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Validation and Verification of Medical Devices

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Abstract:

Every marketable medical device needs deep level engagement, considering the complexities involved due to the requirements, usage patterns, user experience, regulations, associated iterative process, technologies, material, and many more. To stay in line with competition or decrease time-to-market, you may need help from an experienced medical device engineering consultants or service providers. Medical devices are also becoming smaller and more complex in design, sometimes using advanced, engineered plastics. This makes the process of validation and verification (V&V) even more important not only to comply with regulations, but also design the highest quality part and production process. The result is better repeatability, fewer mistakes, less rework and redesign, faster time to market, improved competitiveness, and lower production costs. U.S. Food and Drug Administration (FDA) and international regulatory standards continue to evolve and become more stringent rules in Medical Devices. Validation & Verification (V&V) are required as part of designing and developing a medical device, as part of implementing a manufacturing production process or an automated system, as part of ensuring the appropriateness of a design, production or other process change, and as part of ensuring that a corrective or preventive action is effective and does not adversely impact product.

Keywords: Validation & Verification, Medical Devices, USFDA, International regulatory standards.

Introduction:

The US Food and Drug Administration's Quality System Regulation (Code of Federal Regulations Title 21 Part 820) uses the terms verification and validation (V&V) in several sections. V&V are required as part of designing and developing a medical device, as part of implementing a manufacturing production process or an automated system, as part of ensuring the appropriateness of a design, production or other process change, and as part of ensuring that a corrective or preventive action is effective and does not adversely impact product. The terms are defined at the beginning of the regulation/ FDA registration of medical devices and IVDs requires design validation and design verification.

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Validation means establishing by objective evidence that the particular requirements for a specific intended use can be consistently fulfilled as per Medical Devices Regulations. Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications as per Medical Devices Regulations. Design validation means establishing by objective evidence that device specifications conform to the user needs and intended uses as per Medical Devices Regulations [1-3].

Some Regulatory Controlling bodies of Medical Devices:

- ISO 10993-1:2009 Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process.
- ISO 10993-18:2005 Biological evaluation of medical devices -- Part 18: Chemical characterization of materials
- ISO 13485:2003 Medical devices – Quality management systems -- Requirements for regulatory purposes.
- Directive 93/42/EEC on Medical Devices (MDD) act
- ISO 5833:2002 Implants for surgery -- Acrylic resin cements
- EN 62366:2008 Medical devices - Application of usability engineering to medical devices [4-5]

What exactly does validation and verification means:

Validation is the process of making sure that you have objective evidence that user needs and intended uses are met. It is usually done by tests, inspections, and in some case analysis. However, the target of the validation is to make sure that the user needs are met in a medical device that consistently provides the intended medical benefit in actual use conditions. Verification is typically making sure that you have objective evidence that specified requirements are met. It is usually done by tests, inspections, and in some case analysis as well.

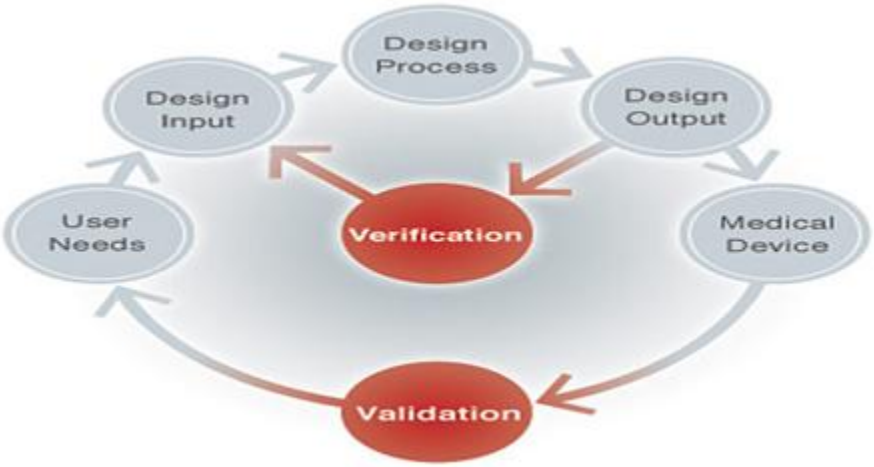

Figure 1: Flow Chart for Validation and Verification

Medical Devices Design Verification and Validation:

In Design Controls, Part 820.30, both design verification and design validation are required. However, they occur at different stages in design. The relevant sections of the regulation are:

- 820.30(f) Design verification shall confirm that the design outputs meets the design inputs requirements.
- 820.30(g) Design validation shall be performed under defined operating conditions on initial production units, lots or batches, or their equivalents. Design validation shall ensure that devices conform to intended uses, including the needs of the user and patient, and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate.

There is often a misunderstanding by many in industry as to the primary differences between design V&V. The differences can best be illustrated by looking at the different requirements in 820.30(f) and 820.30(g). There is no requirement to use a production or production equivalent unit for design verification, but there is for design validation. There is need for a production equivalent unit because successful design validation follows design verification. Design verification includes the inspection, measurement, analysis, or testing that proves that one has the correct output specifications relative to the design input requirements. In effect, it is the data and work that gets one from the initial design input requirements that begin design to the final output specifications that comprise the device master record (DMR). Design verification is less about testing and more about ensuring that as one moves from the initial design input requirements and subsequently translate them to more refined requirements to final design output specifications in the DMR that those specifications are the right specifications and that one has addressed all requirements in the specifications.

Design validation, however, proves that with the final design output specifications, the design (finished, packaged, and labeled device) will perform as intended and as users need. Because of this, design validation follows a frozen design (design verification allows the design to be frozen) and it's primarily functionality and performance testing on production or equivalent units in actual or simulated use conditions. This is well explained in FDA's Design Control Guidance for Medical Device Manufacturers guidance document:

- Verification and validation are associated concepts with very important differences.
- Verification is the process of checking at each stage whether the output conforms to requirements for that stage.' (See my diagram on next page for a visual of this concept).
- In the initial stages of design, verification is a key quality assurance technique; as the design effort progresses, verification activities become progressively more comprehensive.
- Validation follows successful verification, and ensures that each requirement for a particular use is fulfilled. Validation of user needs is possible only after design is finalized and the device is built.

Parts of Medical Devices Design Verification and Validation:

- Section A. General
- Section B. Design and development planning
- Section C. Design input
- Section D. Design output
- Section E. Design review
- Section F. Design verification
- Section G. Design validation
- Section H. Design transfer
- Section I. Design changes
- Section J. Design history file (DHF)

Verification and Validation during Medical Devices Design:

Verification activities are conducted at all stages and levels of device design. The basis of verification is a three-pronged approach involving tests, inspections, and analysis. Any approach which establishes conformance with a design input requirement is an acceptable means of verifying the design with respect to that requirement. In many cases, a variety of approaches are possible." "Complex designs require more and different types of verification activities. The nature of verification activities varies according to the type of design output the manufacturer should select and apply appropriate verification techniques based on the generally accepted practices for the technologies employed in their products. Many of these practices are an integral part of the development process, and are routinely performed by developers. The objective of design controls is to ensure adequate oversight by making verification activities explicit and measuring the thoroughness of their execution."

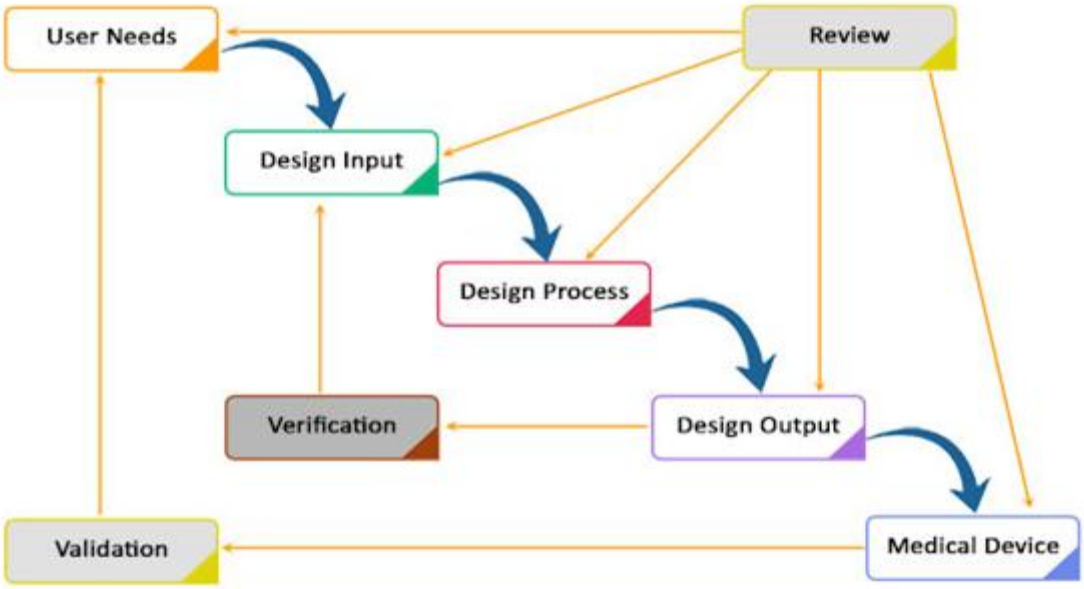

Figure 2: Flow Chart for Medical Devices Design Design Verification and Validation

Documentation of Medical Devices Design Verification Activities:

Some verification methods result in a document by their nature. For example, failure modes and effect analysis produces a table listing each system component, its postulated failure modes, and the effect of such failures on system operation.

Validation should also address product packaging and labeling. These components of the design may have significant human factors implications, and may affect product performance in unexpected ways. For example, packaging materials have been known to cause electrostatic discharge (ESD) failures in electronic devices. If the unit under test is delivered to the test site in the test engineer's briefcase, the packaging problem may not become evident until after release to market.

Validation should include simulation of the expected environmental conditions, such as temperature, humidity, shock and vibration, corrosive atmospheres, etc. For some classes of device, the environmental stresses encountered during shipment and installation far exceed those encountered during actual use, and should be addressed during validation.

Particular care should be taken to distinguish among customers, users, and patients to ensure that validation addresses the needs of all relevant parties. For a consumer device, the customer, user, and patient may all be the same person. At the other extreme, the person who buys the device may be different from the person who routinely uses it on patients in a clinical setting. Hospital administrators, biomedical engineers, health insurance underwriters, physicians, nurses, medical technicians, and patients have distinct and sometimes competing needs with respect to a device design.

Validation Documentation of Medical Devices:

Validation is a compilation of the results of all validation activities. For a complex design, the detailed results may be contained in a variety of separate documents and summarized in a validation report. Supporting information should be explicitly referenced in the validation report and either included as an appendix or available in the design history file. The guidance document reiterated much that was initially explained in the Preamble to the Regulation:

Design outputs are the design specifications which should meet design input requirements, as confirmed during design verification and validation and ensured during design review. The output includes the device, its labeling and packaging, associated specifications and drawings, production and quality assurance specifications and procedures. These documents are the basis for the DMR. The total finished design output consists of the device, its labeling and packaging, and the DMR.

Final design validation, however, cannot be done on prototypes because the actual devices produced and distributed are seldom the same as the research and development prototypes. The final validation, therefore, must include the testing of actual production devices under actual or simulated use conditions.

It is important to note that design validation follows successful design verification. Certain aspects of design validation can be accomplished during the design verification, but design verification is not a substitute for design validation. Design validation should be performed under defined operating conditions and on the initial production units, lots, or batches, or their equivalents.

Medical devices production and Process Verification and Validation:

The regulation defines process validation by using the term "fully verified" as being the opposite of process validation. Yet the regulation fails to define the term "fully verified" [6-9]

820.75 Process validation: "…where the results cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance…"

The preamble to the regulation attempts to explain this: "One of the principles on which the quality systems regulation is based is that all processes require some degree of qualification, verification, or validation, and manufacturers should not rely solely on inspection and testing to ensure processes are adequate for their intended uses."

What are medical device companies requesting these days when it comes to validation and verification?

They want effective, relevant, and well-documented V&V activity that is compliant with medical-device regulations. Medical devices come in many different technologies, shapes, sizes, levels of complexity, etc. V&V activity is typically driven by the regulatory environment and international standards. For example, considerable emphasis is now placed on human factors engineering. From a V&V point of view, there are specialized human factors testing techniques such as formative and summative testing. Two relatively recent standards - ISO's IEC 62366:2007 "Medical Devices - Application of Usability Engineering to Medical Devices" and AAMI's ANSI/AAMI HE75: 2009's "Human Factors Engineering - Design of Medical Devices" - provide guidance for the overall usability engineering process, as well as design and testing techniques. The FDA also provides a great deal of information on this topic in the form of guidance documents.

It is extremely important to consider validation and verification early in the design stage when developing requirement specifications for a product, which streamlines the overall manufacturing process and the approval process. Every medical device must meet the functionality, usability and reliability objectives to get a successful share in the market. Apart from these, end users also look for effectiveness and safety of devices that they use to address a particular problem or condition, which are sometimes critical to life. This is why iterative testing with verification and validation of these medical devices becomes imperative. Verification and validation of medical devices in the design process aim to ensure that the device is aligned with the need of targeted users and it delivers the intended solution. It also helps ensure whether all the requirements are being satisfied or not. It helps to comply with regulation as well as designing the highest quality product and manufacturing processes.

