How to improve the reliability of medical devices given the very limited resources of startups
(스타트업 특성 고려한 의료기기 신뢰성 확보방안)

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(Abstract)
Startups with limited manpower and resources need to focus on the essence (why they started this business) and spend a lot of time and effort on reviewing the requirements and design inputs related to the intended use of the products and services they want to provide to the market, in conjunction with the business model, and then, secure the necessary resources for each subsequent stage (development, verification and validation, design transfer, production, and postproduction activity).

Introduction

No matter what medica device you're developing, the first major milestone is usually a proof of concept (PoC). Typically represented by a working prototype or minimum viable product (MVP), which is used to demonstrate possible and potential medical device for customer needs prior to developing a more fully featured product. For startups, once this proof of concept (PoC) phase is successful, full-scale medical device development may begin with minimal seed investment.

A successful PoC or MVP is, in a word, a cause for celebration. Once you finish it, it's time to enter into the next stage, saying, full-fledged medical device design and development. But how do you go from an minimum viable product to one that can be reliably manufactured at scale? How you choose and execute your next phase would determine whether or not you could get your device to market and succeed in a time and cost-effective manner. This design and development strategy is very critical, especially for startups with very limited manpower and resources.

Development Control Process

Developing a medical device addresses hundreds of tasks, challenges, and regulatory requirements. However, every device starts with a "design and development plan" stage, determining activities from product requirements to postproduction, which is considered the official start of medical device development and is governed by regulatory requirements. Due to the nature of medical devices, where nonconforming products could be dangerous to human life and safety, each country has established regulations on the safety, performance, and reliability of medical devices by law, and manages them through the certification process.

Medical device development must adhere to the following steps set forth by the FDA (FDA 820.30, QSR). The International Organization for Standardization (ISO) also has developed similar quality management system standard which describes the design and development control process in clause 7.3 of ISO 13485. Conformance to these regulatory requirements defined in FDA 820.30 and clause 7.3 of ISO 13485 ensures that the medical device you develop is fit for its intended use and safety.

Following is a brief description of the development control process;

— Development Planning: establish and document development activities, functions and responsibilities impacting device development

— Development Input: determine physical and performance characteristics of a device that are used as a basis for device development.

— Development Output: the results of a development effort at each stage and at the end of the total development, which should meet the development input requirements.

— Development Review: evaluate capability of the development result at each stage of development process and determine whether to go to next stage.

— Development Verification: confirmation by objective evidence that the output meets the input of development.

— Development Validation: comprehensive evaluation whether the performance of the device is appropriate from the user's point of view.

— Development Transfer: transfer development result to production specifications for correct manufacturing.

— Development Change: establish procedures to control all changes before their implementation

Proof of concept (PoC) or minimum viable product (MVP) is the phase before these eight defined stages. Therefore, the "next step" entails going through each of them, paying close attention to fulfilling all the applicable regulatory requirements.

It's important to keep in mind that each of these stages includes engineering, quality, regulatory, and manufacturing factors, and how you determine these stages could impact how and how quickly you get a competitive medical device placed in the market. Before you fully implement the development control process, you need to stop, think, plan, and budget for each stage.

Harmonization of international standards

In order to develop and manufacture reliable medical devices, you must first establish a stable quality management system. The U.S. Food and Drug Administration (FDA) and the International Organization for Standardization (ISO) have developed quality system regulations (QSR, FDA 820) and ISO 13485 (Quality Management Systems), respectively, that describe the requirements for quality management system certification. The development control process is part of this quality management system.

