Quality System Software Validation in the Medical Device Industry

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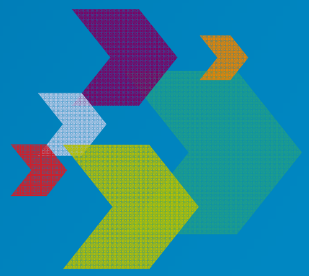


Agenda

- 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

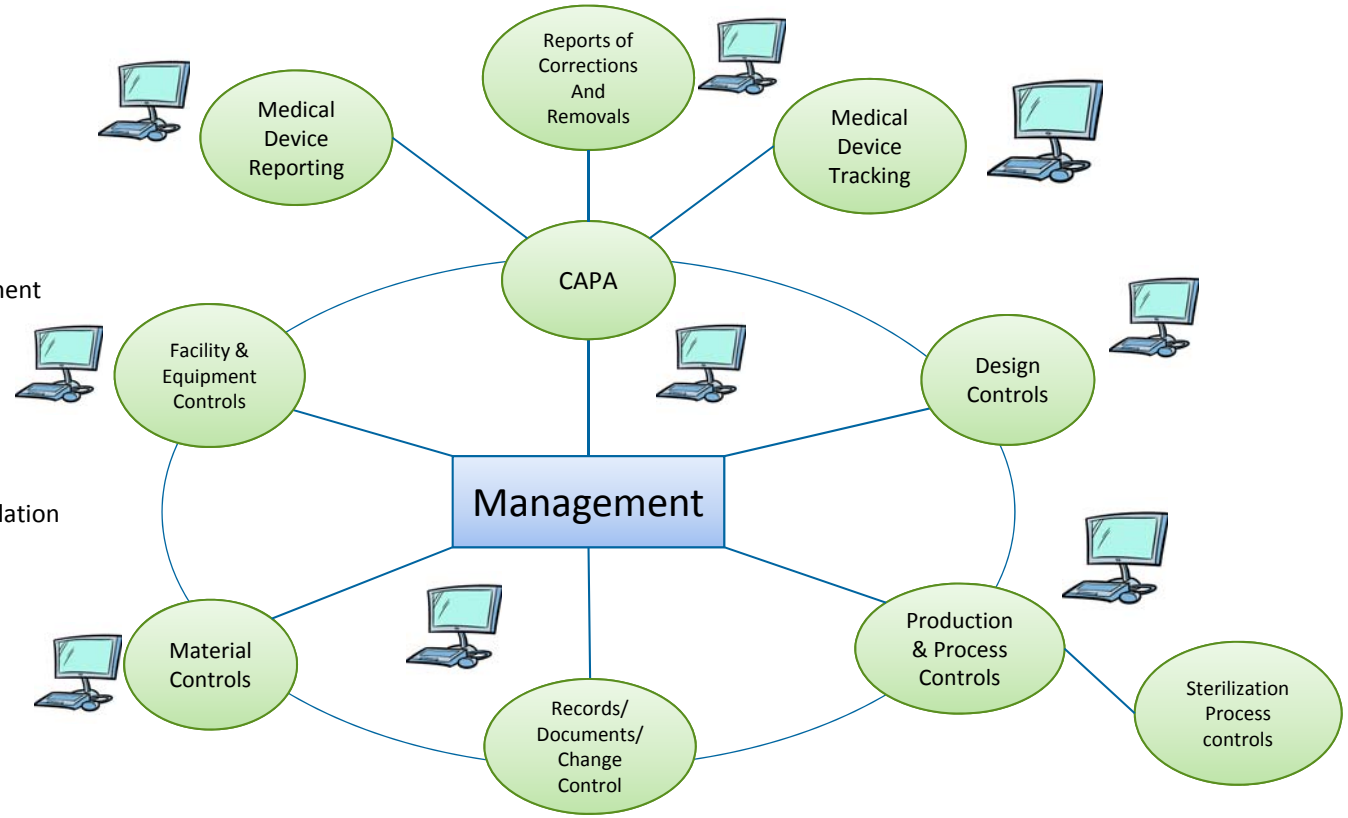
Regulatory Background, cont'd

- 21 CFR Parts

Part	Title
801	Labeling
803	Medical Device Reporting
806	Medical Devices; Reports of Corrections and Removals
814	Premarket Approval of Medical Devices
820	Quality System Regulation
821	Medical Device Tracking Requirements
822	Postmarket Surveillance
830	Unique Device Identification

