Computer System Validation Basics

By Praxis Life Sciences
Computer System Validation Basics

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Your Praxis Facilitator

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- 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
Intro to Praxis Life Sciences

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 required for companies that...

**Activities**
- Design
- Develop
- Conduct clinical trials
- Manufacture
- Package
- Label
- Store
- Distribute
- Install
- Service

**Products**
- Pharmaceuticals
- Biologicals
- Medical Devices
- Blood and Blood Components
- Human Cell and Tissue Products
- Infant Formula

**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.
Validation Center™

**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.

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**USA**

**FDA 21 CFR 106 Infant Formula Requirements Pertaining to Current Good Manufacturing Practice, Quality Control Procedures, Qualify Factors, Records and Reports, and Notifications**

Subpart B—Current Good Manufacturing Practice, Sec. 106.35

(2) A manufacturer shall check and document the accuracy of input into, and output generated by, any system used in the production or quality control of an infant formula to ensure that the infant formula is not adulterated. The degree and frequency of input/output verification shall be based on the complexity and reliability of the system and the level of risk associated with the safe operation of the system.

(3) A manufacturer shall ensure that each system is validated prior to the release for distribution of any infant formula manufactured using the system.

(4) A manufacturer shall ensure that any system that is modified is revalidated following the modification and prior to the release for distribution of any infant formula manufactured using the modified system.
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’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).
9.8 The hardware and software of the computers should be checked regularly to ensure reliability. The software (program) should be validated before use.

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.

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 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.
CSV Regulatory Requirements

Praxis Life Sciences has everything you need for Computer System Validation and Software Quality Assurance

Consulting  Audit Services  Training  Library

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CSV Purpose and Benefits

Part 2
CSV Purpose and Benefits

- Effectiveness
- Safety
- Integrity
- Accuracy

CSV Methodology

Part 3
FDA Definitions

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.

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

CSV Model

**Planning**

- User Requirements Specification
- Functional Specifications
- Design Specifications
- System Build

**Validation Plan**

- Scope
- Approach
- Roles & Responsibilities
- Acceptance Criteria

**Verifies**

- Performance Qualification Tests (PQ)
- Operational Qualification Tests (OQ)
- Installation Qualification Tests (IQ)

**Reporting**
CSV Model

Planning → Verifies → Reporting

User Requirements Specification

- User Needs for the software
- Intended Use of the Software
- Critical Constraints

Functional Specifications

User Requirements Specification

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

Design Specifications

Performance Qualification Tests (PQ)

Operational Qualification Tests (OQ)

Installation Qualification Tests (IQ)

System Build

Functional Specifications

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

Design Specifications

Installation Qualification Tests (IQ)

System Build

Performance Qualification Tests (PQ)
CSV Model

Planning  →  Verify  →  Reporting

User Requirements Specification

Functional Specifications  →  Verify  →  Performance Qualification Tests (PQ)

Operational Qualification Tests (OQ)

Installation Qualification Tests (IQ)

System Build

Design Specifications

Development

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

Planning  →  Verify  →  Reporting

User Requirements Specification

Functional Specifications  →  Verify  →  Performance Qualification Tests (PQ)

Operational Qualification Tests (OQ)

Installation Qualification Tests (IQ)

System Build

Design Specifications

Develop Software /or/ Purchase and Configure

CSV Methodology
CSV Model

Planning → Verifies → Reporting

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

Functional Specifications → Verifies → Installation Qualification Tests (IQ)

Design Specifications → System Build

Operational Qualification Tests (OQ)

Installation Qualification
- Installation and Set Up instructions
- Confirmation that installed and set up according to Design

Operational Qualification
- Confirmation that all functionality is present
- Confirmation that all features are working as specified
CSV Model

CSV Methodology

Planning  →  Verifies  →  Reporting

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

Functional Specifications

Design Specifications

System Build

Operational Qualification Tests (OQ)

Installation Qualification Tests (IQ)

Performance Qualification
- Confirmation that software meets the users' needs and is suitable for their use

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]
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

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

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Examples: Medical Device Software

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

- 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

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

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?

**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

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

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**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.

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: Records Software

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

- Electronic Submissions Software
- IRB Records Software
- Training Records Software
- Prescription Order Fulfilment Software
- Adverse Event Reporting Software
- Clinical Trial Records Software
- Learning Management Software
- Distribution Records
- MDR Reporting Software
- Service Records Software
- Supplier Approval Records
- Warehouse Management Software
- Organ / Tissue Donor Records
- Call Center Records Software
- Validation Records
- Product Rework Records

CSV Scope

FDA Regulations

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Regulatory Information
- Guidance Documents
- Contact Information
- Current on Proposed Regulations
- Stays of Federal Regulations
- Drugs Management
- Federal Register (FR) Notices
- FDA Software
- More Regulatory Information

FOLLOW FDA
- FDA and FDA Home Blog Posts
- FDA Twitter Alerts
- Subscriptions to RSS Feeds
- Follow FDA on Twitter
- Follow FDA and Twitter
- View FDA Webinars on Flickr
- Follow FDA and Patients
- View FDA Images on YouTube
- More Interactive Tools

About FDA
- Compendia Page
- FDA Organization
- FDA Reports
- FDA Business for Industry
- Advisory Committees
- International Programs
- Press Releases
- FDA Advisory Board

CSV Scope
CSV Scope

What About ...

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

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.

FDA, General Principles of Software Validation
What About ...

**CSV Scope**

1. **Off-The-Shelf (OTS) Software?**
2. **Configured Applications?**
3. **Software as a Service (SAAS) Applications?**
4. **Systems in the Cloud?**

**2**

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

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**What About ...**

**CSV Scope**

1. **Off-The-Shelf (OTS) Software?**
2. **Configured Applications?**
3. **Software as a Service (SAAS) Applications?**
4. **Systems in the Cloud?**

**3**

Vendor documentation can be used as the starting point for validation.

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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 fulfil the requirements for performance qualification.

MHRA, GMP Data Integrity Definitions and Guidance

If the vendor can provide information about their system requirements, software requirements, validation process, and the results of their validation, the medical device manufacturer can use that information as a beginning point for their required validation documentation.

FDA, General Principles of Software Validation

Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.

Eudralex Annex 11, Computerised Systems
What About ...

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

The audit should demonstrate that the vendor’s procedures for and results of the verification and validation activities performed for the OTS software are appropriate and sufficient for the safety and effectiveness requirements ...

*FDA, General Principles of Software Validation*

The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.

*Eudralex Annex 11, Computerised Systems*

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

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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

Over 200 Warning Letter citations in the last 3 years (2013-2015) for software and computer system issues

Nearly 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

German manufacturer of endoscopic grasping/cutting instruments

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

- 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

### Consequences

<table>
<thead>
<tr>
<th>Company</th>
<th>System</th>
<th>Warning Expects</th>
</tr>
</thead>
<tbody>
<tr>
<td>California manufacturer of wound bio-engineered alternative tissue devices</td>
<td>Spreadsheet used for calculations</td>
<td>• Your firm did not validate use of an Excel spreadsheet used to calculate the Moisture Vapor Transmission Rate (MVTR)</td>
</tr>
</tbody>
</table>
| New Jersey manufacturer of medical devices | SharePoint used for document management | • 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. |
| Idaho manufacturer of radiopharmaceuticals | Custom developed system for batch records, calculations, and label generation | • 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. |
| 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. |
## Warning Letter Example

<table>
<thead>
<tr>
<th>Company</th>
<th>German manufacturer of sterile and non-sterile needles and sutures</th>
</tr>
</thead>
<tbody>
<tr>
<td>System</td>
<td>Software controlling the machinery making needles</td>
</tr>
<tr>
<td>Warning Letter Except</td>
<td>• 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.</td>
</tr>
<tr>
<td>Company</td>
<td>Kentucky medical center</td>
</tr>
<tr>
<td>System</td>
<td>Blood management</td>
</tr>
<tr>
<td>Warning Letter Except</td>
<td>• 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.</td>
</tr>
</tbody>
</table>

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## CSV Program Implementation

**Part 6**
CSV Program Implementation

**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?

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

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

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CSV Program Implementation

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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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