In addition, to ensure the safety, effectiveness, and reliability of medical devices, each stage of the development control process must be aligned with the requirements of the applicable international standards. Typically, the international standards include following harmonized standards having its own purpose;
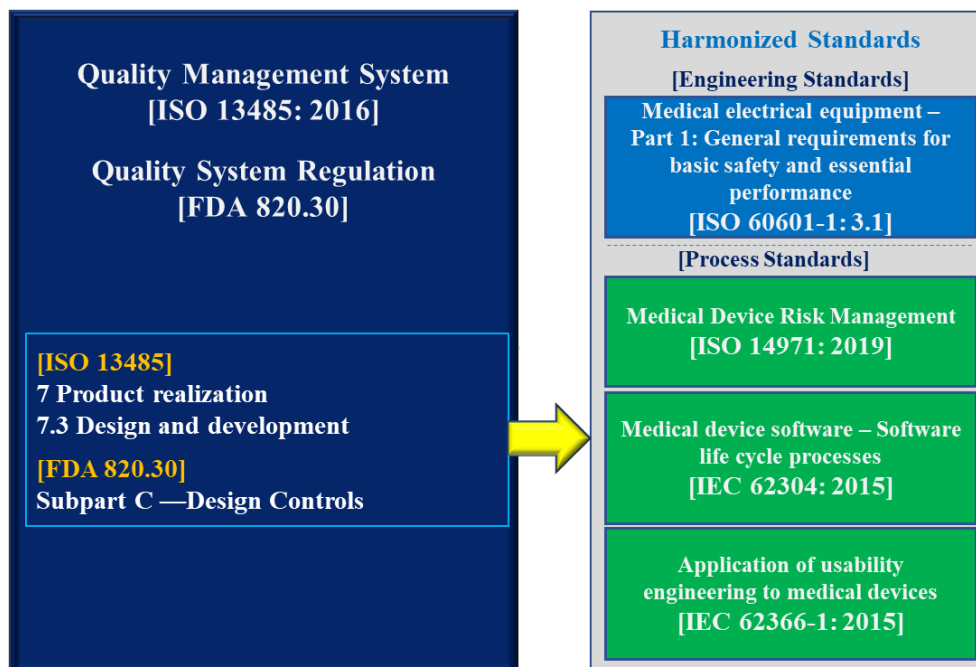
(Fig-1 Harmonizing structure for securing reliability and conformance of medical device, by Teamnubiz)

- ISO 60601-1: General requirements for basic safety and essential performance

- ISO 14971: Medical Device Risk Management

- IEC 62304: Software life cycle processes

- IEC 62366-1: Usability engineering

These engineering and process standards are appropriately incorporated into each sage of the development control process to ensure that, as development progresses, medical devices fulfilling their intended use can be brought to the market. Figure-1 conceptually illustrates harmonizing structure for securing reliability and conformance of medical device between the development control process of quality management system and applicable international standards.

But for startups, this is never easy because they lack experience and manpower.

Harmonizing strategy for efficient development control Process

How you harmonize the above-mentioned international standards could make a big difference in the efficiency of the documentation and development

In Fig-2, you can see an example of harmonizing strategy which can be used for the development control process of startups. This example of harmonization strategy above can be implemented in three main steps:

The first step is to integrate international process standards like below into the QMS processes.

- ISO 14971: Medical Device Risk Management

- IEC 62304: Software life cycle processes

- IEC 62366-1: Usability engineering (If the device is in-vitro diagnostics, IEC 61010 should be considered.)

The second step is to incorporate ISO 60601-1, which sets out engineering requirements for safety and performance, into the early stages of the development control process, such as development planning and development input stage.

