ENGINEERING AND R&D SERVICES

HCL

Test Method Validation for Medical Devices

WHITE PAPER

2 Engineering experiences

Acceleration | Value | Technology

Table of Contents

Abstract

Tests or Inspections are defined as the process of verifying the manufactured product for any defects and conformance to its intended functions. Test methods are the set of procedures defined to execute the tests. Test Method Validation means establishing by objective, evidence that the test method consistently produces a desired result required to satisfy the intended use.

Design verification and design validation phases involve various tests carried out on the medical device to ensure, with objective evidence, that the specified requirements and intended use have been fulfilled. If the test method cannot be objectively justified for the various tests conducted during design verification and validation phase, the resulting data of the test is considered under suspect. This will degrade the medical device quality, reliability, and durability, thus failing to satisfy the end user's intended use. If the test methods are not validated, the entire test and inspections carried out should be verified for the correctness of the test or inspection data. This will increase the cost of quality to a greater extent. Hence validating the test method plays a crucial role in delivering the right product to the customer at the right cost and at the right time.

This paper presents an overview of

- Regulatory expectation of Test Method Validation from the medical device manufacturer.
- Importance of Test Method Validation in a medical device manufacturing facility.
- Appropriate and effective methods of implementing Test Method Validation.

The goal of a quality system is to consistently produce products that are fit for their intended use. Test Method Validation is a key element in assuring that these principles and goals are met.

Abbreviations

TMV - Test Method Validation
FDA - Food and Drug Administration
IPSO - Inter Plant Shipping Order
R&D - Research and Development
SME - Subject Matter Expert
EPOE – Equipment, Process, Operator and Environment

Business challenge/needs

The medical device industry has long understood the requirements of validation of all processes, equipment and software. But still, Test Method Validation remained a bit confusing requirement for the medical device manufacturers. As per the Code of Federal Regulations (CFR) Title 21 Part 820: Quality System Regulation (QSR) 21 remains silent on the topic of method validation. The traditional definition for Test Method Validation has been applied to chemical and to microbial acceptance test method. However, regulatory expectation was evidenced by warning letters dating back to at least 2005, indicating that method validation is an applicable medical device validation activity for both physical and chemical test method.

The Code of Federal Regulations (CFR) Title 21 Part 820 sections: 21 CFR 820.30(f) - Design verification, 21 CFR 820.30(g) - Design validation, 21 CFR 820.70(b) - Production and process controls, 21 CFR 820.75(a) - Process validation, 21 CFR 820.100(a) (4) - Corrective and preventive action, state by the simple fact that methods are clearly stated in the scope and medical device test method validation is very broadly defined. This means to FDA that validation is establishing the documented evidence that provides a high degree of assurance that a specific process will consistently produce a product, meeting its predetermined specifications and quality attributes.

Control of Inspection, measuring, and test equipment: Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection is suitable for its intended purpose and is capable of producing valid results, as required by 21 CFR 820.72

Failure to adequately ensure that when the results of a process cannot be fully verified by subsequent inspection and testing has not been adequately validated and approved according to established procedures, as required by 21 CFR 820.75(a).

Failure to establish and maintain adequate procedure for changes to a specification, method, process or procedure. Such changes shall be verified or, where appropriate, validated according to 21 CFR 820.75 as required or as required by 21 CFR 820.70(b).

A few of the above warning letters from FDA reminded the medical device manufacturers that ignoring medical device test method validation may result in product recalls and negative financial impacts. The present and future market scenario has a clear defined objective of projecting quality as the sole weapon for every medical device manufacturer to survive. Test method validation remains a crucial role in ensuring the medical device validation. Hence, each medical device manufacturer shall establish and maintain an adequate organizational structure to ensure that products are designed and produced in accordance with the regulation, which ensures that the product is safe, pure, and effective to the patients.

The regulatory agency observed that there were inadequate proof of evidence to justify the test methods used in Medical device manufacturing facilities were capable of producing consistent results, satisfying the intended use of the end user. Hence, a warning letter was issued to Medical device manufacturing facilities.

