Quality System Software Validation in the Medical Device Industry

Chuck Offutt, CSQA
Sr. Manager – Software Validation Competency Development
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Agenda

- Regulatory Background
- Why Do We Validate?
- Who Says?
- What If We Don’t?
- How Do We Validate?
- Q&A
Background

Regulatory
Quality Management System
Regulatory Background

♦ FDA (Food and Drug Administration)
  – FDA’s modern regulatory functions began with the passage of the 1906 Pure Food and Drugs Act, a law a quarter-century in the making that prohibited interstate commerce in adulterated and misbranded food and drugs.

♦ CFR (Code of Federal Regulations)
  – The first edition of the CFR was published in 1938 under Roosevelt. CFR is codification of rules & regulations (Administrative Law) published in the Federal Register by the executive departments and agencies of the federal government of the United States.
  – Currently 50 Titles. Ranging from subjects such as Title 3, Executive Office of the President to Title 50, Wildlife & Fisheries.
  – Title 21 is the portion of the Code of Federal Regulations that governs food and drugs within the United States for the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy.
  • It is divided into three chapters:
    – Chapter I — Food and Drug Administration
    – Chapter II — Drug Enforcement Administration
    – Chapter III — Office of National Drug Control Policy
Regulatory Background, cont’d

- 21 CFR Parts

<table>
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<th>Title</th>
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<td>Labeling</td>
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<td>803</td>
<td>Medical Device Reporting</td>
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<td>806</td>
<td>Medical Devices; Reports of Corrections and Removals</td>
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<td>Premarket Approval of Medical Devices</td>
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<td><strong>820</strong></td>
<td>Quality System Regulation</td>
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<td>821</td>
<td>Medical Device Tracking Requirements</td>
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<td>822</td>
<td>Postmarket Surveillance</td>
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<td>830</td>
<td>Unique Device Identification</td>
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Medical Device Quality Management System (QMS)

- Management responsibility
- Quality audit
- Personnel
- Design controls
- Document controls
- Purchasing controls
- Device Identification & Traceability
- Production and process controls
- Inspection, measuring, and test equipment
- Process validation
- Receiving, in-process, and finished device acceptance
- Nonconforming product
- Corrective and preventive action
- Device labeling & Packaging
- Handling, Storage, Distribution & Installation
- General Records requirements
  - Device master record
  - Device history record
  - Quality system record
- Complaint files
- Servicing
- Statistical techniques
Non-Product System Software (NPSS)

- Software that is **not** embedded in a medical device and is not a medical device itself
- Software that is **not** used in the direct manufacturing or R&D of medical devices
- Some examples of NPSS are:
  - Training and learning management software
  - Document management software
  - Software used for purchasing control
  - Software which controls non-conforming products
  - Corrective and preventive action (CAPA) management software
  - Analytical tools used to make quality decisions
  - Spreadsheets used to apply calculations on data to make Quality decisions (e.g. Hold & Release)
Why Do We Validate?
Why do we validate?

Bottom line: Patient and User Safety!

The quality of medical devices patients receive depends heavily on the quality of the decisions made by the manufacturer.

The quality of the decisions made is only as good as the quality of the data used to make those decisions.

The data that is analyzed to make quality decisions is only as good as the quality of the software used to collect and report the data.

The quality of the software is only as good as the processes and procedures used to create, test, control, and maintain it.

Decision Quality

Data Quality

Software Quality

Validation Quality

Bottom line: Patient and User Safety!

Why do we validate?

Decision Quality

Data Quality

Software Quality

Validation Quality

Bottom line: Patient and User Safety!
Who Says We Have toValidate?
Who Says?

♦ FDA – 21 CFR Part 820.70i
  – *Automated processes*. 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.*

♦ ISO 13485, Section 4.1.6
  – The organization shall document procedures for the validation of the application of computer software used in the quality management system. Such software applications shall be validated prior to initial use and, as appropriate, after changes to such software or its application.
  – The specific approach and activities associated with software validation and revalidation shall be *proportionate to the risk* associated with the use of the software.
  – Records of such activities shall be maintained.
What If We Don’t Follow the Rules?
What Can Possibly Happen?

- **Audit Observations – Strike 1**

- **Warning Letters (483’s)** ([https://www.fda.gov/iceci/enforcementactions/warningletters/](https://www.fda.gov/iceci/enforcementactions/warningletters/)) – **Strike 2**
  - An FDA warning letter is an official message from the FDA that it has found that a manufacturer or other organization has violated some rule in a regulated activity.
  - It highlights in detail the rules that were violated.
  - Companies have **15 days** to respond to a Warning Letter with the solutions/timeframes to fix the problems.

- **Consent Decrees – Strike 3**
  - An agreement between the FDA and a company that outlines steps that a company has to take in order to return to full, independent production.
  - The consent decree mandates that a company start initiating change, and that change is usually associated with the way the company is manufacturing a product.
  - And almost invariably, it will involve the company employing outside consultants to come in and re-constitute the manufacturing practices to bring it in alignment with the FDA’s vision of Good Manufacturing Practices (GMPs).
  - The Decree can tell a company that it must stop marketing or even stop manufacturing until agency-perceived defects are corrected.

- **Prison / Felony Charges – You’re Out!**
Does This Really Happen?

FDA Enforcement Statistics
Summary
Fiscal Year 2016

<table>
<thead>
<tr>
<th>Enforcement Type</th>
<th>FY16 Summary Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>4</td>
</tr>
<tr>
<td>Injunctions</td>
<td>17</td>
</tr>
<tr>
<td>Warning Letters</td>
<td>14,590</td>
</tr>
<tr>
<td>Recall Events</td>
<td>2,847</td>
</tr>
<tr>
<td>Recalled Products</td>
<td>8,305</td>
</tr>
<tr>
<td>Drug Product Debarments</td>
<td>1</td>
</tr>
<tr>
<td>Food Importation Debarments</td>
<td>0</td>
</tr>
</tbody>
</table>
Ok – So How Do We Validate?
What Is Validation vs. Verification?

According to the FDA:

– **Software verification** provides objective evidence that the design outputs of a particular phase of the software development lifecycle meet all of the specified requirements for that phase. 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.

– **In other words, verification ensures that “you built it right.”**

– **Software validation** is 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. Since software is usually part of a larger hardware system, software validation typically includes evidence that all software requirements have been implemented correctly and completely and are traceable to system requirements.

– **In other words, validation ensures that “you built the right thing.”**
Validation Methodology – GAMP5 V-Model
QS Impact and Risk Assessment

♦ Quality System Impact Assessment –
  – Does this system have an impact on the Quality System?
    • If Yes, then a validation is required
    • If No, the verification and qualification is still required but not under Regulatory guidance

♦ Validation Scalability
  – What is the degree of safety and regulatory compliance risk?
  – How technically complex is the system?
  – How is the system being delivered?
    • COTS (Commercial Off-the-Shelf)
    • CUSTOM
    • SaaS
  – Based on results, what are the minimum deliverables/documentation required as evidence?

♦ Part 11 Compliance
  – Does the planned system have any gaps in meeting the electronic records/electronic signature requirements of 21CFRPart11?
Validation Planning

- **Validation Plan**
  - Provides scope of validation and overall validation strategy
  - Defines the boundaries

- **Testing Plan**
  - What level of testing will be used
  - Training requirements for team members
  - Location and logistics of required testing phases

- **Data Migration Plan**
  - Details of required data migration are defined and agreed to
  - Sampling plans defined
  - Data transformation defined, if required
Requirements and Specifications

- User/System Requirements Specification (the ‘What’)
  - High level requirements that define what the system needs to do or provide in order for the business users to perform their intended use.

- Functional Requirements Specification (the ‘How’)
  - Decomposition of the user requirements into system functional specification defining HOW the system will be configured to provide the stated user requirements.

- Design Spec (the ‘How to Build’)
  - Further detail needed by developers to actually build/configure the system to meet the functional specifications.
Risk Based Testing

♦ Evaluate Risk Associated with Each User Requirement
  – Variant of FMEA
  – Severity
  – Frequency
  – Detectability

♦ Based on Risk level, Determine Appropriate Level of Testing Required
  – Do I want to put as much testing effort into the ability of the dome light in my car to come on when I open the door as I do to verify the brakes work at highway speeds?

♦ Low Risk Requirements versus High Risk requirements
  – Simple verification vs. extensive positive, negative, and boundary level testing.

♦ Testing Scalability Directly Impacts Cost of Quality
  – Project Timelines
  – Appropriate levels of documentation and testing resources
Construction and Verification Testing

♦ Agile Development
   – Technique of Project Management for software development
   – Manages projects by defining iterative and incremental work sequences (Sprints)
   – Timed releases of functionality using frequent demos to the user
   – Allows for rapid feedback from the user and subsequent changes by the development team

♦ Waterfall
   – Traditional software development methodology
   – Systems can be specified up front and built in a predictable manner.
   – Does not support flexibility in making changes.
   – Saves testing until the end when cost of defects are at their highest
System Environments

- Development Environment
  - Used by IT for development & module testing

- QA Environment
  - Used by IT for IQ and OQ testing.
  - Used by Business for PQ testing
  - Must be functionally equivalent to Production

- Production Environment
  - Used by IT for Production IQ
  - Final Production Use

- Training Environment

- Automated Testing Environment
Formal Testing (IQ / OQ / PQ) in the QA Environment

◦ IQ (Installation Qualification)
  – Establishing confidence that [systems] are compliant with appropriate codes and approved design intentions, and that manufacturer recommendations are suitably considered.
  – In short – installation and configuration of the software according to the design specifications.