The final step is to apply the international standards for verification and validation (V&V) to the development control process, as required by the characteristics of the medical device for successful verification and validation. These international standards include ISO 10993 for biocompatibility, ISO 62366-1 for usability test and ISO 14155 for
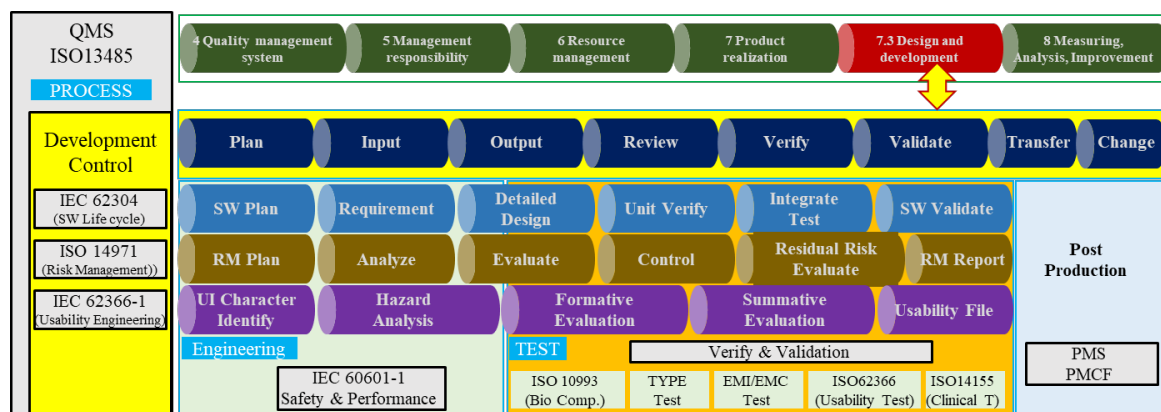
(Fig-2 Harmonizing strategy in medical device design and development process, by Teamnubiz)

process for certification. Reflecting the requirements of international standards in the development process separately would be a very difficult task for startups. If these international standards could be reflected in each stage of the development management process along with the establishment of a quality management system, it would help startups to launch safe and effective medical devices in a timely manner.

clinical investigation and other tests and practices also used for this step.

How to harmonize and incorporate process standards within development control process

Especially for startups, it is important to integrate applicable process standards into the development

control process because resources are limited and efficient development management is required. A possible example is herewith;

Firstly, we need to integrate the risk management process into the development control process, as shown in Figure 3, so that risk management is part of the activities required at each stage of development control process.

Hazards or hazardous situations are often related to user interface characteristics, so the next step is to integrate the usability engineering process with the risk management process to perform comprehensive risk management, as shown in Figure 4.

Software lifecycle processes is basically part of the concept of the development control process and need to be integrated into each stage of the process.

Design and Development Control Process including Risk Management	Design Review

Design and Development Planning

- Define design and development stages
- Plan review(s) needed at each D&D stage
- Plan V&V, and design transfer activities
- Define the responsibilities and authorities for D&D
- Develop traceability of D&D outputs to inputs
- Review the resources including personnel

— Risk Management Plan include risk acceptability criteria

[D&D Plan review]
✓ Is the development plan appropriate in terms of safety and competitiveness? **No**
Yes

Design and Development Input

- Intended use
- Functional, performance, safety & usability requirements
- Regulatory requirements and standards
- Output(s) of risk management
- Information from previous, similar designs
- Other requirements essential for safety

— Identify hazards and hazardous situations
— Risk estimation
— Risk evaluation
— Requirements for risk control measures

[Input, hazard and risk assessment review]
✓ Is the hazard identification and risk assessment acceptable? **No**
Yes

Design and Development Output

- meet the input requirements for D&D
- information for purchasing, production and service
- product acceptance criteria
- specify the characteristics of the product that are essential for its safe and proper use

— Design of risk controls, including device and process control measures, if necessary

[D&D Output review]
✓ Are the outputs acceptable to include inputs and risk control measures feasible? **No**
Yes