Test Method Validation Requirements

All the test and inspection data resulting from the test assuring the product quality, should be verified for the correctness of its data and all the variations. This will result in unnecessary cost to the manufacturer and end user. Test method validation is the only way to validate the method addressing all the variations in test and inspection (including medical device validation), thus eliminating the need of verifying all the data obtained.

Test method validation is initially carried out by tracing out all the regulatory requirements mentioned in table 1 below. These requirements are essential to be addressed by the medical device manufacturer to justify that the inspection and test results are produced consistently.

Table 1 - FDA Inspection, Compliance, Enforcement, and Criminal Investigations surrounding method validation

FDA CFR	Citation ID #	FDA Long Description Phrase
21 CFR 820.30(g)	4070	The results of design validation, including [identification of the design] [**method(s)**] [the date] [the individual(s) performing validation], were not [adequately] documented in the design history file.
21 CFR 820.70(b)	539	Procedures for changes to a [specification] [method] [process] [procedure] have not been [adequately] established.
21 CFR 820.30(f)	3676	The design verification results, including [identification of the design] [**method(s)**] [the date] [the individual(s) performing the verification], were not [adequately] documented in the design history file.
21 CFR 820.100(a)(5)	3304	Changes in **methods** and procedures needed to correct and prevent identified quality problems are not [implemented] [recorded] [effective].
21 CFR 820.70(b)	3681	Changes to a [specification] [**method**] [process] [procedure] were not verified or validated.
21 CFR 820.100(a)(5)	3693	Corrective and preventive action procedures addressing implementation and recording of changes in **methods** and procedures to correct and prevent identified quality problems were not [established] [defined] [documented] [complete] [implemented].
21 CFR 820.75(b)(2)	3432	There is [no] [inadequate] documentation of [monitoring and control **methods** and data] [the date performed] [the individual performing the process] [the major equipment used] for a validated process.
21 CFR 820.70(b)	540	Established procedures were not followed [completely] in making changes to [specifications] [**methods**] [processes] [procedures].

The above regulatory requirements were first traced out for all the equipments used for inspecting, measuring, or testing during receiving , manufacturing, processing, packaging, holding, and distributing of components and products. After clearly defining all the areas to be addressed, the required test

methods to be validated are categorized into physical test and chemical tests. A separate approach is followed for validating the physical and chemical test based on the application.
Physical test method validation is quite different from chemical test method validation, as physical test method validation is executed with more concentration on Method Suitability Evaluation (MSE) or Gage R&R testing. The requirement for chemical test method validation can be obtained from International Conference for Harmonization. Gage R&R is quantitative study used to determine the total variation in the measurement system. This variation can be compared with the defined total allowable variation in the measurement system and ensure that the measurement system produces consistent results. The table 2 below provides information for the analysis of performance of equipments using the Gage R&R testing.

Table 2 – Equipment performance analysis characteristics

Requirement	Description
Analysis of repeatability	The repeatability quantifies the basic precision for the gauge
Analysis of reproducibility	Day-to-day variability is assessed
Analysis of stability	Run-to-run variability is assessed
Analysis of bias/systemic error	The terms 'bias' and 'systematic error' is defined as the difference between the measurement result and its unknown 'true value'.

Elements of data quality in laboratories involve analytical instrument qualification, analytical method validation, system suitability test, and quality control check. Method validation occurs between analytical instrument qualification and system suitability testing, and is linked to all other quality elements. Methods should be validated using qualified instruments. During method validation, parameters and acceptance criteria for system suitability checks and quality control checks are to be defined. The table 3 below provides clear characteristics to be validated based on the type of procedure.

Table 3 – Analytical method validation essential characteristics

	Type of procedure			
		Impurities		
Characteristic	Identification	Quantitative	Limit	Assay
Accuracy	N/A	Yes	N/A	Yes
Precision (Repeatability)	N/A	Yes	N/A	Yes
Precision (Intermediate)	N/A	Yes	N/A	Yes
Specificity	Yes	Yes	Yes	Yes
(LOD) Limit of Detection	N/A	Maybe	Yes	N/A
(LOQ) Limit of Quantification	N/A	Yes	N/A	N/A
Linearity	N/A	Yes	N/A	Yes
Range	N/A	Yes	N/A	Yes

TMV Implementation- Process approach

The Test Method Validation process starts with the inspection requirement, capturing and classifying the test methods based on the test and how it is carried out in the manufacturing facility. Then, Gap Analysis will be done for the requirements captured to check whether similar test method is already carried out in the facility. If the test method is new, then it has to be executed and documented with appropriate Protocol and Final report. The recorded Special reports, Protocols and Final report will be used during FDA Audit in order to comply with the regulations. The below flow chart explains how the test method process has been carried out and this would vary between the facilities based on their input requirements.