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



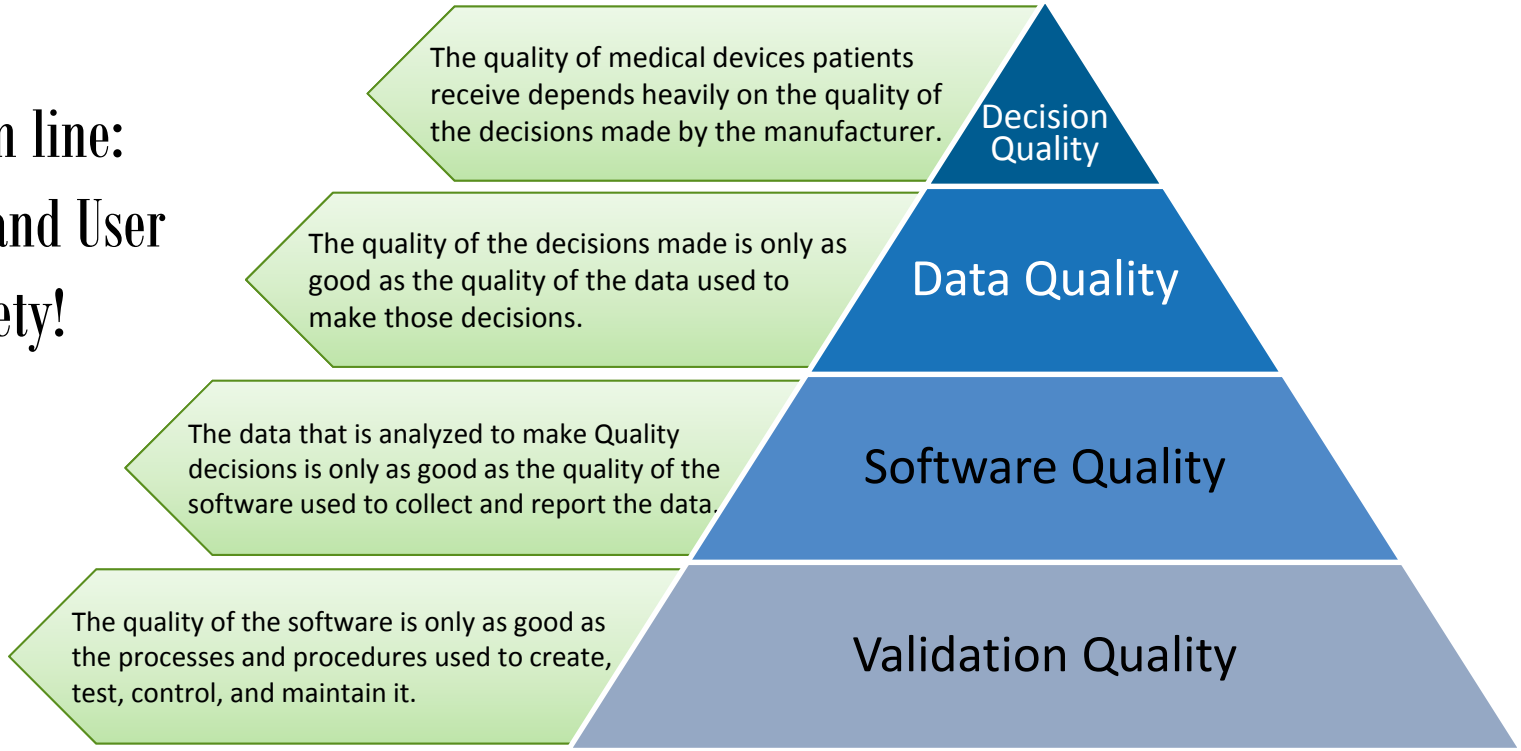
Non-Product System Software (NPSS)

- 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!



Who Says We Have to Validate?

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/) – 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

Enforcement Type	FY16 Summary Numbers
Seizures	4
Injunctions	17
Warning Letters	14590
Recall Events	2847
Recalled Products	8305
Drug Product Debarments	1
Food Importation Debarments	0

Ok – So How Do We Validate?

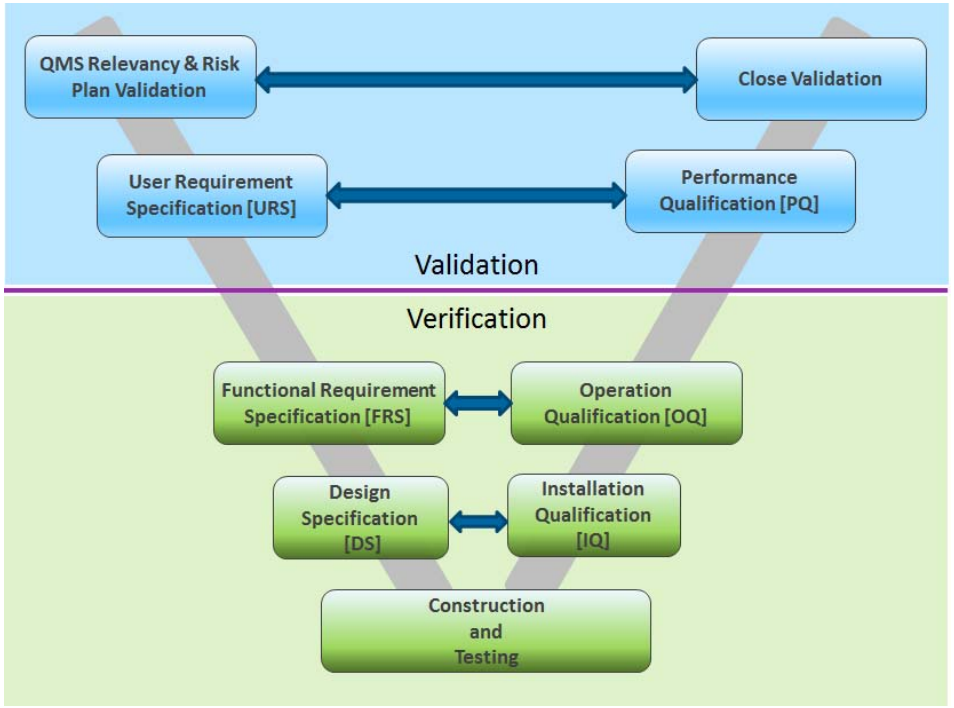
What Is Validation vs. Verification?

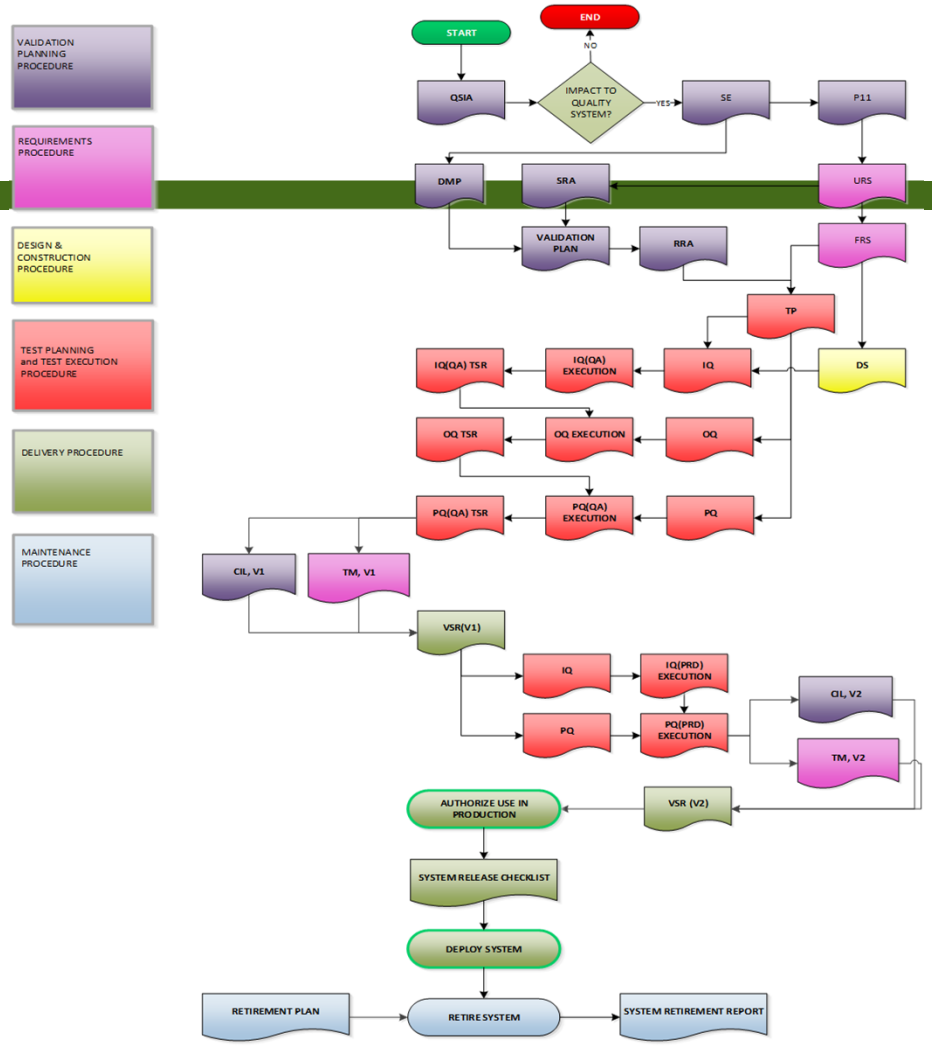
- According to the FDA:
  - *Software verification provides objective evidence that the design outputs of a particular phase of the software development lifecycle meet all of the specified requirements for that phase. Software verification looks for consistency, completeness, and correctness of the software 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