◦ OQ (Operational Qualification)
  – Establishing confidence that [systems] are capable of consistently operating within stated limits and tolerances.
  – In short – verification that the system was built/configured according to the design specifications.
  – Does it do things right?

◦ PQ (Performance Qualification).
  – Sometimes referred to as UAT (user acceptance test)
  – Verification that the system meets the users intended use as defined in the user requirements specification.
  – Can the end user do their job?
  – Does the system do the right things right?
## Testing Documentation

- **Test Protocol (Scripts) Execution**
  - Must adhere to GDP guidelines (Good Documentation Practice)

### Test Script OQ-25.1.1: Children Report Config forms

<table>
<thead>
<tr>
<th>Test Step No.</th>
<th>Requirement</th>
<th>Action</th>
<th>Expected Result(s)</th>
<th>Actual Results</th>
<th>Pass/Fail</th>
<th>Initials &amp; Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td>Logon to System with Role1 permissions.</td>
<td>User is logged into System.</td>
<td>Logged in a Role 1</td>
<td>Pass</td>
<td>CRO 18APR2017</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>Create a Record and the Child record MDR, MDV, MDB, Australia/NZ, China, Korea, Singapore and Taiwan.</td>
<td>Parent and Child records are created.</td>
<td>The Parent and Child records were created.</td>
<td>Pass</td>
<td>CRO 18APR2017</td>
</tr>
<tr>
<td>3. FR-8F1-1</td>
<td></td>
<td>Verify that all Children Report ConfigForms (MDR, MDV, MDB, Australia/NZ, China, Japan, Korea, Singapore and Taiwan) will display the Parent records AEC Report Indicator and the region’s Due Date. And also the following fields displayed: Reporting Decision Notes, Customer’s Problem Description, TestNotes, Communication Notes.</td>
<td>All fields are displayed. Screenshot is captured, labeled and attached to the script.</td>
<td>Only these fields were displayed: Reporting Decision Notes, Customer’s Problem Description, Screenshot captured. See Image-13.</td>
<td>FAIL</td>
<td>CRO 18APR2017</td>
</tr>
</tbody>
</table>
Testing Documentation - Deviation

♦ Issue Description
  – Error Type
  – Severity

♦ Proposed Resolution/Corrective Actions
  – Typically provided by IT and agreed to by Business and Q&R
  – Capture required changed to code as well as documentation

♦ Final Disposition
  – May not be same as proposed.
Test Summary Reports

- Details of Test Results/Deviations for IQ/OQ/PQ

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Test #</th>
<th>Test Script Title</th>
<th>Revision</th>
<th>Run Number</th>
<th>Status (Passed/Failed)</th>
<th>Deviation #</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>QR004412</td>
<td>PQ-60.1.1</td>
<td>Reassign CAPA Facilitator</td>
<td>1</td>
<td>1</td>
<td>Pass</td>
<td>DEV-TWUGRD-PQ-001</td>
<td>Moderate – Correction made on the executed script and test was accepted. The deviation was closed when the protocols were updated and new revision release.</td>
</tr>
<tr>
<td>QR004412</td>
<td>PQ-60.1.2</td>
<td>Mandatory Fields New Tab</td>
<td>1</td>
<td>1</td>
<td>Pass</td>
<td>None</td>
<td>All test steps passed. No errors</td>
</tr>
<tr>
<td>QR004412</td>
<td>PQ-60.1.3</td>
<td>Group Categories permission for task</td>
<td>1</td>
<td>1</td>
<td>Pass</td>
<td>None</td>
<td>All test steps passed. No errors</td>
</tr>
<tr>
<td>QR004412</td>
<td>PQ-60.1.4</td>
<td>Prevent CAPA Child Tasks from being allowed to Close</td>
<td>1</td>
<td>1</td>
<td>Pass</td>
<td>DEV-TWUGRD-PQ-003</td>
<td>Moderate – Error message display had more information than what was written in Expected Results. The appropriate message was conveyed, so the test was accepted and the script updated and released in version of the protocol.</td>
</tr>
</tbody>
</table>

- Acceptance Criteria for Test Phase

- Conclusion of Test Phase
Final Validation Summary Report

♦ Report of Actual Validation Activities Against the Planned Validation Strategy
♦ Summary of All Testing Results
♦ Conclusion that the System is Fit for Business Use and Meets the Intended Use.
♦ This Is Typically The Document We Provide To Audit Investigators When They Want To Know Validation Status Of A System
Change Management

- As the Validated System Goes Through Changes, Validation Status Must be Maintained
- Therefore, the V-Model Is Really a Circle!
Huh?