École polytechnique de Louvain

Set-Up of ISO 13485 Standards for 3D-Printing Technologies in Hospital Environment

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"To invent an airplane is nothing. To build one is something. But to fly is everything."- Otto Lilienthal

Abstract

The ISO 13485 quality management system (QMS) acts as a roadmap for medical device organizations to ensure consistent production of safe and effective products. Since ISO 13485 is harmonized with the QMS part of the Medical Device Regulations (MDR), it is helpful for a medical technology department. In view of this scenario, the work carried out during this internship contributes to the evaluation of the ISO13485 process, focusing on critical elements such as biocompatibility, risk analysis, maintenance, and controls designed to meet the specific needs of the hospital environment.

This internship report details the adaptation of a Quality Management System (QMS) from 3D-Side company to develop a template QMS for a Point of Care 3D Printing (POC3DP) pilot within a hospital, applicable with various compliant 3D printing technologies. Point-of-Care (PoC) can be deceptive; while it typically refers to activities carried out "at the patient's bedside," in the context of 3D printing technology, it denotes actions taking place "at the Healthcare Facility."

Given the specialized nature of 3D printing in the medical field, an in-depth analysis of the ISO 13485 processes is conducted to accurately assess associated risks and implement the necessary controls to ensure the technology's safe use. Ultimately, the development of a well-structured ISO 13485 QMS fosters a culture of quality within the hospital, leading to improved patient safety and increased trust from requesters and regulatory bodies.

Key words : *ISO 13485; MDR; QMS; Hospital; Risk Analysis; Biocompatibility;*

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1. Introduction

1.1. Motivation

Manufacturing of medical devices happens primarily at medical device companies, which operate under strict regulations (Medical Device Regulations (MDR) in Europe, Food and Drug Administration (FDA) in the USA,...) with quality management (ISO 13485 or FDA 21-CFR-820). The companies which employ additive manufacturing use professional 3D printers to ensure compliance and product quality [1, 2]. On the other hand, hospitals typically lack manufacturing experience, as they do not customarily produce their own medical devices [3]. Instead, they rely on external services, for image processing (segmentation), surgical planning, and 3D printing services. Figure 1 illustrates the general workflow for medical devices' manufacturing.

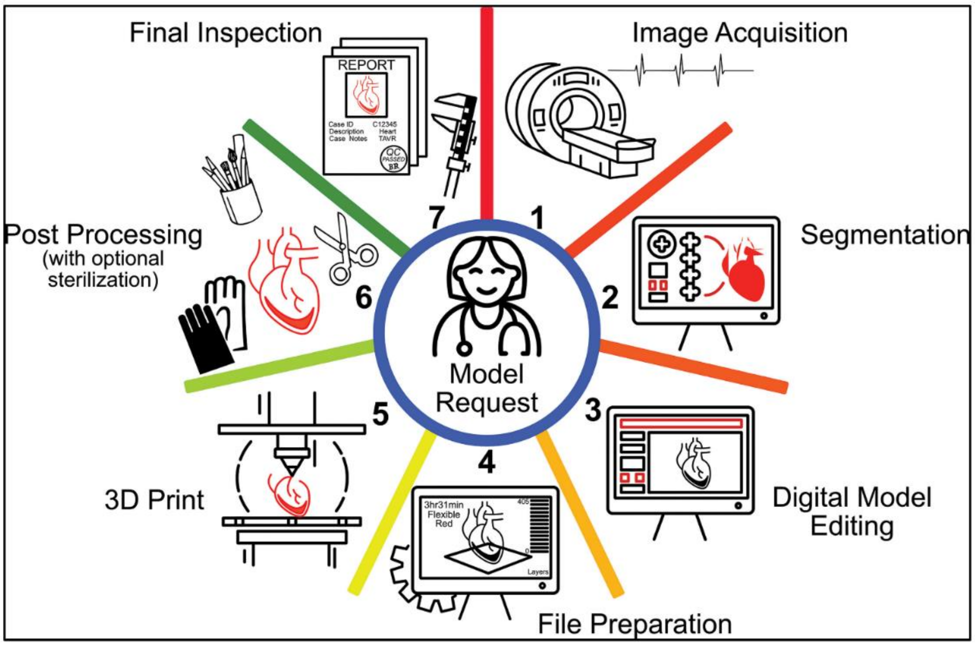


Figure 1. Steps involved in medical devices 3D printing workflow [4].

For surgeons to provide their input, they have to collaborate with engineers at those companies, However, often entails delays due to the company's delivery timelines. As a result, the idea of POC3DP lab is spreading to bring 3D technology in-house, engaging medical staff and adopting specialized 3D software in hospital environments. Once a hospital has a POC3DP lab, the adoption of 3D technology by various departments expedites, thanks to the physical proximity and accessibility of the technology.

Greater accessibility to 3D printing hardware and software technologies has enabled hospital-based 3D printing labs, showing how lead times and costs can be reduced [5]. With the proper equipment and robust quality in place, hospital-based 3D printed products can be safe and efficient and incorporate a hub-and spoke model, where university hospitals equipped with advanced 3D printing capabilities serve as “hubs,” providing support and resources to various departments such as radiology, orthopaedics, neurology, or surgical services. These smaller and specialized departments serve as the “spokes.” [6, 7]. Consequently, the establishment of strong 3D printing alliances becomes achievable, fostering collaboration and innovation within the medical device manufacturing landscape.

Three of hospitals in the EU with centralized 3D printing labs are the University Hospitals Leuven (UZ Leuven), 3D4Med laboratory located at the San Matteo hospital, and University hospital of Salzburg in Austria [8, 9,10]. These hospitals’ in-house 3D-Printing laboratories have been referred to as point-of-care (POC) manufacturing and required pecuniary responsibility, technical competence, biocompatible physical infrastructure, and engaged human resources by assembling a professional team and the necessary resources. The products are then built layer by layer from the digital model using different technologies and materials depending on the final application [11].

The integration of 3D printing technology within hospital settings represents a paradigm shift, transitioning from traditional industry-based manufacturing limitations to Point-of-care manufactures, as presented in figure 2.

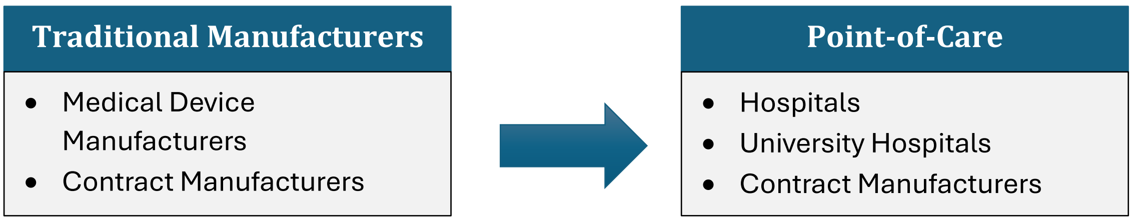


Figure 2. Schema of the traditional and Point-of-Care Manufacturer’s Difference

Despite the benefits mentioned above, the incorporation of 3D printing technology in healthcare facilities poses some challenges, primarily related to quality management and regulatory compliance. Conventional industrial QMS are entirely customized to the distinct environment of hospital-based manufacturing. Main obstacles include:

- Conducting thorough risk analyses to mitigate future safety hazards.
- Developing specific controls to ensure consistent quality and safety of medical devices.
- Implementing systematic maintenance procedures for the lab equipment.

Lack of a hospital-specific QMS framework can led to inconsistencies in product quality, potential regulatory non-compliance, and eventually, patient safety risks.

1.2. Project Summary

This work is part of a research project on Point of Care 3D-Printing bringing together 3D-Side company and the Université Catholique de Louvain (UCLouvain). The project aims to adapt the ISO 13485 quality management system (QMS) framework to suit the requirements of a novel 3D printing technologies setup within a hospital environment for medical devices' production. The primary objective of this internship is to adapt the ISO 13485 QMS from 3D-Side to propose a streamlined, hospital-specific QMS. This includes establishing rigorous quality control measures and validating procedures to guarantee that all medical devices and technologies meet regulatory standards. Concurrently, a team member at UCLouvain was responsible for the selection and validation of 3D printing technology suitable for hospital use. Shared experiences ensured proper equipment selection and quality implementation.

1.3. Objectives

1. Adapt the ISO 13485 QMS framework to align with the unique requirements of a 3D printing setup within hospital infrastructure.
2. Demonstrate the impact of quality aspects on technical outcomes for the manufacturing work instructions. This includes steps from demand to case release.
3. Understand the operational dynamics of hospitals and delineate the tasks and contributions of each personnel category involved in the manufacturing process.

1.4. Scope

1. Develop detailed documentation for QMS procedures adapted for the hospital. Building the QMS was limited to custom-made medical device applications of class I anatomical models and class IIa surgical guides. Appendix A outlines all the specified rules for any applications of these two classes according to MDR 2017/745 in the European Union.
2. Provide specifications, limitations, and constraints for technology selection by conducting risk analysis in accordance with the ISO 13485 quality standards.
3. Work closely with relevant teams (engineering, quality assurance, and regulatory) to deeply understand the need for each role.

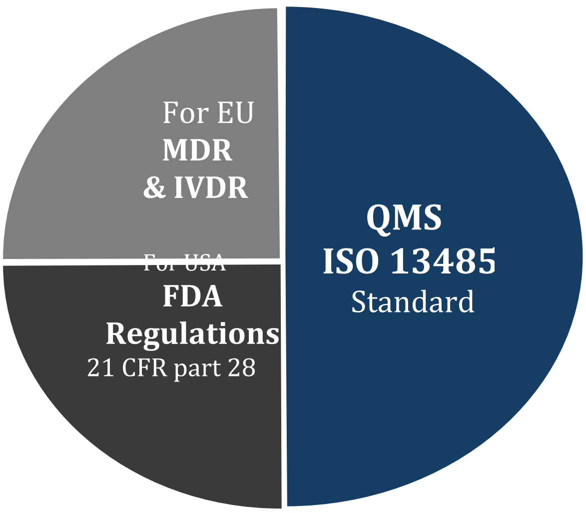
Point of Care could be scalable but requires a fundamental understanding of the framework. The findings from this report will offer valuable insights for healthcare institutions, aiding in the effective implementation of ISO 13485 requirements in their respective 3D printing environments.

2. Foundations of Quality Management and Regulatory Compliance

2.1. Medical Device Regulations and ISO 13485 standard

2.1.1. Overview

ISO 13485:2016, titled "Medical devices — Quality management systems — Requirements for regulatory purposes," provides a framework for organizations involved in the design, development, manufacture, storage, distribution, installation, and support of medical devices. It helps organizations to have smart system in place to obtain all the documentation required by the medical device regulations and authorities to get their device approved in the EU or in the USA. In the EU, to place a new medical device on the market, the organization need to comply with Medical Device Regulations (MDR) or In Vitro Diagnostic Regulation (IVDR) [12]. For US, compliance with 21 Code of Federal Regulations (CFR) part 820 is required for the Food and Drug Administration (FDA) approval [13]. All these regulations always mandate having a quality management system (QMS) to manage medical device industry following ISO 13485 standard. Figure 3 summarizes the relation between EU and USA regulations. It specifically built for medical device manufactures, developers, and distributors.



ISO 1348, first published in 1996 and revised in 2003 and 2016, aims to ensure that medical devices and services consistently meet user needs and relevant regulatory requirements. The standard is crucial for gaining the trust of regulators, stakeholders, and customers, facilitating market access, and demonstrating commitment to quality and compliance in the medical device industry. ISO 13485 is made up of eight clauses that any organization shall apply them all to ISO auditor to get certified. In EU, there were more three annexes; ZA, ZB, and ZC for EN ISO 13485, currently outdated, that bridge the gap between the general requirements of the ISO 13485 standard and the specific requirements outlined in the European Medical Device Directives (MDD, AIMDD, IVDD). These directives were previously in effect but have since been replaced by MDR and IVDR.

The QMS by ISO 13485 standard became harmonized with the MDR (EU) 2017/745. Following harmonized standards means that the organization can expect to meet required EU regulations for the parts of the standard that are harmonized. This means that the QMS requirements from the MDR may be fulfilled by committing to the ISO 13485 standard. However, it is important to notice that all clauses of ISO 13485 may not be applicable to all hospitals. This depends on the hospital's role in front of the regulations whether the hospital also serves as a manufacturer, distributor, or only a user of medical devices. The harmonization of ISO 13485 against MDR, is the main reason why ISO 13485 is a large part of this master work.

2.1.2. Clauses of ISO 13485

The first three clauses are introductory, set the foundational context for the standard which are scope, normative references, and terms and definitions. the last five contain the mandatory requirements for the Quality Management System [14]. Here is what the five main clauses are about:

Clause 4: Quality Management System (QMS)

This clause describes the general requirements, starting with the need to have an effective QMS that meets the regulatory requirements for the type of medical device. It emphasizes the importance of a documented system with defined processes, procedures, and responsibilities, applying a risk-based approach, and defining the sequence and interaction of these processes in a quality manual [15].

Clause 5: Management Responsibility

Management ensures the effectiveness of the QMS. Responsibilities include communicating the importance of regulatory compliance, establishing a quality policy, and setting quality objectives for the whole organization. Top management have to define and document responsibilities and authorities for operating the organization in conformity with its QMS and conduct management reviews at planned intervals.

Clause 6: Resource Management

This clause covers aspects like human resources, infrastructure, and the work environment. It emphasizes the importance of competence training for personnel involved in the medical device lifecycle. It also ensures the provision of a suitable work environment that doesn't compromise the quality of medical devices, such as, health, cleanness, and clothing requirements. Where applicable, the organization have to establish arrangements to prevents contaminations if the product require this kind of control.

Clause 7: Product Realization

This section covers very large set of requirements for the entire operation starting with implementing a design and development procedure for the products. Figure 4 shows the guidance for the design control for medical device manufactures. Effective verification and validation process is crucial at this stage prior to design transfer to manufacturers.

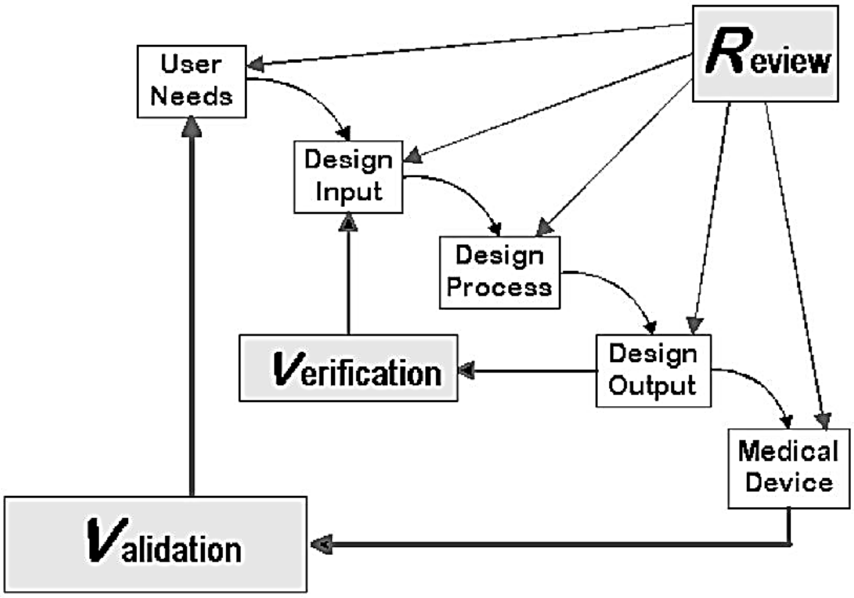


Figure 4. Design control guidance for medical device manufacturers [16].

There shall be a documented procedure to control purchasing orders and services including selecting suppliers, monitoring their performance, and verifying that purchased products conform to specifications. Additionally, it includes establishing arrangements for communicating with customers and medical device regulators.

Clause 8: Measurement, Analysis, and Improvement

Organizations shall monitor and measure processes and products, handle feedback and investigate complaints, and report to regulatory authorities depending on the event occurred. They shall identify any non-conformities, analyse data and implement corrective and preventive actions, and conduct internal audits to determine if the processes are achieving plan results.

ISO 13485 offers a flexible framework that adapts to the size, complexity, and medical device types of the organization. The actual number of documents required varies accordingly. Furthermore, justified exclusions can be made in clauses 6, 7, and 8, if they don't compromise compliant device production. These exclusions are for situations where specific risks make some requirements less necessary. However, the ability to exclude comes with the responsibility to demonstrate robust risk management and prioritize patient safety.

2.1.3. Certification and Compliance

ISO 13485 certification ensures conformity with safety standards for products sold in the European Economic Area and is often a prerequisite for obtaining CE marking. The standard is also significant in the United States, as the FDA plans to align its quality requirements with ISO 13485. By adhering to the requirements of this standard, medical device manufacturers can gain market access and demonstrate a commitment to delivering safe and effective medical products to customers.

2.2. Quality Management at 3D-Side

3D-Side company is one of the legal manufacturers of medical devices in Belgium, where the internship is taking place, encompassing the entire process from the design to production and marketing. The company complaint adheres to the international ISO 13485:2016 and the European Medical Device Regulation 2017/745. Their QMS incorporates ten procedures structured, as shown in figure 5 according to the relevant ISO 13485 clauses. The QMS structure was developed to ensure safety and compliance of their medical devices produced internally. These medical devices include 3D-Cut, a patient-specific surgical guide for bone tumor resection and corrective osteotomy (Class IIa); 3D-Skull, a patient-specific mold for pre-operative cranial implant (Class I); and bone models. Figure 6 shows samples of the company’s products. They also offer "Customize", a medical device software for 3D visualization and planning of orthopaedic, cranio-maxillofacial (CMF), and cranioplasty surgeries.

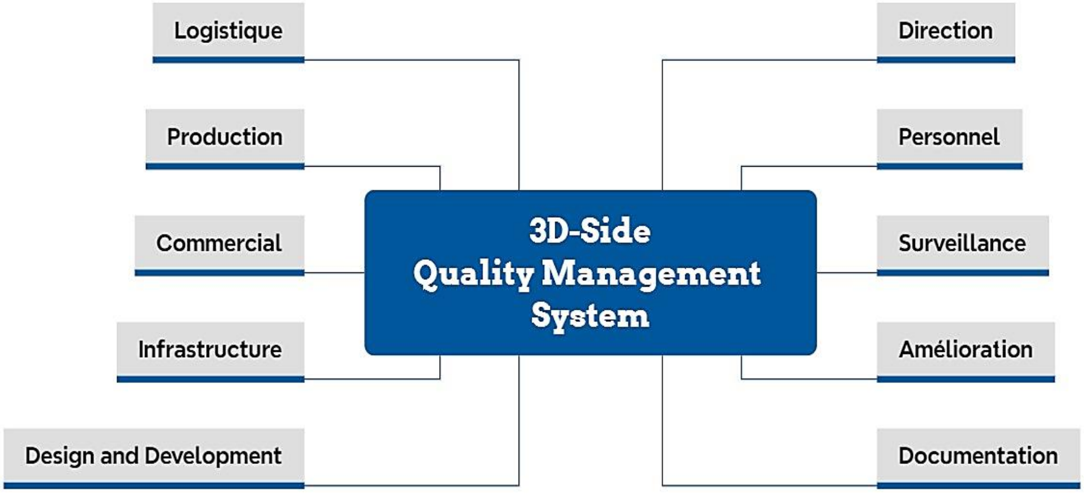
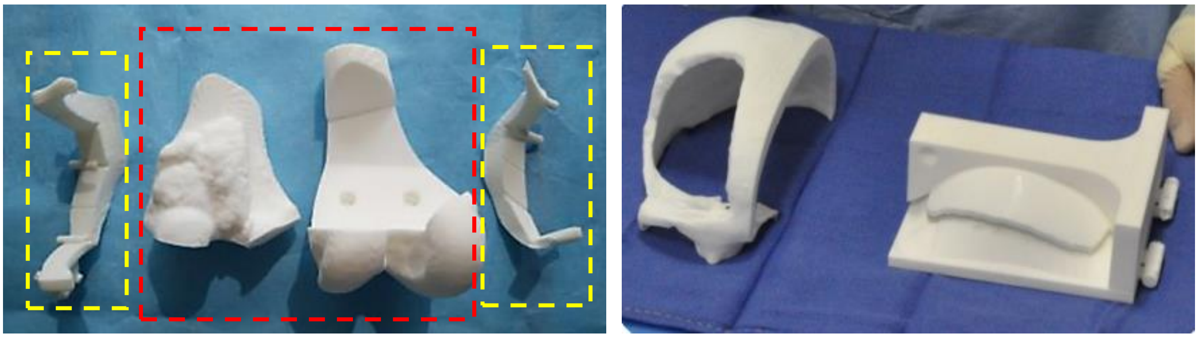


Figure 5. Quality Management System of 3D-Side



A core objective of this internship was to review and adapt these procedures to create a streamlined QMS suitable for Point of Care 3D-Printing (POC3DP) lab. The primary concern for the hospital is to ensure the 3D printed devices they produce meet relevant regulations and are safe for their intended use. This can be achieved through a well-defined QMS based on best practices. While an adapted QMS from ISO 13485 certified company provides a strong foundation. The following chapter explores how 3D-Sides's QMS was further adjusted for seamless integration within a hospital environment, focusing on the necessary aspects of managing and optimizing the 3D printing process to ensure quality and safety compliance.

3. Quality Management System Development

3.1. Approach Structure for the Hospital

Important variables for the successful implementation of QMS in the healthcare context are: education and training, continuous quality improvement, patient focus/satisfaction, top management commitment and teamwork. QMS implementation in the healthcare context, containing the variables above, will lead to higher levels of performance in the long run. The findings of this internship would be useful for stakeholders to introduce and implement a QMS in hospitals.

Among the ten major aspects of QMS of 3D-Side, all must be considered for a hospital, except for "Design and Development (DND)" procedure which is too complex for a hospital. Instead, the focus would shift to material control, process control, nonconformance management, and recordkeeping for the products. As the project would focus on the production of only surgical guides and anatomical models rather than developing new products. However, if hospitals need a new application, they can approach 3D-Side for development or assistance. So that the process of DND is excluded and explained separately. The following sections will delve deeper into the nine adapted processes proposed for the hospital QMS.

3.1.1. Order Management Process

This process is conducted prior to the POC3DP facility's commitment to supply product to a requester (e.g. acceptance of orders or contracts). So, it is mainly to evaluate the received order and ensure applicable regulatory established specifically for this project are met. A flowchart explaining the procedure of managing new orders from the receipt of a requester’s order to the product delivery is show in figure 7. A guide to flowchart symbols is explained in appendix B.

Order management for the POC3DP project would start without a standard document, allowing orders to be transmitted via various means such as email, phone, or through hospital processing-orders platform. There are three main controls to check while receiving new order:

A. Requesters are deemed qualified if they have signed a contract or offer; otherwise, the person who contacted the requester evaluates the qualification with the supervisor of the POC3DP lab and communicate the decision to the requester.
B. Verification of offer conditions, both technical and financial, is essential. Tables 1 and 2 explain the authorized and non-authorized applications provided for POC3DP project.

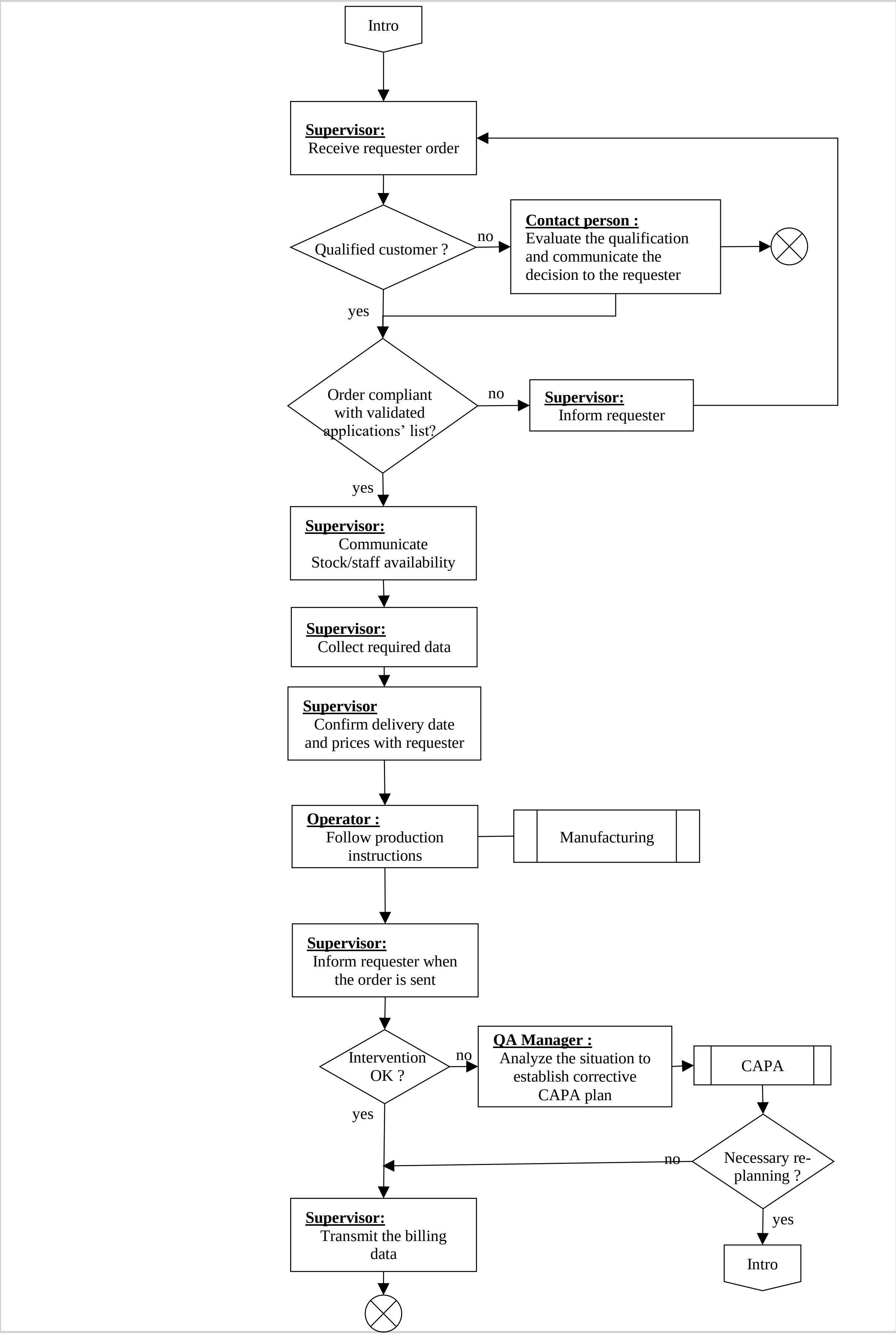


Figure 7. Requester Communication Process

C. Availability of stock and stuff to ensure delivering the product in a timely manner.

After ensuring the compliant of the order, the supervisor must collect the following data from the requester:

- The surgeon (prescriber) name,
- Department name in the hospital
- The type of surgical procedure
- Patient identifier
- And required data such as images, specifics (if applicable), date of the planned operation, etc.

A patient record shall then automatically created. A unique 5-digit patient number is assigned to the order.

Once the manufacturing step finished by the lab operator, notification is sent to the department or surgeon. The operating theatre and sterilization can also be notified of the dispatch to ensure that the order is followed up and processed. In case of dissatisfaction, the quality manager is informed, and requester specifications are reviewed to address any issues if feasible following the procedure of corrective and preventive actions (CAPA) explained.

Printing parts for uses other than their initial intent would lead to invalidation of the product. An authorization list is created for POC3DP to ensure that the demand is compliant with the applications approved by the project stakeholders. That list is a living document could be updated in the future but should be sent each time for approval each time before implementation.

Table 1: List of Authorized Applications for POC3DP

Product Reference	Product Name	Specifications	Limitations
01-PSI	3D-CUT	Max. contact duration with patient: 60 minuets Resection of bone tumor for femur, tibia and pelvis including sacrum & corrective osteotomy	Exculded Surgeries are: - Spine - Cardiology interventions - Acute, joint replacing osteotomies - metacarpals and phalanges - Tarsal bones, metatarsal bones, and phalanges
02-BM	3D-BONE MODEL	Bone Model of any size	_
03-AM	3D-ANATOMICAL MODEL	Anatomical Model for any size	_

Table 2: List of Non-Authorized Applications for POC3DP

Application	Risk
Bone model for stent evaluation if direct contact with the stent	Biological issue - pollution of the stent
Bone model for accurate measurement of an anatomy	Depend only on the accuracy of printer and the image size

The product reference can be used to identify the final product name for each patient e.g. 01-PSI-XXXXX. Otherwise, hospitals shall refer to their own reference for patients. Moving on to production and infrastructure procedures which are the core where one can implement controls for the hospital.

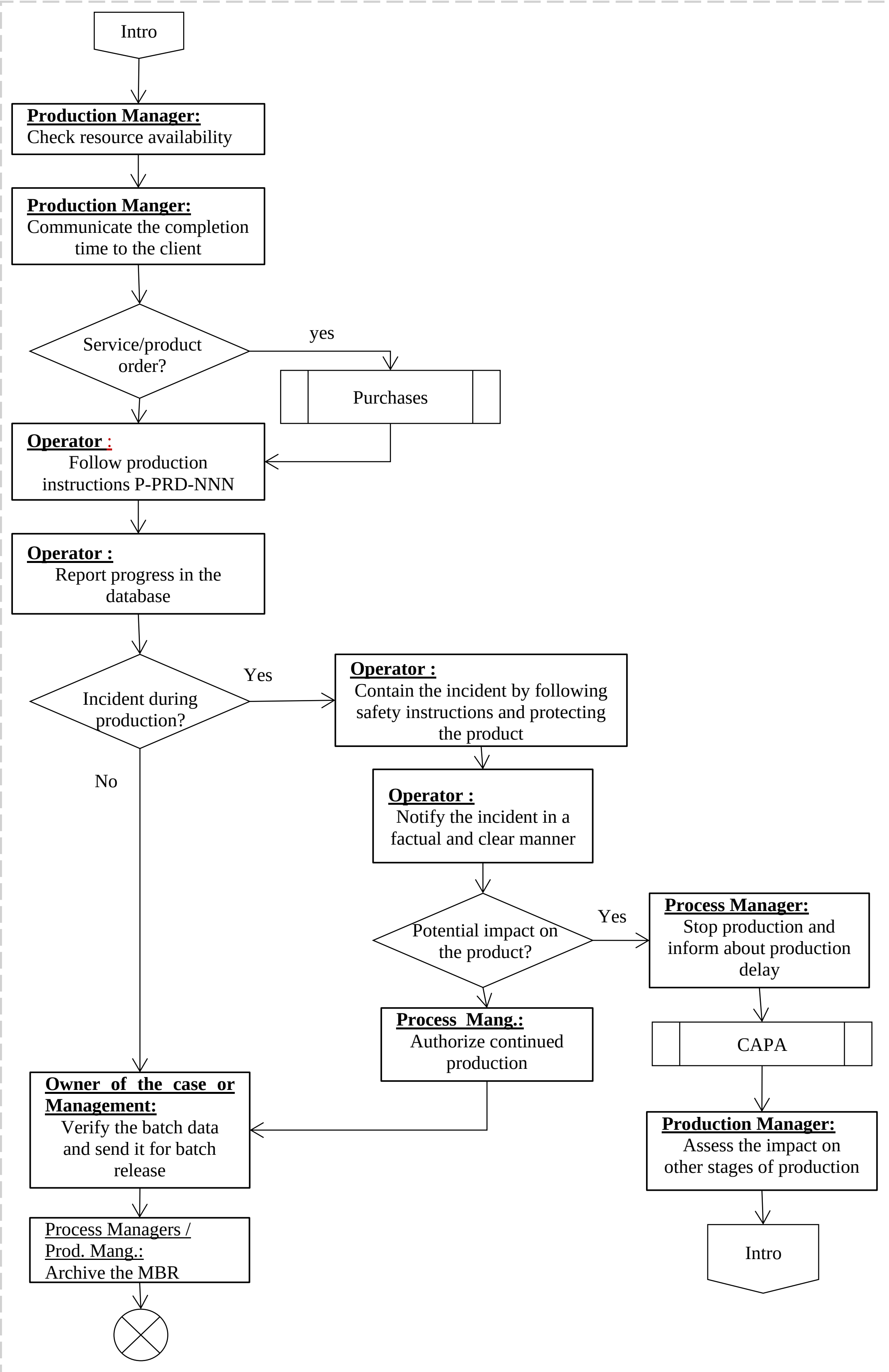
3.1.2. Product Requirements Process

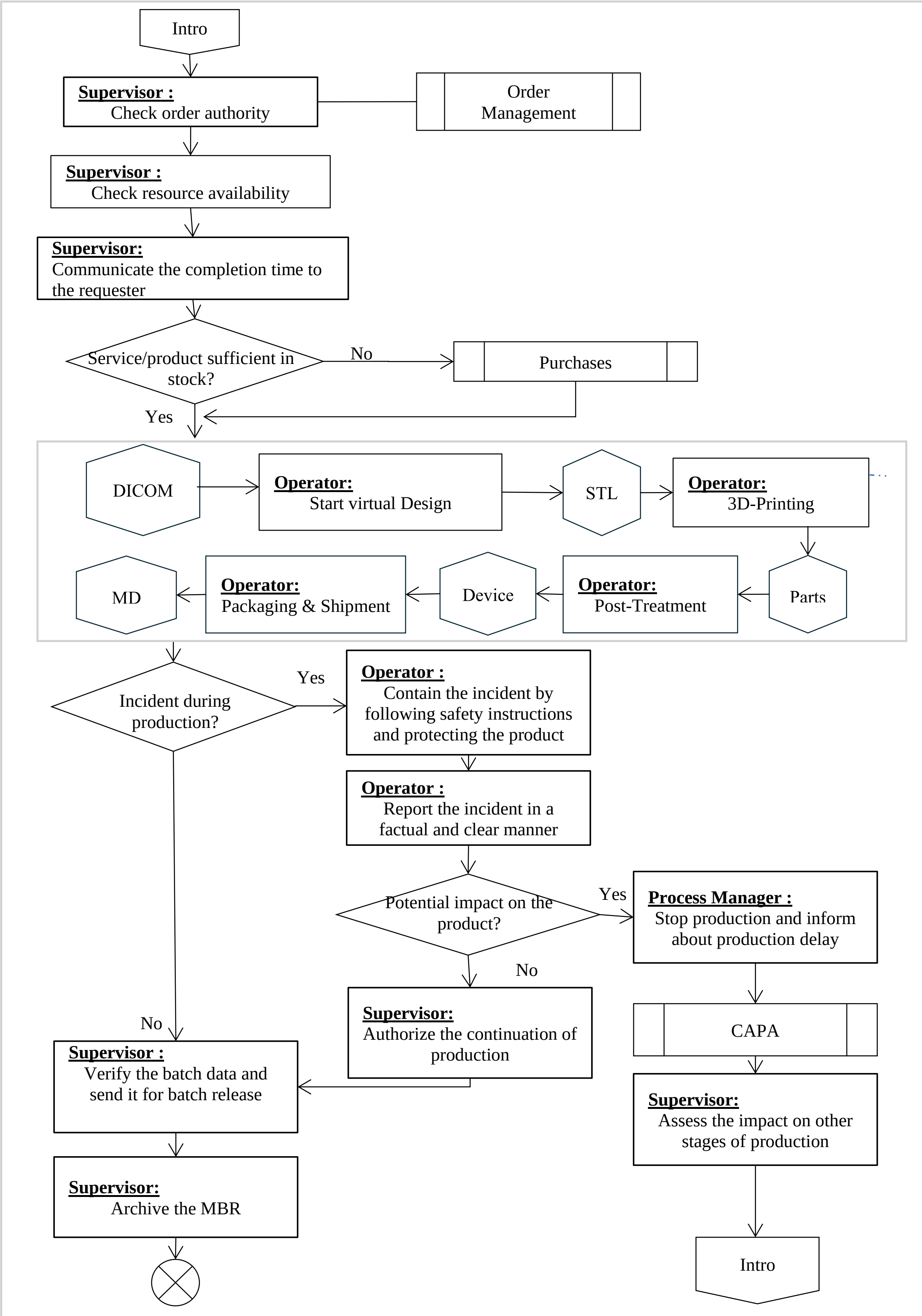
The production planning process initiates upon the receipt of a request, facilitated by the production team for POC3DP project. From the expression of a demand to the planning of production, to the finalization of the product packaged and ready for delivery. The previous version of production procedure shown in figure 8, featured a complex flowchart comprising more than twenty-five separate processes. However, following restructuring efforts, these procedures were consolidated into a unified workflow.

This transformation facilitates ease of comprehension, particularly during training sessions. So, it delves into the process of analysing and understanding the requirements of both operators and ISO standards, while also emphasizing the importance of practical and actionable forms for efficient implementation. Each stage of the process is meticulously designed and executed to ensure efficiency, quality, and requester satisfaction. The separate procedures are globalized into four processes:

1. Virtual Design
2. 3D-Printing
3. Post-Treatment
4. Packaging and shipment

Explore the flowchart in figure 9 to gain insights into how the requests are transferred into medical device products for the POC3DP pilot. Upon receiving the request, the lab supervisor conducts an eligibility check to ensure that both the requester and the requested product meet the necessary criteria for processing following the pre-defined “Order Management” process rules.


Intro
Production Manager:
Check resource availability
Production Manger:
Communicate the completion time to the client
Service/product order?
yes
Purchases
Operator :
Follow production instructions P-PRD-NNN
Operator :
Report progress in the database
Incident during production?
Yes
Operator :
Contain the incident by following safety instructions and protecting the product
No
Operator :
Notify the incident in a factual and clear manner
Potential impact on the product?
Yes
Process Manager:
Stop production and inform about production delay
CAPA
Process Mang.:
Authorize continued production
Owner of the case or Management:
Verify the batch data and send it for batch release
Production Manager:
Assess the impact on other stages of production
Process Managers / Prod. Mang.:
Archive the MBR
Intro


Intro
Supervisor :
Check order authority
Order Management
Supervisor :
Check resource availability
Supervisor:
Communicate the completion time to the requester
Service/product sufficient in stock?
No
Purchases
Yes
DICOM
Operator:
Start virtual Design
STL
Operator:
3D-Printing
Parts
Operator:
Post-Treatment
Device
Operator:
Packaging & Shipment
MD
Incident during production?
Yes
Operator :
Contain the incident by following safety instructions and protecting the product
Operator :
Report the incident in a factual and clear manner
Potential impact on the product?
Yes
Process Manager :
Stop production and inform about production delay
No
Supervisor:
Authorize the continuation of production
CAPA
No
Supervisor :
Verify the batch data and send it for batch release
Supervisor:
Assess the impact on other stages of production
Supervisor:
Archive the MBR
Intro

Following the eligibility check, the Production Manager assumes responsibility for identifying the essential resources required for the production process. These resources include:

- Raw materials
- Production Line Equipment & Premises
- Necessary Documentation.
- Cleaning, Servicing, Maintenance, etc.

After identifying the key resources, the supervisor verifies their availability and communicates the expected completion time to the requester or the contact person, ensuring transparency and effective coordination throughout the production process. Operators are required to adhere strictly to the process steps and controls provided in each manufacturing procedure. This adherence ensures consistency and quality in the manufacturing procedures.

Each process is documented separately and contain an overall detailed description of production instructions and techniques. The parameterization of the virtual design is an ongoing process and to be verified for the subsequent steps, e.g. for bone tumor resection case shown in figure 10, to produce the final design in STL format to be 3D-printed:

1. From the surgery page on “Customize” platform; operator can perform co-registration of a CT with an MRI while ensuring similar field of view (FOV).
2. Bone segmentation for necessary manual adaptations (e.g. filling holes, separating bones,…)
3. Resection Planning. The operator or process owner shall confirm this step first with the surgeon before moving to the next step.
4. Designing the surgical guides and placing kirschner wires to provide stability as needed to enhance overall surgical precision.

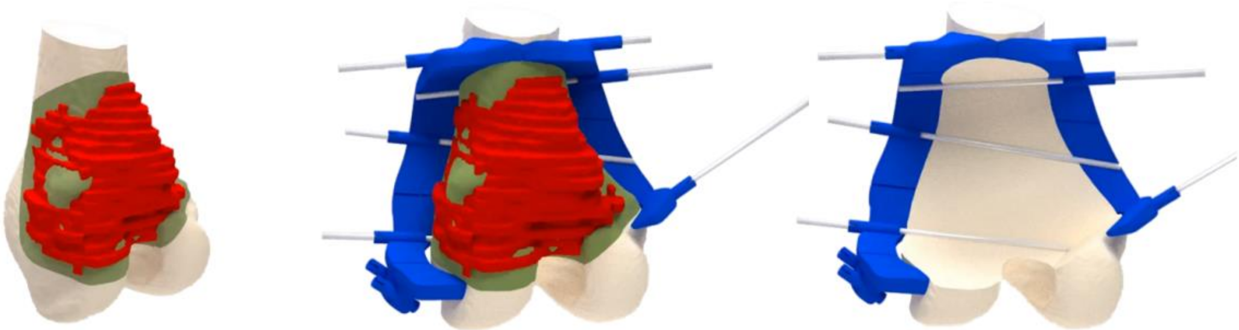


Figure 10. Virtual Design Process A) Resection planning based tumor delineated on the MRI and matched on the CT (Red areas). B) Design of the surgical guides (blue shapes). C) A shared K-wire ensures the final stability of this guide. Source: 3D-SIDE (2022) [Complex Distal Femoral Tumor Resection]. Retrieved from https://www.3d-side.com/case-studies-tumor.

In consequence, the graphs in Figures 11 and 12 illustrate a template procedure for 3D-Printing and Post-Processing workflow of manufacturing the surgical guides with the main controls identified on the right. After the operator ssecurely package and label the boxes, they become medical devices and could be delivered for sterilization. And the supervisor of the lab ensures that all steps have been completed and sign off for case release. If an incident occurs during manufacturing, the supervisor is responsible for promptly documenting it in the Manufacturing Batch Record (MBR) and may authorize, with the quality manager, the continuation or cessation of production to mitigate risks and maintain product quality.

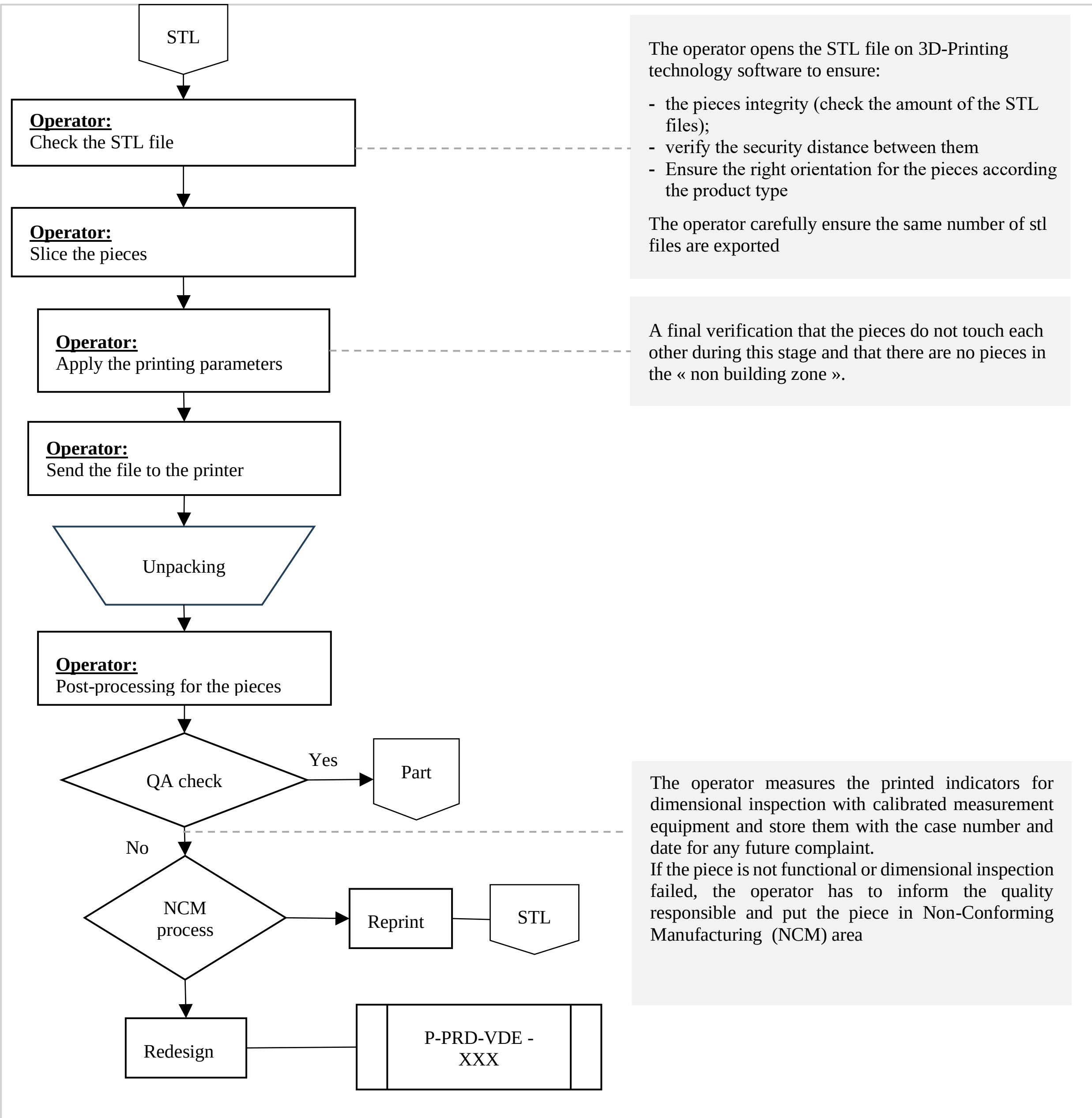


Figure 11. 3D-Printing Process for POC3DP Lab

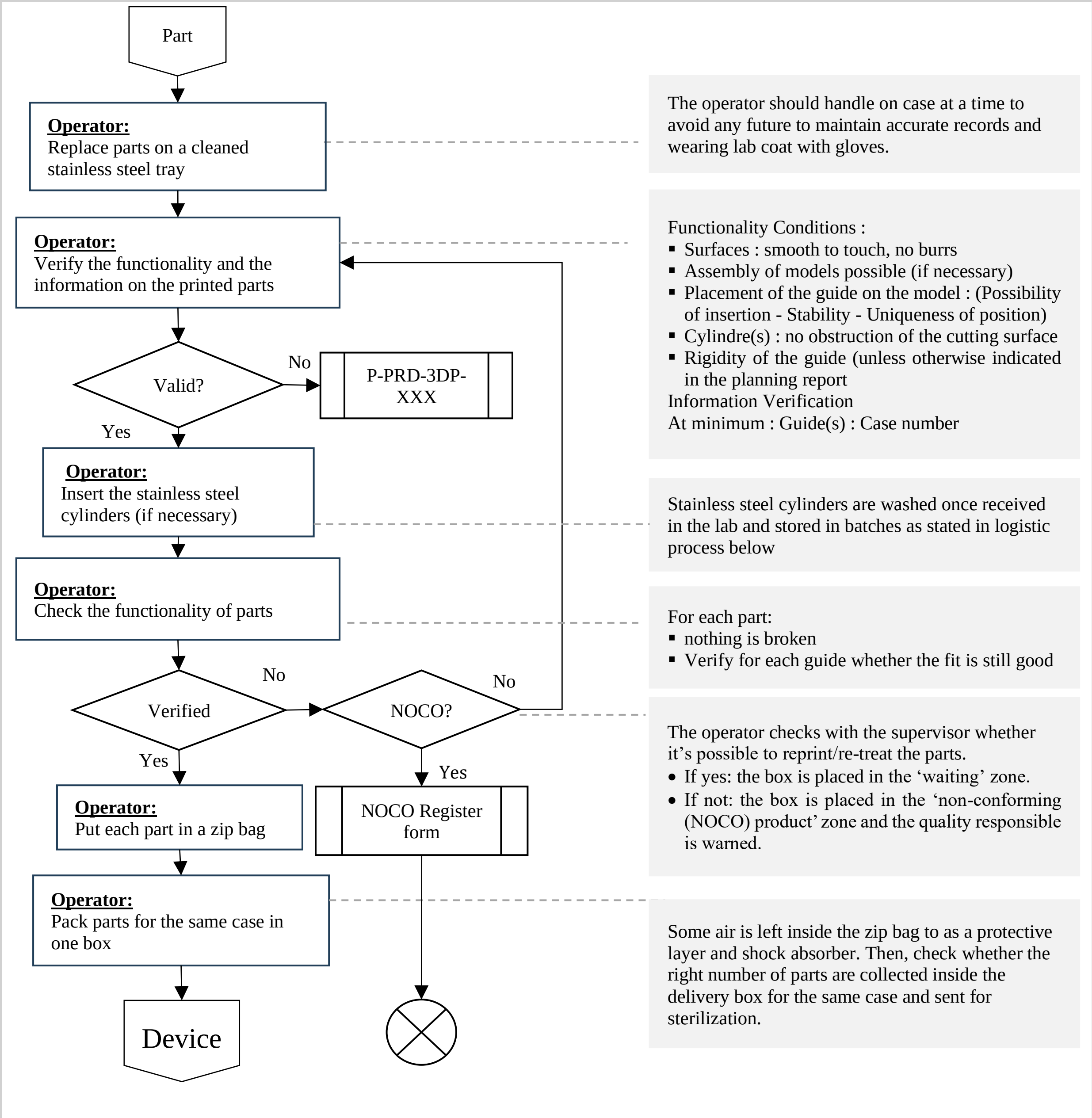


Figure 12. Post-treatment Process for POC3DP Lab

The documentation includes details such as the date and time of the incident, the affected step, the equipment or products involved, and the immediate actions taken to contain the incident. Furthermore, the operator collects relevant data related to the incident, such as taking photos or recording additional data if feasible. Validation of a manufacturing batch is conducted by the lab supervisor for quality verification. Only a trained professional is authorized to release an order (a case), ensuring adherence to quality standards and regulatory requirements. Ensuring thorough traceability of raw material used in each production batch is important. This comprehensive approach to traceability aligns with MDR (EU 2017/745) requirements, which require to trace back trace each single released product back to its source materials. This necessitates including travel forms, work instructions, incoming inspection reports, outgoing quality control reports, and proper labeling of the device. The following two sections provide the procedures for verifying the received equipment and critical materials for manufacturing, further solidifying the foundation for robust traceability.

3.1.3. Infrastructure and Maintenance

During the planning phase for procuring new equipment or infrastructure components, an impact analysis should be conducted to assess their potential effects on design, production, and quality control activities. This analysis categorizes the equipment into four main groups: Direct, Indirect, No impact, environmental safety impact equipment. Equipment falling into the "Direct" or "Indirect" categories requires a comprehensive maintenance program. Table 3 provides a template form with all the necessary evaluations has to be conducted receiving new equipment in the lab of the infrastructure and the associated maintenance planning.

Table 3: Infrastructure and Maintenance Plan

<table>
<tr><th colspan="8">Infrastructure Manufacturing List</th></tr>
<tr><th>N°</th><th>Type</th><th>Device Name</th><th>State</th><th>Qualification done?</th><th>Maintenance program is implemented in the global maintenance FORM</th><th>Location of use</th><th>Date of comissioning</th></tr>
<tr><td></td><td>(Scale/3D-Printing/ PTR/ calibration)</td><td></td><td>(Compliant/ Declassified, under evaluation/ Non-compliant)</td><td>(Yes/No/NA)</td><td>(Yes/No)</td><td></td><td></td></tr>
<tr><th>IFU</th><th>Intervenant (externe)</th><th>Type of Contract</th><th>calibration expiry date is applied on the equipment?</th><th>Supplier Reference</th><th>Serial Number</th><th>Model</th><th>Price</th></tr>
<tr><td>(Yes/ No)</td><td></td><td></td><td>(Yes/No)</td><td></td><td></td><td></td><td></td></tr>
<tr><th colspan="8">Maintenance Planning</th></tr>
<tr><th colspan="2">Task</th><th colspan="2">Frequency</th><th colspan="2">Reference FORM</th><th colspan="2">Comment</th></tr>
<tr><td colspan="2"></td><td colspan="2">Daily/Weekly/Monthly, Quarterly, Annually/ Every X years</td><td colspan="2">QMS file > Infrastructure file > Maintenance file > NNN Task</td><td colspan="2"></td></tr>
</table>

Each equipment shall assign a tag and recorded in this reference. For the 3d-printing technologies and their associated post-treatment devices, Installation Qualification (IQ) / Operational Qualification (OQ) / Performance Qualification (PQ) processes are essential for validating the performance and reliability, ensuring that this equipment can consistently produce high-quality parts for their intended use. A Tracking system is a part of the proposed quality management for hospitals to take on the IQ-OQ-PQ responsibility.

I. Installation Qualification (IQ)

During the IQ phase, the equipment manufacturer ensures proper installation and identification of key components components (equipment, piping, zone), connection to utilities (electricity, ventilation, etc), and necessary documents for use and maintenance (user manual, operating procedures, manufacturer's recommendations...). The printer should be tested for: building temperature, dimensions of the pieces, and laser scanning works properly; additional tests shall be performed if necessary. If these tests meet the acceptance criteria identified during technology validation tests carried out at UCLouvain; this machine can move to the OQ phase.

II. Operational Qualification (OQ)

This process ensures that the printing parameters are compliant with the specifications for the size of printed medical devices by measuring the indicator printed with the first batch. As significant error can happen with laser scanning but not with calipers measurement in the post-treatment step. Successful IQ/OQ enables commissioning of the equipment, facilitating PQ steps and process validation.

III. Performance Qualification (PQ)

PQ process should be done regularly with each time a new batch is printed. Then, the operator shall use e.g. a caliper to measure the indicator for a specific range. Any defects identified during PQ are recorded and addressed, with non-conformities investigated to determine root causes and establish CAPA plans if necessary. Finally, The POC3DP lab should feature appropriate signage outlining protective measures. This includes ensuring operator(s) wear necessary safety clothes, preventing any mechanical shocks on work surfaces, and installing room temperature sensors to maintain conditions suitable for the technology specifications.

3.1.4. Logistic

Infrastructure procedure was for receiving the necessary devices in the lab and to ensure their safety and effectiveness. On the other hand, logistics outlines the process to receive and procure the critical raw goods to be used inside the POC3DP lab for production.

I. Vendor Qualification

Suppliers shall be evaluated to ensure they meet established quality standards, including relevant certifications (e.g., ISO 9001, ISO 13485, Good Manufacturing Practices) for biocompatibility assurance. Hospital with a POC3DP lab might categorize suppliers of raw materials (e.g. specific resins) as critical suppliers. Applying the Pareto principle, the hospital might find that 20% of these suppliers account for 80% of the total value of supplies or potential risks [17]. Thus, the hospital will prioritize reviewing and managing these critical suppliers closely to ensure uninterrupted operations and high-quality outputs. A form to review these suppliers for their compliance is added to the QMS for the following points:

- Valid Certification for ISO ISO9001 (Biocompatibility assurance), ISO13485, and Good Manufacturing Practices (GMP) (The scope of the certificates must cover the type of supply)
- Criticality
- Supplier Risk Evaluation on score 1-4 for their:
  - Regulatory Compliance (RC),
  - Quality System(QS), conclusions of the supplier's latest audit,
  - Product Supply (PS), the impact on the lab of a non-compliant product

II. Receiving Inspection

Critical incoming goods such as, raw material for printing process, stainless steel cylinder, etc., shall be tracked and recorded while ensuring that the specification sheets, used for biocompatibility certification, including parameters such as, density, pourability, and temperature, meet the specifications required while order purchasing. Vendors should notify if they no longer have these specifications. For instance, a standard Formlabs resin cartridge contains 1 liter of resin. Assuming an average surgical guide requires about 25-30 ml of resin (a rough estimate based on typical surgical guide designs), 33 to 40 guides could be produced per cartridge, exposing 33 to 40 patients to these products.

If batch number and material are non-compliant, the operator should request it and ensure it is correct before proceeding. Otherwise, notify the quality manager. The purchase order form was updated to check these specifications. Hence, the philosophy of ISO 13485 is to structure an organization to be robust.

III. Traceability

Record the entry into stock, including item code, quantity, supplier batch number, internal reference, expiration date. Each of the received product is identified by the expiration date on its label. Their internal reference identified upon receiving is used on the final name manufactured products to ensure complete traceability during any investigation in case there is a non-conforming product. At any given time, there is only one batch of raw materials in circulation. Therefore, with the date of manufacture, it is possible to determine which batches were used during production.

The database allows complete traceability of products from raw materials to delivery through the input/output movements of materials which identify the product, the relevant batch, and the reference of the operation at the origin of the movement (production batch number, delivery number, etc.)

IV. Storage conditions

The POC3DP lab supervisor shall assign a minimum stock to items with a long lead time. The manufactured products, single use devices, should be delivered immediately and not stored, as they are custom-made devices. Raw materials are not managed in stock (consumables); only the batch number used is recorded not the quantity. Therefore, there is no inventory. While a minimum stock should be maintained. Below this minimum, the POC3DP lab supervisor is notified and triggers the purchase to renew the stock. The processes for storing new goods, verifying their conformity to specifications, and conducting quality control checks should be carried out once new goods are received to ensure they are stored correctly. According to the materials specification sheets, labels with tags for some parameters to be maintained are implemented for ensuring optimum temperature range, light exposure, sealed containers to prevent contamination, and expiration dates.

This approach not only facilitates the swift identification and resolution of any issues with materials or finished products, but also ensures the quality and safety of manufactured devices. Traceability records are essential for effective recalls and corrective actions, ultimately protecting patient safety and regulatory compliance.

3.1.5. Documentation Management

This procedure outlines the comprehensive process for managing documents from creation or modification requests to distribution and records management, including creation, archiving, and destruction. Effective documentation facilitates auditing and ensures compliance. The document management structure follows a specific format: "X-NNN-MM Short Name," where X identifies the type of document (P for Procedure, F for Form, R for Reference document), NNN represents the letters identifying one of the QMS procedure related to the document (e.g., PRD for Production), MM is a unique number for ordering the documents related to each X document, and the Short Name represents the document. For example, "P-DOC-01 Document Management."

When creating or editing a document, the editor must work outside the main directory and distinguish the provisional document from the original by adding a suffix or prefix "-draft". All documents should be written in a unified language that is understood by all relevant hospital staff. The editor ensures the document includes a version number and effective dates. Before finalizing the draft document, the consequences of change should be analysed including:

- Cascading changes in other documents (references, changes to propagate, etc.)
- Impact on product quality (ex.: no longer register a data)
- Impact on the training. A reference for all training documents shall be updated. Figure 13 shows the distribution of various document types, essential for training, across different QMS procedures for the POC3DP pilot. While figure 14 shows the allocation the remaining documents that do not require training but still need to be followed.

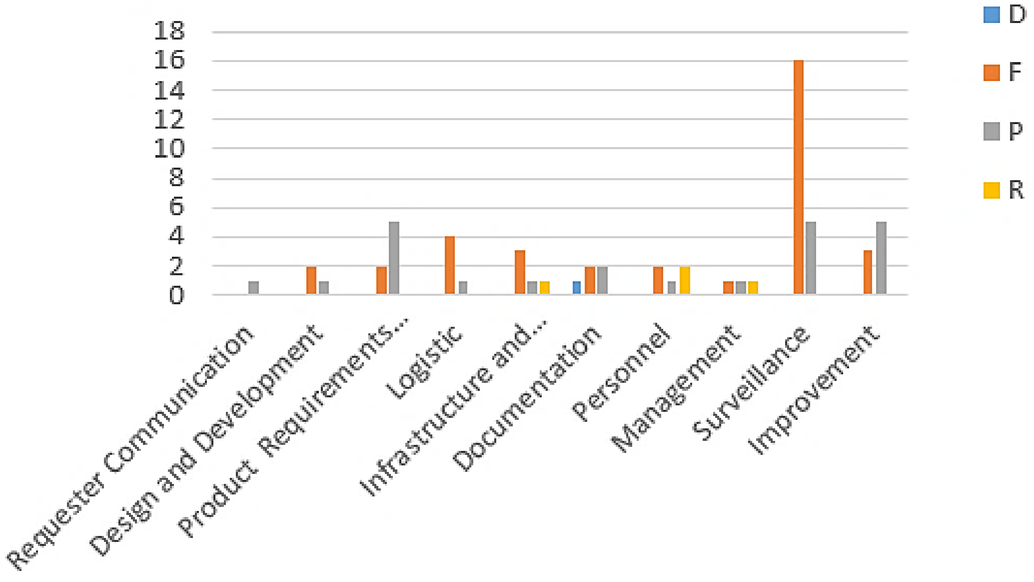


Figure 13. Documents Requiring Training

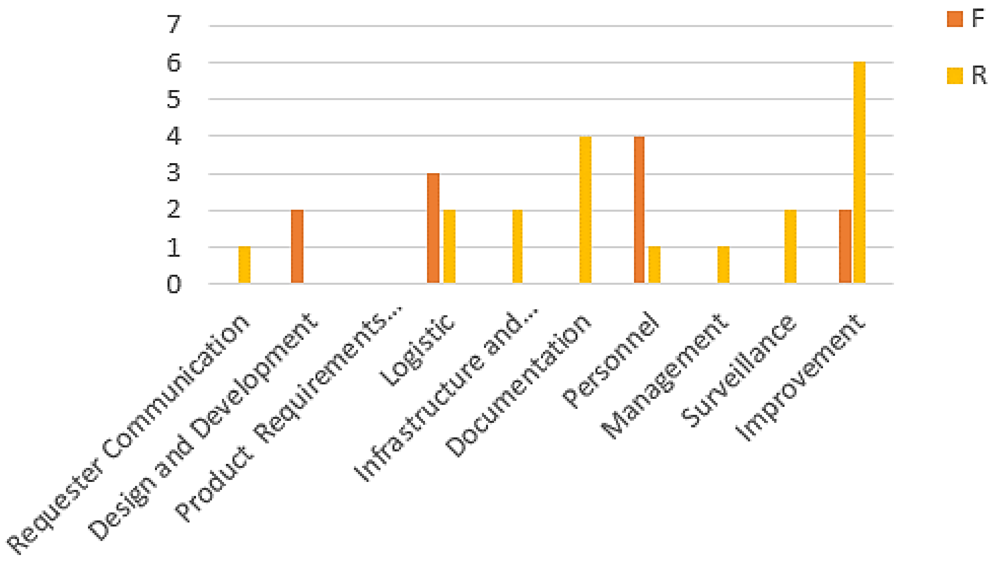


Figure 14. Documents Requiring Compliance Only

For documents with significant regulatory impact, such as the list of authorized applications or design specifications, approval from POC3DP project stakeholders is required. Otherwise it's the responsibility of the final user, e.g. the surgeon, of the medical device to determine if the conditions are sufficient to use the device with required performances.

Records demonstrate compliance or non-compliance with regulations and the effectiveness of operations. Forms and databases used for record-keeping must be completed according to the respective procedures. Table 4 clarifies the distinction between documents and records.

Table 4: Difference between documents and records

Documents	Records
Communicate information through policies, processes, and procedures	Demonstrate compliance, performance, and historical accuracy.
Need regular updating	Fixed after date entry and signature
Provide the framework and guidelines to ensure processes meet regulatory compliance	Capture objective facts such as audit reports, batch records, information on worksheets, labels, forms, and charts.

The retention period for records and associated documents is typically fifteen years after the device has been placed on the hospital, as per Medical Directive Regulation 2017/745. After the retention period, the quality manager ensures the destruction of the documents, dating and signing the archiving form.

3.1.6. Personnel

The personnel procedures for the POC3D lab differ from traditional models in that they focus on adapting existing hospital staff to produce the medical devices following the quality and safety standards. During the implementation phase of the project in the future, identifying the most suitable personnel shall be identified through their existing competence or evaluating and reviewing of their past work experience. If a staff member's skills don't fully meet the project's requirements, targeted training, provided in forms for each manufacturing task with the QMS, should be conducted before working in the lab. The minimum number of persons required for the POC3DP lab is illustrated in figure 15 for smooth operation and adherence to ISO 13485 standards. Roles within the hierarchy can be filled by biotechnicians, surgeons, clinicians, nurses, or other qualified hospital staff.

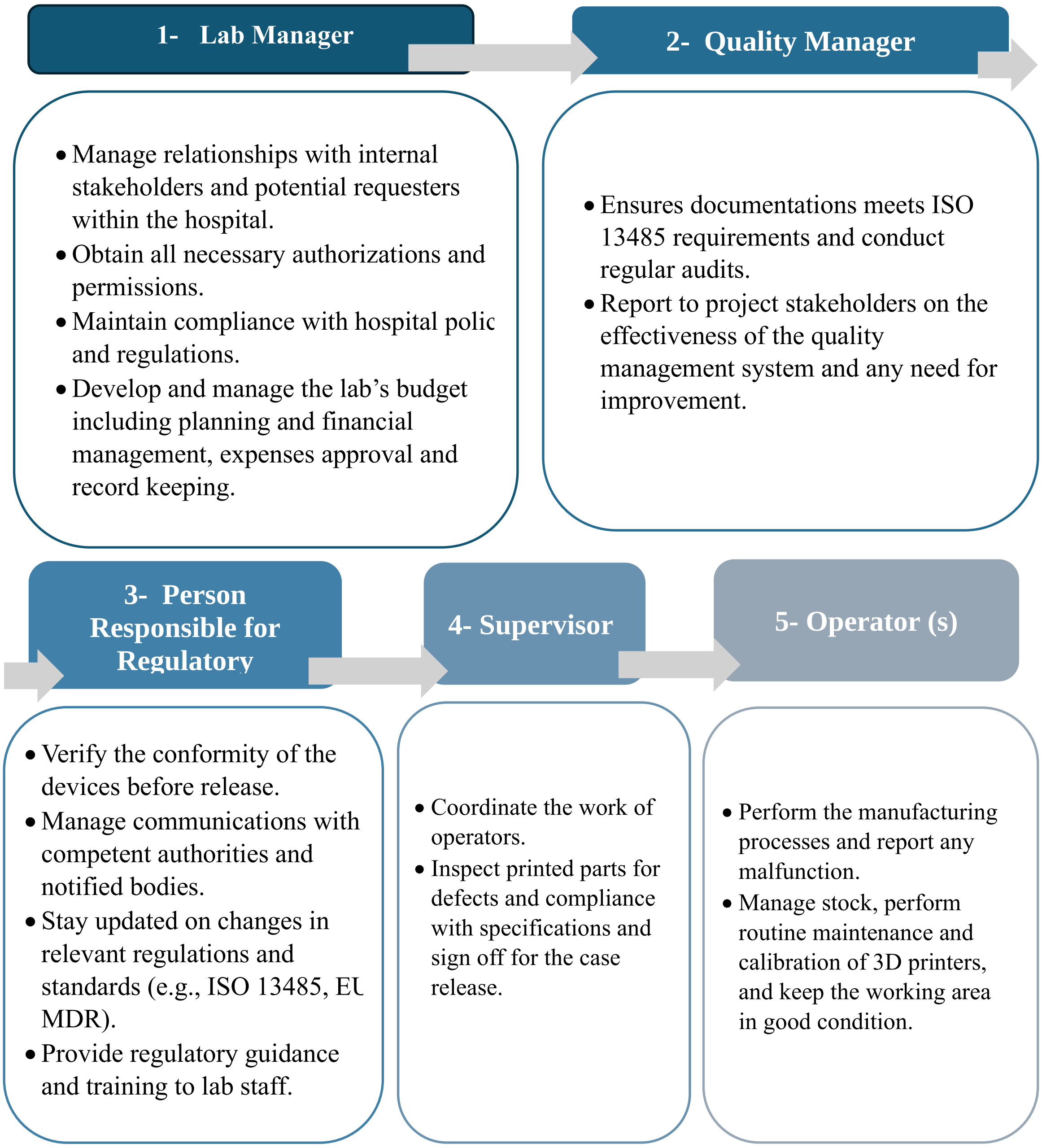


Figure 15. Roles and Responsibilities in the POC3DP Lab

Following the competence assessment system and training evaluation forms, the POC3D lab will have a qualified team to operate the equipment effectively and comply with regulatory requirements.

3.1.7. Management Responsibility

Management procedure, primary performed by the lab manager with the quality assurance manager, includes mechanism for collecting feedback from audits reports (internal and external), requesters, post-market surveillance, actions from previous reviews, suppliers review, quality policy and other relevant sources. This process facilitates continuous improvement for the lab. The results of these reviews shall be documented in the form "Management Review Report," which covers the decisions and actions related to:

- Improving the effectiveness of the quality management system and its processes.
- Improving the product in relation to requester requirements.
- Verifying the effectiveness of corrective and preventive actions.
- Resource requirements e.g. financial, infrastructure, and personal training.
- Assessing the relevance and adequacy of the risk policy, especially when new risks were introduced. A guidance for establishing criteria for risk acceptability to consider incorporating:
    - Utilize Failure Mode and Effects Analysis (FMEA) to analyse potential failure modes of 3D printed devices, their effects on patients, and the likelihood of occurrence.
    - High risks should be addressed with additional control measures until they are reduced to low or moderate values.
    - Avoid further risk mitigation that would diminish the benefit outcomes or efficiency of the lab.
    - Overall benefits from the POC3DP lab outweigh any residual risks.
    - Critical protective measures such as, room temperature sensor for effective printing and storage condition, can not be eliminated.

The management review must be conducted at least once a year. A second review may be organized, if necessary, to verify the progress of actions to be implemented. The next two processes are standard procedures that the hospital should be aware of, especially in the context of medical device manufacturing. Standard procedures refer to established guidelines to maintain quality and safety in operations.

3.1.8. Post-Market Surveillance

Medical devices have to be monitored after release to gather new information about safety and performance. This information should be proactively collected and can be used as input for the risk management, clinical evaluation and design development of the products. For each product, forms for a post-market surveillance plan and post-market surveillance report (for class I products) or Periodic Safety Update Report (for class IIa products) are created. These reports should be updated whenever new relevant data is identified. Data collection and necessary reporting forms proposed for the project are explained in the following sub-sections.

I. Post-Market Surveillance Plan

For class IIa medical devices, post-market surveillance cycles may extend to no longer than two years, concluding with the compilation of a PSUR. For class I devices, longer surveillance cycles may be defined, (e.g., every two or three years), with a post-market surveillance report compiled at the end of each cycle. The post-market surveillance plan is created following MDR Annex III [18]. The quality manager and lab supervisor collect information from all the categories described below and enter them into the report template. At minimum, the following information categories have to be taken into consideration:

- Post-Market Clinical Follow-Up (PMCF) activities: This is particularly important for Class IIa devices, which present a medium risk to patients. This includes collecting and analyzing data from spontaneous adverse event reports submitted by healthcare providers or patients.
- New research and development in the market: Information regarding similar medical devices and technologies on the market.
- Recalls and reportable events: Includes unintended side effects for similar products or other lab devices.
- Regulatory updates: An up-to-date list of applicable regulations, norms, standard, and other laws is maintained.
- Software verification: Ensure versions are up to date and the software is functioning as intended.

Feedback from other stakeholders shall be also documented. The severity of impact on device safety and performance is rated. Based on the rating, the quality manager and the Person Responsible for Regulatory Compliance (PRRC) can initiate the appropriate actions, other roles (e.g. medical staff) should be involved if needed. Actions may entail design changes, updating the product risk management document, initiating the vigilance process, or corrective and prevention action (CAPA). If a CAPA is identified based on post-market surveillance information, the competent authority and/or notified body are informed.

II. Vigilance Reporting Process

The lab maintains an up-to-date guidance on how to handle (potentially) serious incidents and report to competent authorities (if necessary) like Federal Agency for Medicines and Health Products (FAMHP) for hospitals in Belgium. Any staff member who become aware of any event with a potentially negative impact on the state of health should immediately notify the Person Responsible for Regulatory Compliance (PRRC) to initiate this process. The Vigilance reporting applies if the 3 following criteria are met:

- An incident occurred (malfunction, performance degradation, unexpected side effect, error notices...),
- A lab device is suspected of having contributed to the incident,
- The incident is evaluated as serious (e.g., death, serious health deterioration, public health threat).

Within the applicable reporting timeframe, the PRRC informs the competent national authority about the event using designated reporting forms.

III. Trend Analysis

All collected post-market surveillance information should be reviewed against the device's risk management file. Any statistically significant increase in the frequency or severity of non-serious incidents and expected undesirable side effects are reported to the competent authority along with the Vigilance process. Records of the conducted trend analysis shall be stored with other technical documents records of the device.

IV. Field Safety Notice and Regulatory Reporting

The lab communicates safety information to healthcare providers and users through field safety notices. Additionally, required reports like FSCAs and periodic summary reports are submitted to regulatory authorities. Following a risk and root cause analysis of the event, the PRRC decides if field safety corrective actions are required to reduce existing risks. Finally, the effectiveness of implemented FSCAs is evaluated as part of the CAPA. As soon as the

CAPA is closed, a final report is sent to the responsible authorities to verify that all actions taken are deemed sufficient for completion.

V. Periodic Safety Update Report (PSUR)

Product manager/lab supervisor finalizes the PSUR, reviewed at least reviewed by the PRRC. The report should contain at least the following information:

- Key findings of post-market surveillance activities throughout the surveillance interval as set out in the Post-Market Surveillance Plan
- A rationale and description of any preventive and corrective actions taken
- Implications for risk management, clinical evaluation, and overall risk-benefit determination.
- Findings from the PMCF
- Device sales volume, e.g. number of users and, where practicable, the usage frequency of the device.

Through diligent monitoring, data analysis, and implementation of corrective actions, the lab can continuously improve its products and maintain compliance with regulatory standards.

3.1.9. Improvement Procedure

Improvement process involves several steps specifically to control and investigate non-conforming products through identifying a corrective and preventive actions (CAPA) management plan. A number of things can provide inputs for CAPA, such as product or QMS non-conformities, requester complaints, audit findings, post-market surveillance outcomes, and management review results.

Once an issue is clarified, quick actions are implemented if required, and the event is documented. The quality manager is then informed, to assess the impact on product conformity. If a major non-conformity is identified, either a batch recall or vigilant reporting to the relevant authorities shall be required. If not, the CAPA management procedure is used to guide the process ahead. The current procedure at 3D-Side is compatible for implementation in the hospital setting. Figure 16 demonstrates an example of the problem investigation process for CAPA. The next phase involves root cause analysis to identify for the problem and suggesting solutions based on these likely causes. The findings should be documented and the gathered information is examined. Following an assessment of these measures' efficacy, the CAPA is closed, and the CAPA reference list is updated.

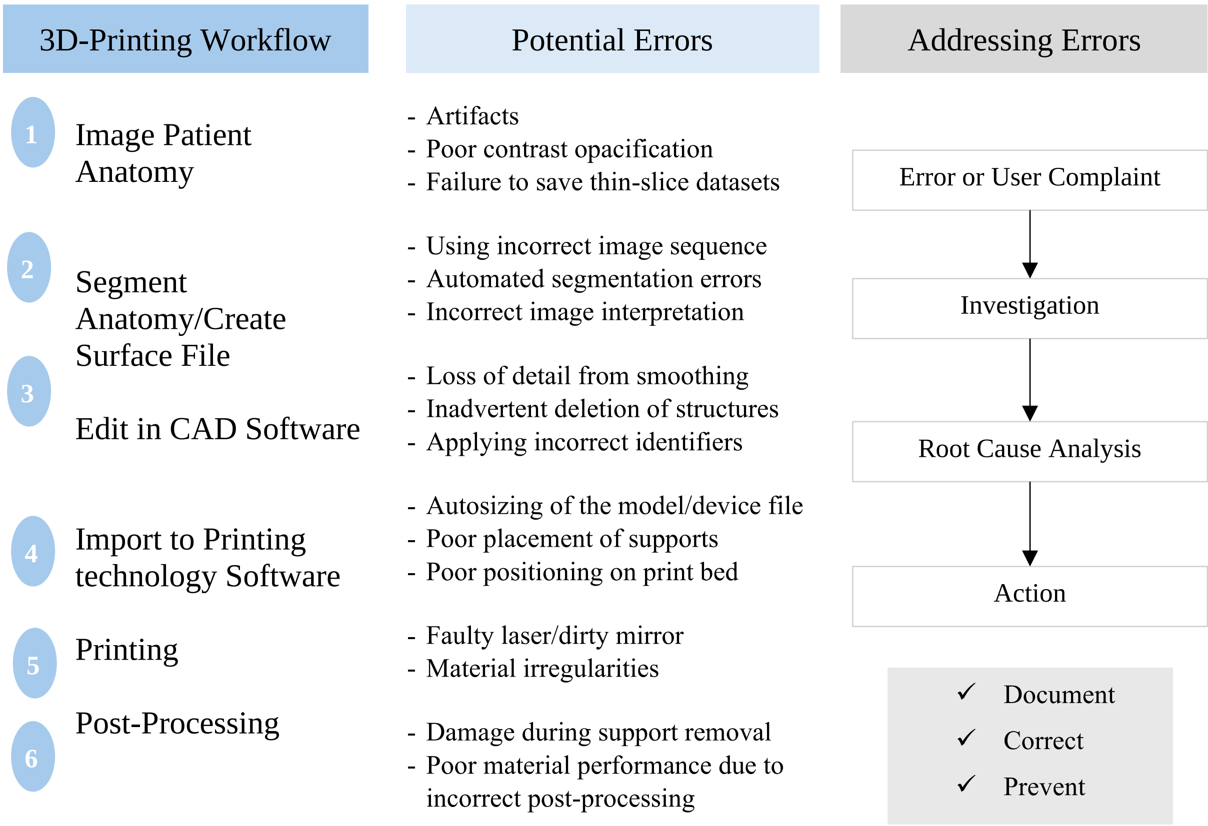


Figure 16. Examples of potential errors can occur during each workflow step

The second goal for the POC3DP research project is centered on design and development, a critical procedure towards introducing new business or product applications for 3d-printing technology. While project stakeholders lead this development, it's crucial for the hospital to consider implementing risk analysis outcomes from this work as a foundation for their future QMS processes.

3.2. Approach for Technology Selection

3.2.1. Biocompatibility Evaluation

The second objective of this work is to assist and evaluate the limitations and risks associated with the 3d-printing technologies, an important milestone to successfully achieve. The first step was to evaluate the available 3D-printing materials on the market. Referring to Table 5, it demonstrates the biocompatibility evaluation endpoints and the corresponding categorization of medical devices based on the nature of body contact as per ISO 10993:2018

[19]. The contact duration is divided into three categories; A (Limited): Less than 24 hours; B (Prolonged): More than 24 hours but less than 30 days; and C (Permanent): More than 30 days.

Compliance with ISO 10993 standards is essential for assessing the biological safety of materials used in medical devices. In the context of 3D-printing, adherence to ISO 10993 standards guarantees the suitability of printed materials for clinical applications; ensures biological safety; and mitigate potential risks associated with patient contact.

As stated in the scope, the applications were limited to class I and class IIa custom-made medical devices, so only the highlighted section in the table was the most important to take into consideration for external communicating device category. The recommended endpoints for consideration include cytotoxicity, Sensitization, Irritation or Intracutaneous Reactivity, Material-Mediated Pyrogenicity for a limited contact duration (usually less than one hour for surgical guides).

Table 5: Current approach of ISO 10993:2018 for Biocompatibility Evaluation Endpoints

Medical device categorization by Nature of body contact			Biological Effect													
Category	**Contact**	**Contact Duration**	**Physical and/or chemical information**	**Cytotoxicity**	**Sensitization**	**Irritation or Intracutaneous Reactivity**	**Material-Mediated Pyrogenicity**	**Acute Systemic Toxicity**	**Subacute Toxicity**	**Subchronic Toxicity**	**Chronic Toxicity**	**Implantation**	**Hemocompatibility**	**Genotoxicity**	**Carcinogenicity**
Surface device	Intact skin	A	X	E	E	E									
		B	X	E	E	E									
		C	X	E	E	E									
	Mucosal membrane	A	X	E	E	E									
		B	X	E	E	E		E	E			E			
		C	X	E	E	E		E	E	E	E	E		E	
	Breached or compromised surface	A	X	E	E	E	E	E							
		B	X	E	E	E	E	E	E			E			
		C	X	E	E	E	E	E	E	E	E	E		E	E
External communicating device	Blood path, indirect	A	X	E	E	E	E	E					E		
		B	X	E	E	E	E	E	E				E		
		C	X	E	E	E	E	E	E	E	E	E	E	E	E
	Tissue^{+}/bone / dentin	A	X	E	E	E	E	E							
		B	X	E	E	E	E	E	E			E		E	
		C	X	E	E	E	E	E	E	E	E	E		E	E
	Circulating blood	A	X	E	E	E	E	E					E	E	
		B	X	E	E	E	E	E	E			E	E	E	
		C	X	E	E	E	E	E	E	E	E	E	E	E	E
Implant device	Tissue+/bone	A	X	E	E	E	E	E							
		B	X	E	E	E	E	E	E			E		E	
		C	X	E	E	E	E	E	E	E	E	E		E	E
	Blood	A	X	E	E	E	E	E				E	E	E	
		B	X	E	E	E	E	E	E			E	E	E	
		C	X	E	E	E	E	E	E	E	E	E	E	E	E

Physical and/or chemical information is prerequisite for a risk assessment. As mentioned previously in the logistic procedure within the adapted QMS, this information is used as a reference to compare the specification sheets for any new received materials in the lab and ensure they are compliant.

3.2.2. Comparison: Risk/Benefit Analysis

Since surgical guides have the higher medical device classification, the focus for printer selection was on these class IIa devices. The final shortlisted technologies were FormLabs Fuse Selective Laser Sintering (SLS) and FormLabs 3B Stereolithography/ Digital Light Processing (SLA/DLP). These technologies are recognized for their high accuracy, biocompatibility, and sterilization tolerance. To make the final decision and select one technology, a comparison based on the risk is made. After in-depth discussion between team members, table 6 summarizes the risks associated with the manufacturing, cleaning, subcontracting, and storage processes for FormLabs Fuse (SLS) and FormLabs 3B (SLA/DLP). The risks are evaluated based on three factors: severity (Sev.), evaluated upon the final impact on patient, probability (Prob.), and detectability (Det.), which together determine the overall priority score for each risk. