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White Paper

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The λ Validation Model

for Regulatory Application Development

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Overview

Healthcare applications are largely governed by provisions of regulatory standards such as 21 CFR Part 11. These requirements span through the lifecycle stages of software development. Validation activities contribute significantly to the overall cost of software development in the regulatory context due to implementation of additional controls required for regulatory compliance. Performing validation by following traditional testing models such as the V-Model for Regulatory Application Development, to validate healthcare applications tends to take longer time to execute multiple cycles of IQ, OQ and PQ and hence cost more to comply with regulatory requirements. With the worldwide IT spending for healthcare organizations is ever increasing, it is very critical to provide and implement optimal IT solutions for healthcare organizations. This paper examines the current limitations of using the V-model for Regulatory Application Development and proposes an improved model and a suggestive new perspective on this subject to reduce time and cost of qualification.

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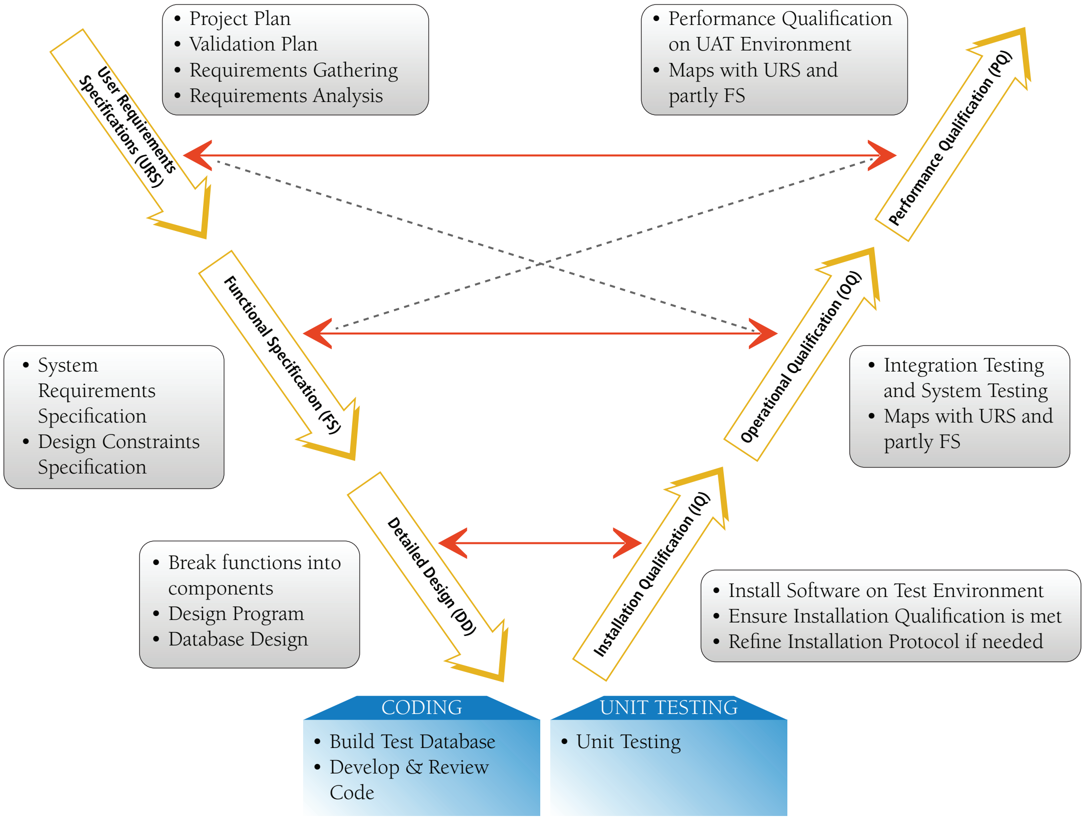
Qualification in Regulatory Application Development

Qualification, in Regulatory Application Development, establishes confidence that software product / application and auxiliary systems is capable of consistently operating within established limits and tolerances with sufficient documented evidence that the phases were executed. Producing sufficient evidence typically includes evidence that all the steps mentioned in the test case were executed with screen captures and prints as described in the respective test case, final test results and results at respective verification points recorded with executer's signature & date/timestamp, and approval of Project Manager / Compliance Manager that the test case was indeed executed as described. However, the definition of 'sufficient evidence' may change from project to project based on the client requirement and is typically discussed with client and documented in the Computer System Validation Plan. Conventional Integration Testing, Functional Testing and System Testing is typically not considered as sufficient form of testing evidence in Regulatory context because it fails to produce documented "sufficient" evidence with screen captures and e-signature/wet-signature of the tester with date/timestamp. The V-Model for Regulatory Application Development details various qualification phases such as Installation Qualification, Operational Qualification and Performance Qualification that addresses the requirements for testing software applications complying regulatory requirements.

Reviewing the V-Model for Regulatory Application Development

The V-Model of Validation is a widely accepted sequence of steps in the project development life cycle. The left arm of the "V" represents the planning / specification phases such as User Requirements Specification, Functional Specification, Detailed Design, and the right arm of the "V" represents the execution-validation phases such as Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) and both the arms converge at the Build and Unit Testing phases at the V-Point.

Figure 1: The V-Model of Validation



• Project Plan
• Validation Plan
• Requirements Gathering
• Requirements Analysis
• Performance Qualification on UAT Environment
• Maps with URS and partly FS
User Requirements Specifications (URS)
Performance Qualification (PQ)
Functional Specification (FS)
Operational Qualification (OQ)
• System Requirements Specification
• Design Constraints Specification
• Integration Testing and System Testing
• Maps with URS and partly FS
Detailed Design (DD)
Installation Qualification (IQ)
• Break functions into components
• Design Program
• Database Design
• Install Software on Test Environment
• Ensure Installation Qualification is met
• Refine Installation Protocol if needed
CODING
• Build Test Database
• Develop & Review Code
UNIT TESTING
• Unit Testing

Limitations of V-Model from a Regulatory Application Development perspective

1. Installation Qualification (IQ) is establishing confidence that the software product /application and auxiliary systems have been installed in compliance with approved design intentions. Installation Qualification requires integration of the various modules to be completed successfully so that software deployment could be performed in a comprehensive manner. The software integrated for the first time in the development cycle most often than otherwise have integration issues which can potentially result in multiple IQ cycles being executed. Installation Qualification may not yield value without performing a successful conventional Integration Testing on the integrated components.

2. Operational Qualification (OQ) is establishing confidence that software product / application and auxiliary systems is capable of consistently operating within established limits and tolerances. Operational Qualification requires evidence that the software performs as per the requirements specification. Operational Qualification is expected to cover System, Functional and Integration Testing aspects. However, OQ typically requires screen shots to be taken at verification points and final result, unlike conventional system / functional testing, as evidence that system performs as required and also OQ requires wet signatures (or e-signatures) from the Tester and Approver for each of the Test Cases executed. Failures in Test Cases results in multiple cycles of OQ being executed. Executing multiple cycles of OQ due to defects detected by taking screen shots and wet signatures increases cost significantly as the steps required for executing OQ are more than that of System / Functional Testing (see Table 1 below).

Table 1: Operational Qualification Vs Conventional System / Functional Testing

Parameters / Steps	System / Functional Testing (for Conventional Testing)	Operational Qualification (for Regulatory Application)
Test Case Execution	Required	Required
Record Results	Required	Required
Screen Shots at data input, at each Verification Point and during recording the Test Results	Not Required	Required
Wet Signature of the Tester for each Test Case	Not Required	Required
Wet Signature of the Approver for each Test Case	Not Required	Required

3. Performance Qualification (PQ) is establishing confidence through appropriate testing that the software product performs in the production area as desired by system users. Performance Qualification is typically considered as an equivalent of User Acceptance Testing. PQ is required to be performed on the User Acceptance Environment which is required to be a Production like environment (as comprehensive end-to-end testing on Production Environment may not be desirable) or on Production Environment. PQ is typically executed by the users and executing multiple rounds of PQ becomes very expensive especially when the test cases are executed by business users / system users of the Software Application as availability of the users is usually sparse.

Case Study

Clinical Trials Application – Estimating the Validation Effort

Before elaborating the proposed new validation model, the amount of effort spent for operational qualification and conventional system / functional testing has been detailed below in the form of a case study. The case study attempts to provide a glimpse of all the activities required / not required in each of the cases and to provide the readers better context of the proposed new validation model.

- Time taken was recorded for trial executions of Operational Qualification.
- Total number of Test Cases used for Trial run: 5 Test Cases (sample space)

Table 2: Execution Time for Operational Qualification

Steps	Operational Qualification – Activities	Time Taken for OQ (in mins approx.)
1	Input Data, take Screen Shot of the input data, add title to the screen shot and Execute Test Case	5 mins
2	Record Results at Verification Points, take Screen Shot of the results and add title to the screen shot	5 mins
3	Record Final Results in the Tool, take Screen Shot of the results and add title to the screen shot	5 mins
4	Generate and Print Document with Test Case Execution and Results (with basic formatting)	10 mins
5	Paste Screen Shots in Generated Document along the Test Cases and format	5 mins
6	Tester to sign each Test Case and date	2 mins
7	Approver to sign each Test Case and date	2 mins
8	Sign the Signature Page and Baseline the cycle of Test Execution	1 min
	Total Time Taken	35 mins

Note:

1. The trial did not include time taken to log defects in the defect management tool for failed test cases.
2. Trial runs were actually executed faster than the formal real-time execution of operational qualification.

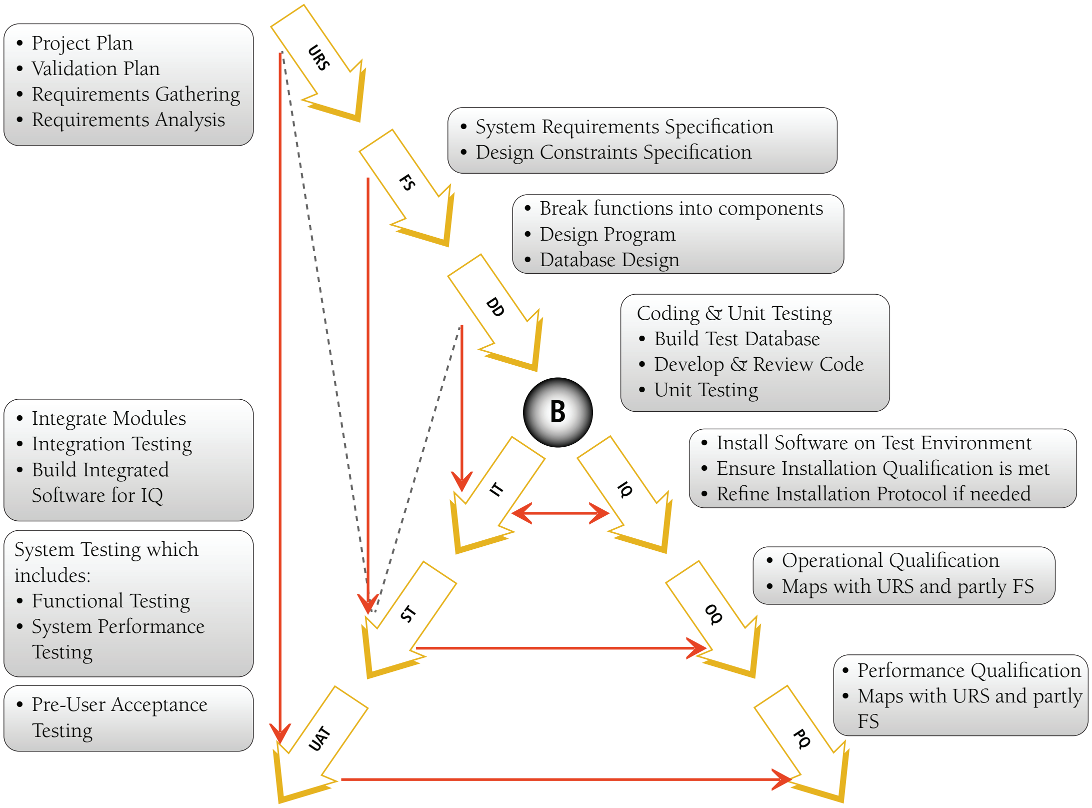
Please make note of the effort consumed (35 mins) during trial run of the Operational Qualification.

Please Note: The case study continues after introducing the new λ model.

The proposed λ-Model of Validation for Regulatory Application Development

The following diagram presents the proposed new λ-Model of Validation:

Figure 2: λ Validation Model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• Build Test Database
• Develop & Review Code
• Unit Testing
B
• Integrate Modules
• Integration Testing
• Build Integrated Software for IQ
IT
IQ
• Install Software on Test Environment
• Ensure Installation Qualification is met
• Refine Installation Protocol if needed
System Testing which includes:
• Functional Testing
• System Performance Testing
ST
OQ
• Operational Qualification
• Maps with URS and partly FS
• Pre-User Acceptance Testing
UAT
PQ
• Performance Qualification
• Maps with URS and partly FS

Salient features of the proposed λ Validation Model:

1. The λ model proposes that the Integration Testing to be performed before and optionally after Installation Qualification.

   The sequence of steps proposed:

   a. Integration of various software modules

   b. Perform Integration Testing

   c. Ensure success criteria for Integration Testing is achieved

   d. Perform fresh installation of the software as per specification

   e. Perform Installation Qualification

   f. A round of Integration Testing may be performed after IQ but it can be optional. The Integration Testing will be required to be performed, if the success criteria for Integration Testing were not met completely and yet Installation Qualification was not affected by the failure of those Integration Test Cases

This method is advantageous in many ways:

   a. The results of Installation Qualification are more valid as it will be performed on integrated software that has been tested for integration issues and is stable. This improves the quality of Installation Qualification results.

   b. Integration issues could be resolved earlier in the cycle resulting in stable build earlier.

   c. Once the modules are integrated and stable, a comprehensive deploy of the software could be made as per specifications. A holistic software deployment may not be even possible without stable integrated software product.

   d. Multiple Installation Qualification cycles performed due to Integration issues could be avoided.

2. The λ model proposes that successful Functional / System Testing be made as the entry criteria for proceeding to the Operational Qualification phase. The cost of executing multiple cycles of System / Functional testing is much lesser (see case study) than that of executing multiple cycles of OQ due to defects detected in the software. A successful System / Functional Testing would result in successful execution of OQ faster, avoiding multiple cycles of Operational Qualification being required to be executed. System performance testing such as required response times of the system, capacity growth / consumption of the system resources etc as mentioned in the requirements should also be performed as part of System Testing before proceeding to OQ.

3. The λ model also proposes that pre-testing (pre-UAT) of the Performance Qualification Test Cases be performed by the Testing Team so that multiple cycle of Performance Qualification could be avoided. This step can be perceived as an additional step which might increase the cost. However, considering the fact that most of the times, users who are involved in mainstream operations of the firm are required to take time-off their busy schedule to perform Performance Qualification, a pre-UAT could save cost especially when the user's availability is sparing.

Limitations of V-Model that are addressed in λ Validation Model

1. Operational Qualification in V-Model attempts to address multiple aspects of testing such as Integration, Functional, System, System Performance testing etc within the OQ phase while the λ Model provides clarity in the sequence of testing that needs to be executed

2. Due to defects detected during testing, multiple cycles of testing will be required to be executed. Significant cost could be saved by executing multiple cycles of conventional system / testing and finally executing one round of OQ to produce the documented evidence required for regulatory compliance. This aspect is addressed in λ Model.

3. Since conventional system / functional testing consume lesser time cycles, the stability of the software product / release is achieved much faster than by following the V-Model for Regulatory Validation.

Case Study

Continued…

Quantitative Benefit of the proposed λ Validation Model

- Time taken was recorded for trial executions of System Testing using the same Test Cases.
- Total number of Test Cases used for Trial run: 5 Test Cases (sample space)

Table 3: Execution Time for System Testing

Steps	System / Functional Testing – Activities	Time Taken for ST (in mins approx.)
1	Input Data and Execute Test Case	3 mins
2	Record Results at Verification Points	3 mins
3	Record Results in the Tool	2 mins
4	Generate and Print Document with Test Case Execution and Results (with basic formatting)	10 mins
5	Sign only the Signature Page and Baseline the cycle of Test Execution	2 mins
	Total Time Taken	20 mins

Salient Observations by comparing Table 2 and Table 3:

1. Clearly, the effort required to execute Operational Qualification is almost twice the effort that is required to execute conventional System Testing
2. The effort required grows significantly when there are a significant number of test cases required to be executed for multiple cycles of Operation Qualification

To derive the quantitative benefit using the case study, let us consider that 3 cycles of Testing is planned to be executed.

In this case, 1 cycle of OQ is going to consume 35 mins (*Please refer Table 2*)

Therefore 3 cycles of OQ = 35x3 = 105 minutes …………………………………………….. (1)

In this case, 1 cycle of System Testing is going to consume 20 mins (*Please refer Table 3*)

Therefore 3 cycles of System Testing = 20x3 = 60 minutes ………………………………….. (2)

However, there is at least one cycle of Operational Qualification that needs to be executed to generate sufficient documented evidence of validation for regulatory compliance to establish confidence that software product / application and auxiliary systems is capable of consistently operating within established limits and tolerances.