Q&R and Business

IT




VALIDATION PLANNING PROCEDURE
REQUIREMENTS PROCEDURE
DESIGN & CONSTRUCTION PROCEDURE
TEST PLANNING and TEST EXECUTION PROCEDURE
DELIVERY PROCEDURE
MAINTENANCE PROCEDURE
START
END
NO
QSIA
IMPACT TO QUALITY SYSTEM?
YES
SE
P11
DMP
SRA
URS
VALIDATION PLAN
RRA
FRS
TP
IQ(QA) TSR
IQ(QA) EXECUTION
IQ
DS
OQ TSR
OQ EXECUTION
OQ
PQ(QA) TSR
PQ(QA) EXECUTION
PQ
CIL, V1
TM, V1
VSR(V1)
IQ
IQ(PRD) EXECUTION
PQ
PQ(PRD) EXECUTION
CIL, V2
TM, V2
AUTHORIZE USE IN PRODUCTION
VSR (V2)
SYSTEM RELEASE CHECKLIST
DEPLOY SYSTEM
RETIREMENT PLAN
RETIRE SYSTEM
SYSTEM RETIREMENT REPORT

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

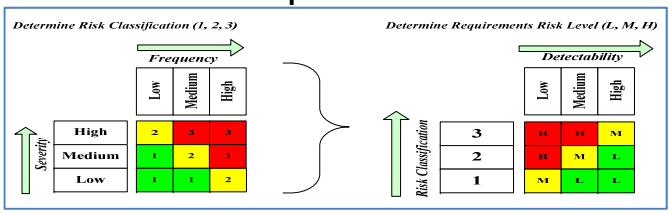
- Validation Plan
  - Provides scope of validation and overall validation strategy
  - Defines the boundaries
- Testing Plan
  - What level of testing will be used
  - Training requirements for team members
  - Location and logistics of required testing phases
- Data Migration Plan
  - Details of required 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

- Used by IT for development & module testing

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

- 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

Test Step No.	Requirement	Action	Expected Result(s)	Actual Results	Pass/ Fail	Initials & Date
1.		Logon to System with Role1 permissions.	User is logged into System.	*Logged in a Role 1*	*Pass*	*CRO 18APR2017*
2.		Create a Record and the Child record MDR, MDV, MDB, Australia/NZ, China, Korea, Singapore and Taiwan.	Parent and Child records are created.	*The Parent and Child records were created.*	*Pass*	*CRO 18APR2017*
3.	FRS-SF1-1	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 • Test/Notes • Communication Notes **Capture Screen Print**	All fields are displayed. Screenshot is captured, labeled and attached to the script.	*Only these fields were displayed:* • *Reporting Decision Notes* • *Customer's Problem Description* *Screenshot captured. See Image-13*	*FAIL* ❶	*CRO 18APR2017*

❶ *DEV_TWUPGRD_OQ_015 CRO 18APR2017*

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

9 Test Results

Protocol	Test #	Test Script Title	Revision	Run Number	Status (Passed/Failed)	Deviation #	Comments
QR004412	PQ-60.1.1	Reassign CAPA Facilitator	1	1	Pass	DEV-TWUPGRD-PQ-001	Moderate – "Correction made on the executed script and test was accepted. The deviation was closed when the protocols were updated and new revision release.
QR004412	PQ-60.1.2	Mandatory Fields New Tab	1	1	Pass	None	All test steps passed. No errors
QR004412	PQ-60.1.3	Group Categories permission for task	1	1	Pass	None	All test steps passed. No errors
QR004412	PQ-60.1.4	Prevent CAPA Child Tasks from being allowed to Close	1	1	Pass	DEV-TWUPGRD-PQ-003	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.

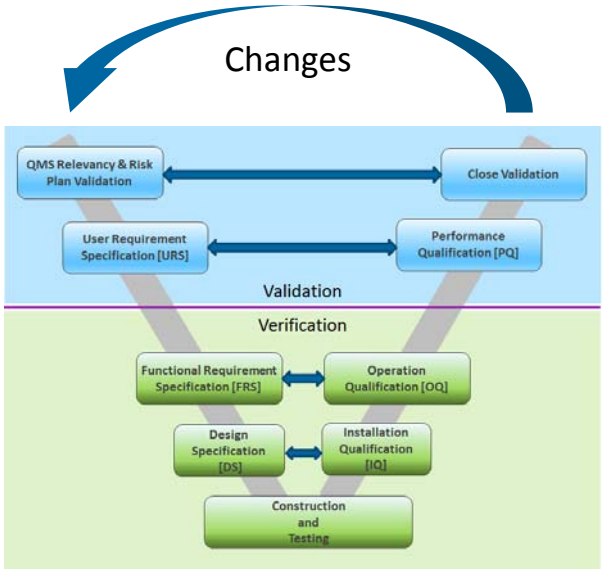
- Acceptance Criteria for Test Phase
- Conclusion of Test Phase

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?