Verification is internal process, which evaluates whether a design output meets the specified requirements, specification or regulation defined in the design input. Whereas validation is an internal to an external process**,** which evaluates if your product delivers benefits, according to the need of targeted users or not. Medical devices may consist of different technology shapes, sizes, and different level of complexity. Verification and validation (V&V) activity is driven by regulatory environment and must follow international standards. Standardized V&V activities can streamline the manufacturing process as well as enhance approval process. Additionally, automated testing, diagnostic techniques, and data collection tools can enhance the V&V process.

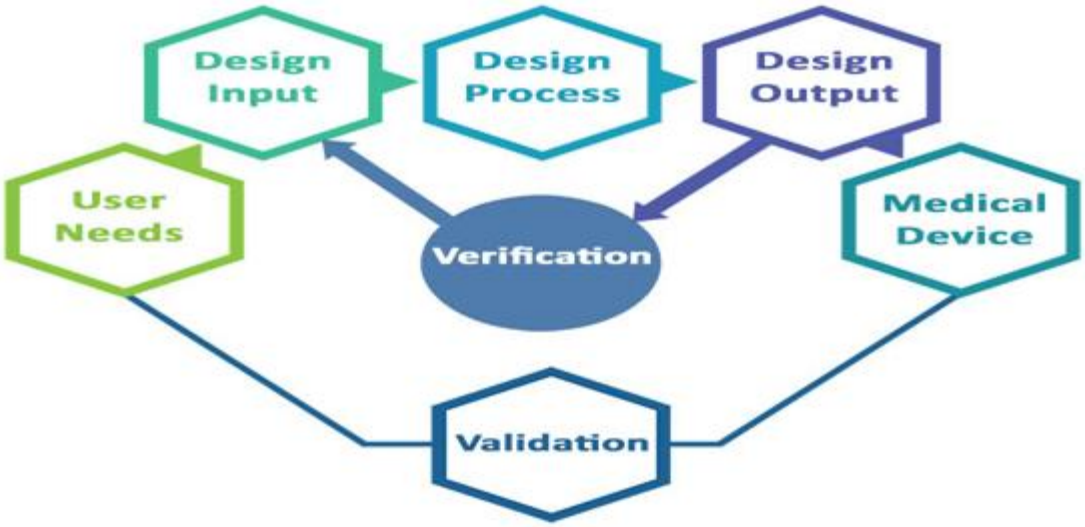

Figure 3: Flow Chart For Medical Devices Process and Production Verification and Validation

V&V being an iterative process consumes a lot of money, when planned poorly. A strongly defined test strategy can help you optimize cost as well as the test period to make the product market ready on time. The complexity of any testing strategy depends on technologies to be used and geographical target markets. The test strategy should cover at least six parameters mentioned below:

- Targeted geographies and associated standards
- Time to market
- A standard to be followed with version
- Testing Labs - internal or independent labs
- Defining the sequence of tests
- Presenting the test result

Risk Management Procedures in Medical Devices:

Risk management procedures for medical devices are enforced under internationally accepted compliance standard ISO 149711:2007 Medical Devices - "Application of Risk Management to Medical Devices". Apart from this, risk management policies need to be incorporated across all the stages of medical device design and development and should be also associated with design control aspects as well [7-9].

Why is risk management procedure important?

Considering the complexity of medical device design, focused risk management practices help ensure usability, safety, and regulatory compliance. It is a process of identifying, controlling and preventing the failure that may cause hazards to users. It also mandates identifying associated risks. Upon reaching an unacceptable level of risk, it notifies developers to decrease at least up to an acceptable level.