Therefore, if 2 of the earlier cycles are executed using conventional system / functional testing and then 1 cycle of OQ is executed, then:

The total time taken is going to be (20x2) + 35 = 75 minutes …………………………… ... (3)

Net saving in Time = (1) – (3) = 105 – 75 = 30 minutes

Implementing the new λ Validation Model

The following steps need to be followed for implementing the λ Validation Model

1. Include plan for Integration Testing, System / Functional Testing and Pre-UAT Testing during Computer System Validation Planning phase.
2. Define Entry Criteria for Installation Qualification, Operational Qualification and Performance Qualification such that:
    a. Successful Integration Testing is the entry criteria for Installation Qualification

    b. Successful System / Functional Testing is the entry criteria for Operational Qualification

    c. Successful Pre-UAT is the entry criteria for Performance Qualification

    Note: Define what "successful" means in System Validation Plan; for example cosmetic defects in System Testing could be ok and not a hard-stop criterion to enter Operational Qualification phase.
3. Test Cases used for executing conventional Testing and Qualification could remain the same. However, additional Test Cases for black box testing could help during functional testing.
4. Most importantly, discuss with the customer about the validation approach before documenting the approach in the Computer System Validation Plan.
5. The λ Model could be tailored as well. For example, it may be required to execute Integration Testing and System / Functional Testing before IQ and OQ but a pre-UAT testing may not be required to be performed before Performance Qualification.
6. The rigor at which Qualifications phases are executed should remain the same and only the number of times qualification phases are executed is reduced / substituted by conventional testing during its earlier cycles.

Pros and Cons

of the new λ Validation Model

Pros

1. Significantly reduces cost when multiple cycles of test cases / qualification are required to be executed.
2. Stability of the code is attained much faster as turn-around time is faster and test cycle time is reduced.
3. Clarity in the sequence of testing during validation planning is much better in λ model than in V-Model as OQ attempts to cover multiple aspects of testing such as Integration, Functional, System, System Performance testing etc within the OQ phase.

Cons

1. Typically conventional Integration Testing, Functional Testing and System Testing is not a sufficient form of testing evidence in Regulatory context because it fails to produce documented "sufficient" evidence with screen captures and e-signature/wet-signature of the tester with date/timestamp. Therefore at least one round of IQ, OQ and PQ needs to be executed to produce the documented evidence required.
2. If the code is very stable and if multiple rounds of IQ, OQ and PQ is not anticipated to be executed then, there may not be a necessity to execute System / Functional Testing additionally as it could be covered under OQ.

Conclusion

Producing sufficient documented evidence for regulatory compliance purposes that a system is working as intended can be considered as an independent activity and need not be necessarily executed in multiple cycles through qualification. The λ Model of Validation for Regulatory Application Development eliminates redundancy of executing multiple cycles of IQ, OQ and PQ and hence reduces time and cost. The Qualification phases of IQ, OQ and PQ will still be required to be executed for producing documented evidences with screen shots and signatures of the tester and approver for both the executed test cases and the defects. However, the number of cycles of Qualification that needs to be executed is reduced by substituting the earlier cycles of qualification with conventional testing and yet addressing the regulatory requirements more directly.

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   Available on www.21cfrpart11.com/files/library/validation/new_csv_model.pdf

About the Author

Madhu Expedith has more than 11 years of combined experience in IT Process and Quality Consulting, Project Management, Quality Management and Software Development. Madhu is currently a Lead Consultant in the Process and Quality Consulting practice, Enterprise Quality Solutions (EQS), at Infosys Technologies Limited. He has executed projects involving end to end process definition, implementation, quality management, driving and managing organizational process changes, anchored process improvement programs including training & facilitation. His expertise includes models and frameworks such as Agile, CMMI, ITIL, TPI, TPI NEXT, RUP and regulations such as GCP and 21 CFR Part 11. He has worked on software projects with leading Pharma companies and Contract Research Organizations (CRO) and has experienced in providing guidance to customers to build systems and processes that addresses validation requirements of the US FDA. He holds the following professional certifications:

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- Certified ScrumMaster (CSM)
- Certified Software Quality Analyst (CSQA) (To be renewed)
- ITIL Foundation v3.0
- Project Management Professional (PMP)

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