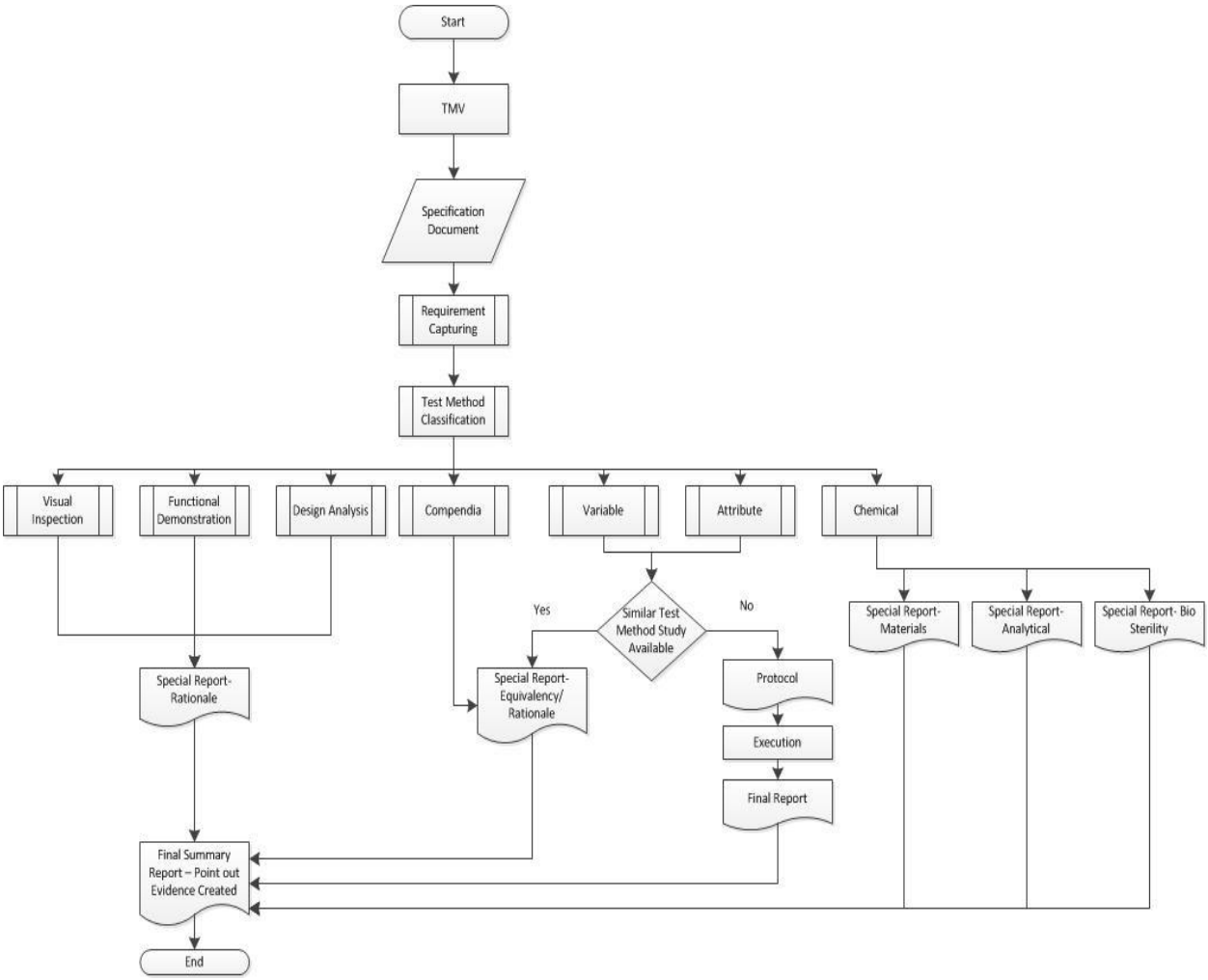

Figure 1: TMV Process Flow

The below table contains the list of TMV documents to be prepared for the inspection requirements based on Gap Analysis:

Table 4 – Documents to be created for TMV based on Gap Analysis

Sl. No.	List if Documents	Brief of the documents
1	Standard Operating Procedure (SOP)	SOP is a detailed step by step process that is followed in the plant or lab on how to use the equipment for execution and on the procedure to take readings/measurements.
2	Special report (Visual Inspection rationale)	Providing the justification or evidence for the requirements/defects, which is satisfied with the visual inspection, without using any gauge or any operator interpretation.
3	Special report (Functional Demonstration)	Providing the justification or evidence for the requirements/defects, which insists for demonstrating functionally.
4	Special report (Compendium Report)	Providing the justification or evidence for the requirements/defects having test procedure similar to standards; that is established and accepted in standards, such as Pharmacopoeia, ISO, ASTM, FDA, NF, and IEC. They are established standards which have been defined and published by an industry standards organization or regulatory body. Evidence provided for the requirements will avoid the execution in lab and further validating.
5	Special report (Equivalency rationale)	Providing the justification by taking already validated study (similar test cases) and comparing with our requirement. Evidence provided for the requirements will avoid the execution in lab and further validating.
6	Special report (Equivalency memo)	Providing the justification taking already validated study (similar test cases) comparing EPOE (Equipment, Process, Operator and Environment) with our requirement. Force tests, pressure tests, and flow rate test cases, may require this type of justification. Evidence provided for the requirements will avoid the execution in lab and further validating.
7	Protocol for test execution (Attribute and Variable)	Step by step procedure for lab execution
8	Final report	Report generation after lab execution with analysis of gauge R&R produced.
9	Final Summary Report	Used as reference in plants: Addresses all defects, requirements, and Test methods evidence details in a consolidated format.

HCL's Communication Governing Bridge and Integrated Approach for TMV

HCL implemented an innovative team architecture as shown in below figure 3 that can tie up the plants together and bring effective communication within the team to handle the situation. They can accordingly react to the regulatory agency in order to maintain the reputation and make sure that all the products are safe enough for the patients.

Innovative team architecture

This innovative team architecture enabled

- Assisting each manufacturing facility with a Subject Matter Expert and an experienced Verification and Validation engineer at onsite HCL.
- Onsite HCL team engineer coordination with Subject Matter Expert for guiding them with all the test method validation activities that are required per regulatory bodies.
- Collection and organization of all manufacturing facility validation requirements by the onsite SPOC (onsite representative) from SME's. This information is transferred to the offshore HCL team SPOC (offshore representative).
- Forming a dedicated team for every TMV activity irrespective of the manufacturing facility. Based on the test method requirement, the respective team took the responsibility for carrying out the test method validation activity similar to grouping of requirements.
- Assigning offshore plant lead who ensured that the prepared document addresses onsite plant lead input and is applicable to the respective plant. This output is delivered to onsite plant lead for review which is then submitted to the respective plant Subject Matter Expert.

In this way, the innovation team architecture ensured fulfilling every specific plant requirement within a short interval of time. This strategy also enabled to produce homogenous document preparation with quality for manufacturing facilities at different location.

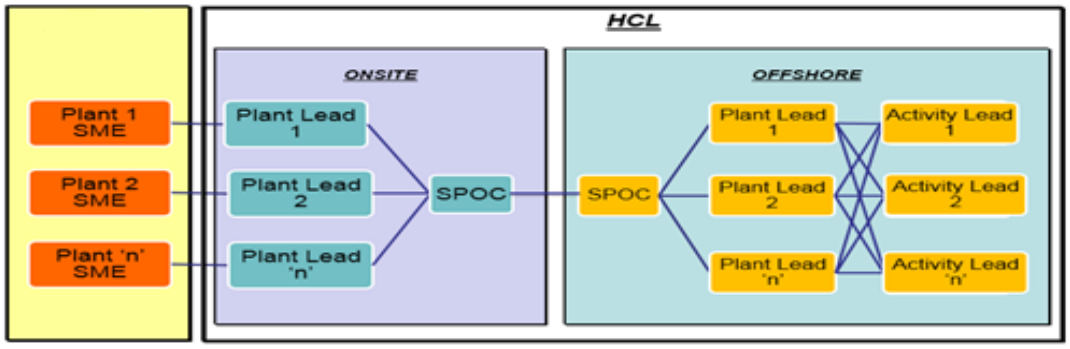

Figure 3: Integrated Approach

HCL acted as communication governing bridge between the manufacturing facilities. It created an awareness among the Manufacturing facilities about the Test methods and Equipment's used in different Manufacturing facilities to measure or validate the similar kind of requirements or components. The HCL communication governing bridge eliminated duplication of work and saved substantial man efforts.

Similar test methods were performed in several Manufacturing facilities. Repetition of test execution of similar test methods led to duplication of work and incurred surplus time. Hence huddling of test methods was brought into existence as the best practice. Identical requirements/ Test methods are grouped together and justified with single test method validation execution through a special report. For timely accomplishment of activity, homogenous templates were created across the plant for ease of audit by FDA.

Benefits of TMV Implementation and Integrated approach

- ✓ To make decisions on design and the output of processes. Therefore, we can make sure that we have methods that are repeatable, reproducible, and valid.
- ✓ By understanding the variability/uncertainty in our measurement systems, we can assure that we are using a suitable test method for the requirement being tested.
- ✓ The methods validated during design and development can easily be transferred into manufacturing and service.
- ✓ Bad methods leading to increased rejections, increased scrap, complaints and customer dissatisfaction, CAPA's, and field corrective actions can be eliminated.
- ✓ Reduces the effort by avoiding repetitive works and keeps the engineer hassle free.
- ✓ Reduces SME Bandwidth to review the documents.
- ✓ Enables organizing a common inventory of reference documents for all location plants, which makes the future tasks easier.
- ✓ Common point of communication completely eradicates duplication of work among plants at different locations.
- ✓ Harmonized method of documentation across all the plants results in quality document generation.
- ✓ Increased ability to meet customer expectation within the stipulated time period.

Conclusion

This paper has established the importance of Test Method Validation during the design and development phase of a product per regulatory guidelines with a well exhibited case study performed by HCL Technologies on Medical products. This impacts the crucial factor to ensure that the end product is fit for intended consumer use. This paper outlines a few of the FDA observations on non-compliance, in order to be aware of key parameters that need to concentrate upon in method validation.

References

- http://www.fda.gov
- http://www.iso.org
- http://www.fda.gov/ICECI/Inspections/ucm250729.htm

Authors Info

Vinoth Kumar Kannan

Vinoth Kumar has a Master's degree in Mechanical Engineering. He has over 5 years and 6 months of experience, of which 1 year and 6 months experience is in a Test method validation project for a medical device manufacturing facility.

Boopathi Rajarathnam

Boopathi Rajarathnam has a Master's Degree in Mechanical Engineering. He has over 12 years' experience, of which 4 years were spent in the Medical Devices domain as R&D Lead for Class I and Class II devices. He also worked in diversified domains like Spacecraft and Semiconductor for more than 8 years. He is currently working in an engagement for a large Medical Devices OEM for sustaining service and Test Method Validation.

Hello, I'm from HCL's Engineering and R&D Services. We enable technology led organizations to go to market with innovative products and solutions. We partner with our customers in building world class products and creating associated solution delivery ecosystems to help bring market leadership. We develop engineering products, solutions and platforms across Aerospace and Defense, Automotive, Consumer Electronics, Software, Online, Industrial Manufacturing, Medical Devices, Networking & Telecom, Office Automation, Semiconductor and Servers & Storage for our customers.

For more details contact**: ers.info@hcl.com**
Follow us on Twitter: http://twitter.com/hclers & LinkedIn: http://lnkd.in/bt8hDXM
View our blog-site: http://www.hcltech.com/blogs/engineering-and-rd-services
Visit our website: http://www.hcltech.com/engineering-rd-services

HCL