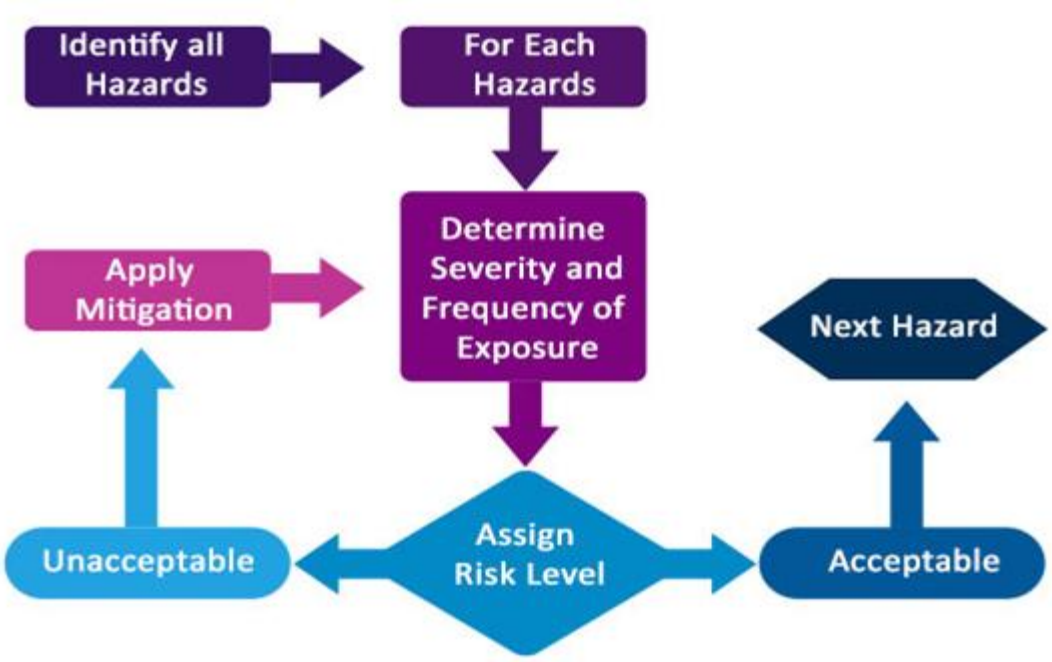

Figure 4: Assessment of risk management procedure in Medical Devices

How is Risk Management Procedure Followed?

The above image shows all the steps involved in the risk management process. The process starts with the identification of hazards and then associated risk is measured based on the consequences of hazards and their possibility of risk. If the identified risk level is above the defined criteria, then it needs to be mitigated. The risk level depends on many parameters such as the device, technologies or even company's risk acceptability policy. Before finalizing a design, it is good practice to conduct a hazard analysis to get an idea about the standard hazards associated with the device. Primary hazard analysis can be done easily by considering major components and operational requirements such as raw materials and wastes, hardware, monitoring and control systems, human-device interfaces and services; and then identifying potential hazards associated.

There are certain hazards that must be evaluated:

- Raw materials and wastes: toxicity, flammability, and reactivity of material
- Environmental factors: sensitivity to temperature and humidity and more
- Mechanical or electronic hazards
- User device interface: hazards associated with human factors like ineffective delivery, drug administration, incorrect or incomplete information, control of life-sustaining operations

When multiple hazards are identified, they can be prioritized according to severity associated with them. Often, there is a scenario where you have insufficient information to identify hazards. In such cases, you may consider similar devices and their history for identification purpose. During the prototype development phase, there is a need for detailed hazard and risk analysis.

There are two approaches for hazard analysis: Top-down and Bottom-up approaches:

- A hazard and operability (HAZOP) and Failure Mode Effects Analysis (FMEA) are analysis techniques with a bottom-up approach. HAZOP is ideal for complex design, which involves multiple step processes. While FMEA is ideal for devices having multiple mechanical components, it is time-consuming.

- Fault tree analysis is a top-bottom approach to identifying top-level undesired output by analyzing combination and a series of lower level events.

What are the Latest Advancements in Medical Devices Validation and Verification:

Validation and Verification activities are more standardized than in the past, which has streamlined overall manufacturing process and the approval process. V&V is further enhanced by automated testing and powerful diagnostic and data collection tools. Medical-device companies typically follow a formal development process defined by deliverables at each step. Every specification needs evidence of verification and/or validation. So do risk control measures [10-12].

When is the best time to consider Medical Devices Validation & Verification in product development?

V&V covers all phases of product development and many different technologies. Examples include electronics, mechanical/physical, fluids, thermal systems, electromechanical component evaluation, instrumentation, biologic aspects, etc. It is extremely important to consider V&V early in the design stage when developing requirement specifications for the product. For example, adding test points on circuit boards, having accessible connectors, providing data storage/retrieval capabilities, and making products modular can enhance the ability to test a product, which saves time and money. V&V costs can also be reduced if previously tested materials or coatings are used for the product. Clarity, conciseness, measurability, appropriate tolerances, accuracy, and testability can all impact the final design and overall manufacturability. These specifications also provide the acceptance criteria for later V&V activities.

Where do you see Medical Devices Validation & Verification going in the next few years:

V&V activity in medical devices does not change quickly because the regulatory environment does not lend itself to quick changes. Strategies to improve outcomes and efficiencies will continue to evolve. Improved V&V methods, automated testing tools, and documentation tools will undoubtedly become available as the regulatory climate continues to evolve.

Conclusion:

Every marketable medical device needs deep level engagement, considering the complexities involved due to the requirements, usage patterns, user experience, regulations, associated iterative process, technologies, material, and many more. To stay in line with competition or decrease time to market, you may need help from an experienced medical device engineering consultants or service providers. If you want to explore more, here is the bonus research for you. We had asked 35 medical device developers on what is the most critical factor to the success of their medical device design, read here about what they think.

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