Design and Development Verification

- D&D verification shall be performed to ensure that the D&D outputs have met the input requirements.
- Document verification plans including methods, acceptance criteria and statistical techniques with rationale for sample size
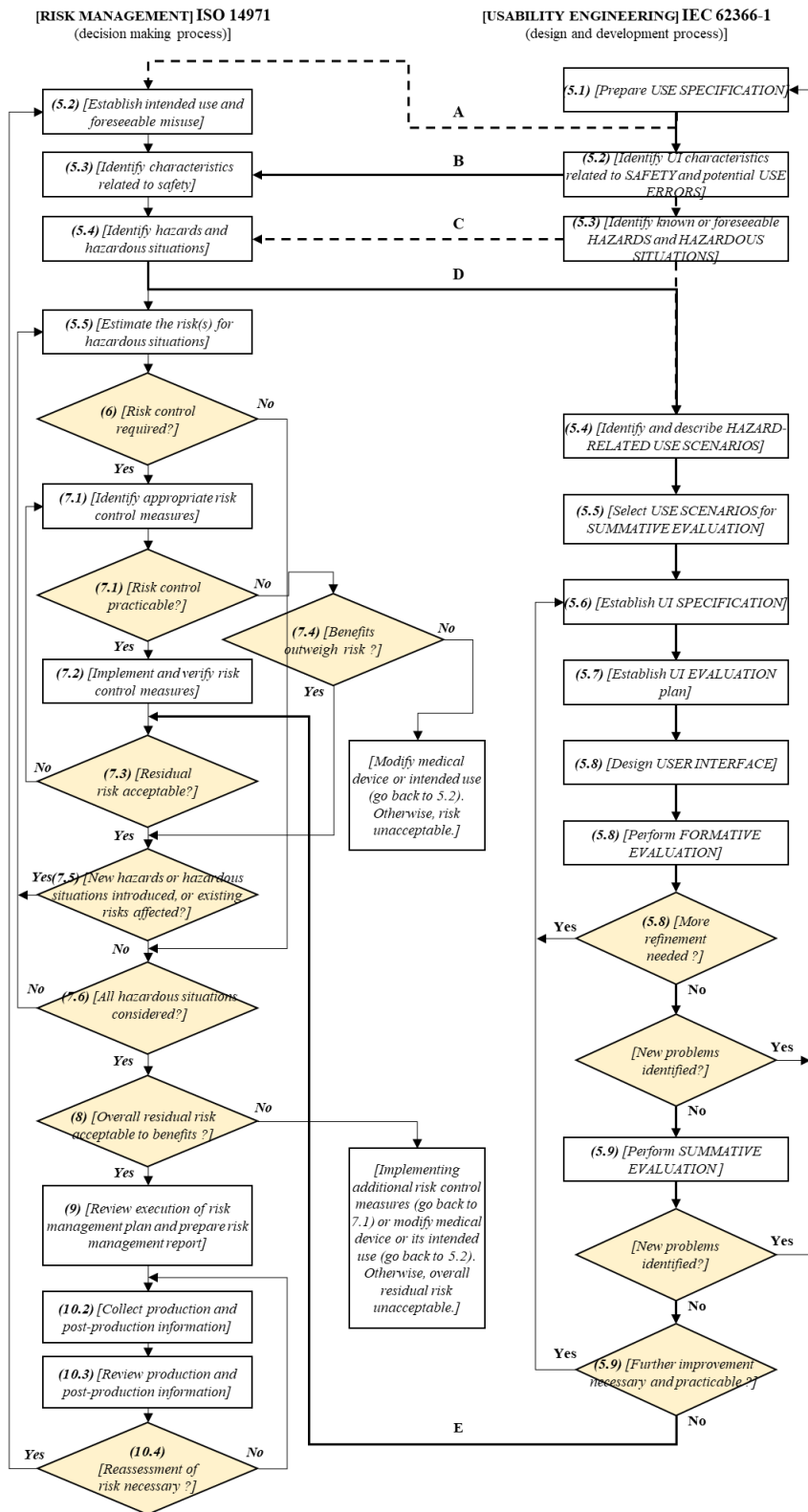- If the intended use requires that the medical device be connected to other medical device(s), verification shall include confirmation that the design outputs meet design inputs when so connected.

— Determination of individual residual risk after the application of risk control

[Benefit-risk review]
✓ Does the benefit outweigh the risk?
Yes / **No**

Change medical device or intended use

[D&D Verification review]
1) Do outputs meet input requirements?
2) Are the risk control measures acceptable? **No-1** / **No-2**
Yes

Design and Development Validation

- D&D validation shall be performed to ensure that the resulting product can meet the requirements for the intended use
- Document validation plans including methods, acceptance criteria and statistical techniques with rationale for sample size
- Validation shall be conducted on representative product
- Clinical evaluations or performance evaluation shall be performed]

— Evaluate overall residual risk
— Benefit-risk analysis

[Benefit-overall residual risk review]
✓ Do the benefits outweigh the overall residual risk?
Yes / **No**

Project cancellation or device redesign

[D&D Validation review]
1) Does final product meet user requirements?
2) Are the overall residual risks acceptable? **No-1** / **No-2**
Yes

Design and Development Transfer

- Document procedures for transfer of D&D outputs to manufacturing
- Ensure that D&D outputs are verified as suitable for manufacturing before becoming final production specifications and that production capability can meet product requirements.

— Design transfer including risk control specifications and requirements

[D&D transfer review]
✓ Is D&D transfer including risk control specifications acceptable? **No**
Yes

Production and Post-production Activity

- Receiving and recording information
- Evaluating information to determine if the feedback constitutes a complaint
- Investigating complaints
- Determine to initiate corrective actions.

— Collection and analysis of information related with risks]

No
[Production & Post-production review]
✓ Do deficiencies appeared? / Is risk reassessment necessary? **Yes**

(Fig-3 Flow for integrating the risk management process into the development control process)
Source: refer IEC 14971:2019(E) and developed by Teamnubiz

(Fig-4 Flow for integrating the usability engineering process into the risk management process)

Source: IEC 62366-1:2015(E) and modified by Teamnubiz

Understanding the correlation between the startup scale-up phases and quality management system
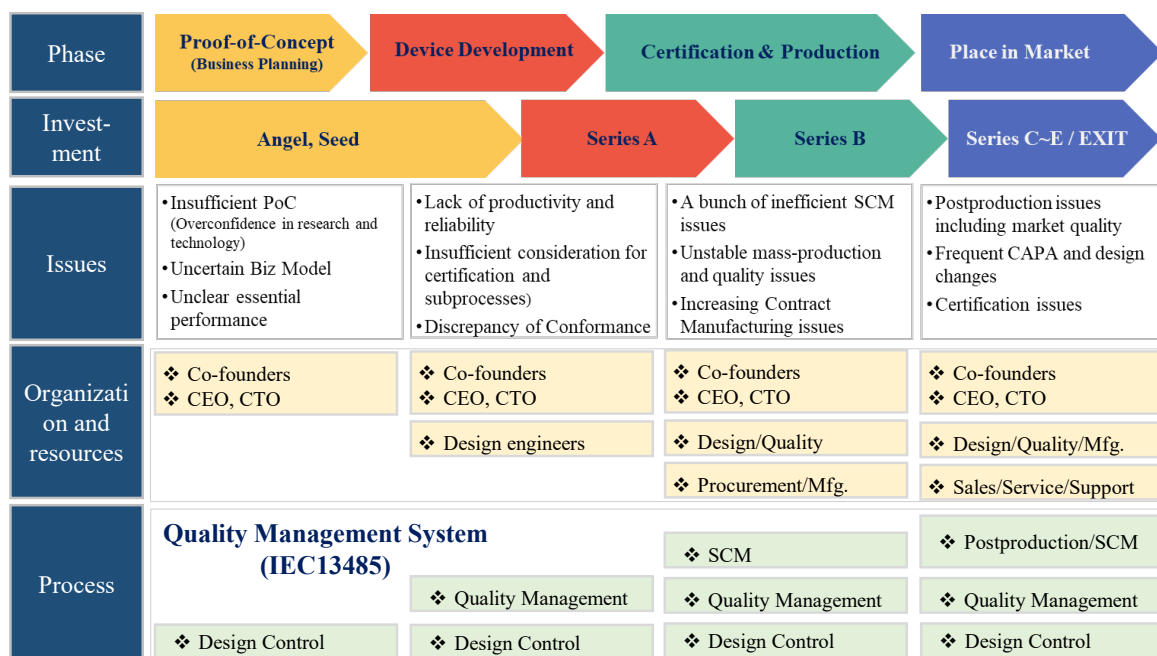
So far, we've seen how an integrated development control process can help ensure conformance to essential requirements to increase the reliability of medical devices.

However, we also realize that this process of development control is the core of the product realization stage defined by the quality management system (ISO 13485) and quality system regulation (FDA 820). After all, through the successful execution of the development control process, we can realize a medical device that is safe, effective, and reliable, which is also connected to the certification of the quality management system such as good manufacturing practice (GMP).

addressing every issues brought at each scale up stage.

However, implementing a reliable medical device by establishing a quality management system and obtaining certification for it is only possible when all of these things are in place at once. In other words, the good manufacturing practice (GMP) confirmation means that all organizations would perform their roles according to the pre-established procedures, and among them, the development team would perform the right activities according to the development control process and the deliverables of products must contain the right documents and records. So, It's a chicken-and-egg dilemma.

Based on our experience in providing certification development support to deep tech startups in

Phase	Proof-of-Concept (Business Planning)	Device Development	Certification & Production	Place in Market
Invest-ment	Angel, Seed	Series A	Series B	Series C~E / EXIT
Issues	• Insufficient PoC (Overconfidence in research and technology) • Uncertain Biz Model • Unclear essential performance	• Lack of productivity and reliability • Insufficient consideration for certification and subprocesses) • Discrepancy of Conformance	• A bunch of inefficient SCM issues • Unstable mass-production and quality issues • Increasing Contract Manufacturing issues	• Postproduction issues including market quality • Frequent CAPA and design changes • Certification issues
Organizati on and resources	❖ Co-founders ❖ CEO, CTO	❖ Co-founders ❖ CEO, CTO ❖ Design engineers	❖ Co-founders ❖ CEO, CTO ❖ Design/Quality ❖ Procurement/Mfg.	❖ Co-founders ❖ CEO, CTO ❖ Design/Quality/Mfg. ❖ Sales/Service/Support
Process	**Quality Management System (IEC13485)** ❖ Design Control	❖ Quality Management ❖ Design Control	❖ SCM ❖ Quality Management ❖ Design Control	❖ Postproduction/SCM ❖ Quality Management ❖ Design Control

(Fig-5 Correlation between the startup scale-up phases and quality management system, by Teamnubiz)

As mentioned above, reliable medical devices should be based on building a successful quality management system, but what about startups that lack the organization and resources to build one?

As shown in Figure 5, once a medical device startup has a successful proof of concept (PoC), it can raise basic funding and move into the scale-up phase of its business. As they develop their product for certification and raise Series A and latter rounds of funding, they gradually put together necessary manpower and establish organizational structure for

Hongneung Digital Healthcare Special Zone (Hongneung Innopolis) and other innovative medical device startups in Korea, we propose the following thoughts that could be a solution;

Startups with limited manpower and resources need to focus on the essence (why they started this business) and spend a lot of time and effort on reviewing the requirements and design inputs related to the intended use of the products and services they want to provide to the market, in conjunction with the business model, and then, secure the necessary resources for each

subsequent stage (development, verification and validation, design transfer, production, and postproduction activity).

Conclusion

Implementing a reliable medical device is no small job, requiring many tasks to be performed systematically and in accordance with the processes required by international standards and regulations. It's even more challenging for startups with limited organization and resources.

However, the more difficult the task, the more necessary it is to take a back-to-basics, build-up approach. In particular, it is necessary to successfully evaluate the core performance of the medical device that meets user needs, or in other words, the fundamental innovative idea that meets clinical indication or intended use, and then, integrate the development control process with other international standards that must be applied. Once these steps have been taken, it would be possible to attract investment and to seek the assistance of expertise organizations that provide support of full-fledged medical device development including certification to these start-ups.

References;

[1] ISO 13485: Third Edition 2016(E), Quality Management System

[2] ISO 14971: Third Edition 2019(E), Risk Management

[3] IEC 62366-1: First Edition 2015(E), Application of usability engineering to medical devices

[4] IEC 62304: Edition 1.1 2015, Software life cycle processes

[5] FDA 820, Quality System Regulation

[6] DESIGN CONTROL of FDA 21 CFR 820.30, GUIDANCE FOR MEDICAL DEVICE MANUFACTURERS

[7] ISO 14969, Medical devices - Quality management systems - Guidance on the application of ISO 13485:2003

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