users need to be able to provide evidence for their computerised systems to demonstrate their range, complexity, functionality, control and validation status.
- 16.1 Retrospective validation is not equivalent to prospective validation and is not an option for new systems.
WHO

WHO Specifications for Pharmaceutical Preparations

6.3 Critical computerized systems should be validated before use.

WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles

4.11 Particular attention should be paid to the validation of analytical test methods, automated systems and cleaning procedures.

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CSV Purpose and Benefits
Part 2

Effectiveness
Safety
Accuracy
Integrity
The FDA defines software validation as…

**Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.**

The examination needs to confirm that the software will work in all anticipated situations.

Document all validation activities and test results.

Define what the user needs to do with the software and how they will use the software.

Examine the software to confirm that it functions as defined in requirements and it will be suitable for the intended use.

Define how the software needs to work to enable the intended use.

Source: General Principles of Software Validation: Final Guidance for Industry and FDA Staff
CSV Model

Planning → Verifies → Reporting

User Requirements Specification → Verifies → Performance Qualification Tests (PQ)

Functional Specifications

- How the software should look
- What data the software should capture
- Logic, calculations

System Build

Design Specifications

- Database design
- Process design
- Security design
- Interface design
- Architecture design
- Network requirements

Installation Qualification Tests (IQ)

Operational Qualification Tests (OQ)

Performance Qualification Tests (PQ)

Performance Qualification Tests (PQ)
CSV Model

Planning ➔ Verifies ➔ Reporting

User Requirements Specification ➔ Verifies ➔ Performance Qualification Tests (PQ)

Functional Specifications ➔ Verifies ➔ Operational Qualification Tests (OQ)

Design Specifications ➔ Verifies ➔ Installation Qualification Tests (IQ)

System Build ➔ Verifies ➔ User Requirements Specification

Performance Qualification
• Confirmation that all functionality is present
• Confirmation that all feature are working as specified

Performance Qualification
• Confirmation that software meets the users’ needs and is suitable for their use
CSV Model

Planning

User Requirements Specification

Verifies

Functional Specifications

Verifies

Design Specifications

Verifies

System Build

Installation Qualification Tests (IQ)

Operational Qualification Tests (OQ)

Performance Qualification Tests (PQ)

Reporting

Validation Report

• Confirmation of Validation Plan
• Testing Summary
• Confirmation that Acceptance Criteria Met
• Authorize Deployment

Terminology

VALIDATION
Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled. [FDA]

VERIFICATION
Software verification looks for consistency, completeness, and correctness of the software and its supporting documentation, as it is being developed, and provides support for a subsequent conclusion that software is validated. [FDA]

QUALIFICATION
Formal testing to demonstrate that the software meets its specified requirements. [IEEE]
**Terminology**

**VALIDATION**
Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

**VERIFICATION**
...consistency, completeness, and correctness of the software and its supporting documentation, ....

**QUALIFICATION**
Formal testing to demonstrate that the software meets its specified requirements.

**CSV Methodology**

**CSV Scope**
Part 4
What Software Requires Validation?

Medical Device Software
- Software used as a component, part, or accessory of a medical device
- Software that is itself a medical device

What Types of Computer Systems and Software Require Validation?

Medical Device Software
- Software used as a component, part, or accessory of a medical device.
- Software that is itself a medical device.

Examples: Medical Device Software

Blood Supply Management Software
Radiation Treatment Control Software
Infusion Pump Software
Heart Arrhythmia Detection Software
Blood Donor Management Software
Defibrillator Software
Patient Monitoring Software
Injury Treatment Machine Software
Medical Imaging System Software
Laser Treatment Software
Robotic Surgery Software
Hospital Bed Software
Laboratory Diagnostics Software
Oxygen Regulating Software
Pacemaker Software
Wheelchair and Scooter Software

Sources: General Principles of Software Validation: Final Guidance for Industry and FDA Staff
Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application
What Software Requires Validation?

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- Software used as a component, part, or accessory of a medical device
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**Production Software**
- Software used in the production of the FDA regulated product

What Types of Computer Systems and Software Require Validation?

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**Production Software**
- Software used in the production of the FDA regulated product

Examples: Production Software

**Production Software**
- Software used in the production of the FDA regulated product

- Manufacturing Automation Software
- Production Monitoring Software
- Laboratory Instrument Software
- Batch Release Software
- Programmable Logic Controllers (PLCs)
- Bill of Material Software
- Laboratory Management Software
- Product/Part Inspection Software
- Computer Numerical Controls (CNCs)
- Material Control Software
- Laboratory Calculations (e.g., spreadsheets)
- Product Testing Software
- Building Management Systems
- Work Order Management Software
- Yield Calculations
- Labeling Software

Sources:
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Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application
What Software Requires Validation?

Medical Device Software
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Production Software
- Software used in the production of the FDA regulated product

Quality Management Software
- Software used to implement the FDA-required quality management system

Sources: General Principles of Software Validation: Final Guidance for Industry and FDA Staff Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application

Examples: Quality Management Systems

Quality Management Software
Software used to implement the FDA-required quality management system

- Change Control Software
- Calibration Software
- Document Management Software
- Non-Conformance Tracking Software
- Inventory Control Software (e.g., ERPs)
- Preventive Maintenance Management
- Device History Software
- Deviation Tracking Software
- Product Returns Management Software
- Quality Trending Software
- Specification Management Software
- CAPA Software
- Product Recall Management Software
- Internal Audit Tracking Software
- Specification Setting Software
- Complaints Software
- Internal Audit Tracking Software
- Specification Setting Software
- Complaints Software
## What Software Requires Validation?

### Medical Device Software
- Software used as a component, part, or accessory of a medical device
- Software that is itself a medical device

### Production Software
- Software used in the production of the FDA regulated product

### Quality Management Software
- Software used to implement the FDA-required quality management system

### Software for FDA-Regulated Records
- Software used to create, modify, maintain, archive, retrieve, or transmit FDA-required records. And electronic records submitted, per FDA requirement.

### Examples: Records Software

<table>
<thead>
<tr>
<th>Software for FDA-Regulated Records</th>
<th>Electronic Submissions Software</th>
<th>IRB Records Software</th>
<th>Training Records Software</th>
<th>Prescription Order Fulfillment Software</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adverse Event Reporting Software</td>
<td>Clinical Trial Records Software</td>
<td>Learning Management Software</td>
<td>Distribution Records</td>
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<tr>
<td></td>
<td>MDR Reporting Software</td>
<td>Service Records Software</td>
<td>Supplier Approval Records</td>
<td>Warehouse Management Software</td>
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<tr>
<td></td>
<td>Organ / Tissue Donor Records</td>
<td>Call Center Records Software</td>
<td>Validation Records</td>
<td>Product Rework Records</td>
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<table>
<thead>
<tr>
<th>Topic</th>
<th>Part</th>
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<td>21 CFR 50</td>
<td>Protection of Human Subjects</td>
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<tr>
<td>Clinical Trials</td>
<td>21 CFR 56</td>
<td>Institutional Review Boards</td>
</tr>
<tr>
<td>Nonclinical Lab Studies</td>
<td>21 CFR 58</td>
<td>Good Laboratory Practice for Nonclinical Laboratory Studies</td>
</tr>
<tr>
<td>Drugs</td>
<td>21 CFR 210</td>
<td>Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs; General</td>
</tr>
<tr>
<td>Finished Pharmaceuticals</td>
<td>21 CFR 211</td>
<td>Current Good Manufacturing Practice for Finished Pharmaceuticals</td>
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<tr>
<td>Drugs</td>
<td>21 CFR 312</td>
<td>Investigational New Drug Application</td>
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<td>Drugs</td>
<td>21 CFR 314</td>
<td>Application for FDA Approval to Market a New Drug</td>
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<td>Biological Products</td>
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<td>Biological Products: General</td>
</tr>
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<td>Blood &amp; Components</td>
<td>21 CFR 606</td>
<td>Current Good Manufacturing Practice for Blood and Blood Components</td>
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<tr>
<td>Medical Devices</td>
<td>21 CFR 803</td>
<td>Medical Device Reporting</td>
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<tr>
<td>Medical Devices</td>
<td>21 CFR 806</td>
<td>Medical Devices: Reports of Corrections and Removals</td>
</tr>
<tr>
<td>Medical Devices</td>
<td>21 CFR 820</td>
<td>Quality System Regulation</td>
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<td>Cells and Tissue Products</td>
<td>21 CFR 1271</td>
<td>Human Cells, Tissues, and Cellular and Tissue-Based Products</td>
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Validation scope can be limited to the features that will be used by the regulated company.

For example, a device manufacturer who chooses not to use all the vendor-supplied capabilities of the software only needs to validate those functions that will be used and for which the device manufacturer is dependent upon the software results as part of production or the quality system.

Validation must be specific to the regulated company’s planned and documented use of the application.

The acceptance of vendor-supplied validation data in isolation of system configuration and intended use is not acceptable. In isolation from the intended process or end user IT infrastructure, vendor testing is likely to be limited to functional verification only, and may not fulfill the requirements for performance qualification.
What About ...

- Off-The-Shelf (OTS) Software?
- Configured Applications?
- Software as a Service (SAAS) Applications?
- Systems in the Cloud?

Vendor documentation can be used as the starting point for validation

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What About ...

- Off-The-Shelf (OTS) Software?
- Configured Applications?
- Software as a Service (SAAS) Applications?
- Systems in the Cloud?

The regulated company needs to audit the vendors of critical applications and services – depending on risk

---
What About ...

- Off-The-Shelf (OTS) Software?
- Configured Applications?
- Software as a Service (SAAS) Applications?
- Systems in the Cloud?

Formal agreements are required to document responsibilities

When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party.

Eudralex Annex 11, Computerised Systems

CSV Failure Consequences

Part 5
FDA Enforcement Tools

- Warning Letter
- Injunction
- Product seizure
- Import restrictions
- Clinical hold
- Delay in approval of new products or facilities
- Consent decree
- Rejection of application data
- Disqualification of clinical investigators
- Debarment
- Criminal prosecution

Warning Letter Statistics

Nearly 200 Warning Letter citations in the last 3 years (2012-2014) for software and computer system issues

Over 1/3 of these were for validation issues

A majority of the validation issues were for simply failing to validate the software or computer system
### Warning Letter Example

**Company**
German manufacturer of endoscopic grasping/cutting instruments

**System**
Purchased, configured ERP used for production planning and quality records. **NOTE:** Software vendor performed installation and upgrades

**Warning Letter Excepts**

- There are no procedures that describe the qualification and maintenance of the Majesty Enterprise Resource Planning (ERP) software for production planning and maintenance of quality records.
- There are no records documenting that the Majesty system is validated or meets user needs and intended uses.
- There are no documents that define the system's features and functions, operating environment, or hardware requirements.
- The procedure which addresses vendor selection qualification and requalification of suppliers, has not been not implemented. There is no documentation that the supplier of Majesty software, was qualified or re-qualified as a supplier.

---

### Warning Letter Example

**Company**
California manufacturer of wound bio-engineered alternative tissue devices

**System**
Spreadsheet used for calculations

**Warning Excepts**

- Your firm did not validate use of an Excel spreadsheet used to calculate the Moisture Vapor Transmission Rate (MVTR)

---

**Company**
New Jersey manufacturer of medical devices

**System**
SharePoint used for document management

**Warning Excepts**

- Off-the-shelf software (Microsoft SharePoint) is being used to manage quality system documents for document control and approval. However, firm has failed to adequately validate this software to ensure that it meets your needs and intended uses.
- There were two different versions of your CAPA & Customer Complaint procedure; however, no revision history was provided on the SharePoint document history. Your firm has failed to validate the SharePoint software to meet your needs for maintaining document control and versioning.
### Warning Letter Example

<table>
<thead>
<tr>
<th>Company</th>
<th>System</th>
<th>Warning Letter Except</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idaho manufacturer of radiopharmaceuticals</strong></td>
<td>Custom developed system for batch records, calculations, and label generation</td>
<td>• Firm's custom software for Master Batch Production record has not been validated. This software is responsible for generating the batch production record, performing calculations to produce varying concentrations of drug product, and generating label information for customer vials and lead pigs.</td>
</tr>
</tbody>
</table>
| **Italian manufacturer of laser devices** | Custom developed system for tech calls, complaints, and service records | • The software developed by your firm to record, evaluate, investigate, correct and repair incoming technical assistance calls, complaints, and service records was implemented in 2012, and has not been validated.  
• No validation documentation was available for an established protocol, any testing data, or a finished report for the validation of this system. |
| **German manufacturer of sterile and non-sterile needles and sutures** | Software controlling the machinery making needles | • Your firm uses custom automatic machines in the needle production process. Your firm stated that it performed software validation for the automatic machines and that the software protocol was tested, but these validation activities were not documented. |
| **Kentucky medical center** | Blood management | • Your firm went live with version 2.0.0 of the Hemocare Lifeline (HCLL) Donor Module; however, the validation of Module 15, Product Labeling, was incomplete in that it was not reviewed, accepted, or signed off by a responsible individual. |
CSV Program Implementation

Part 6

Procedure Examples
- How to validate
- How to perform risk assessment
- How to audit vendors

Policy Examples
- Which systems and software require validation?
- When does validation occur?
- When do vendors need to be qualified? Audited?

CAPA (if out of compliance)
Validation Master Plan
- Policies, Procedures
- Inventory
- Validation Timeline

Example
- Which systems and software require validation?
- What is the risk level of each?
- What is the priority for validating each system?
CSV Program Implementation

- Define Policies
- Develop SOPs and Templates
- Train Staff
- Inventory Systems and Software
- Assess and Prioritize Systems and Software
- Document Plan
- Validate!

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Independent Audits

Thank You!

Thanks for your interest in Computer System Validation

Any questions about what we have discussed today? Please, feel free to contact me:

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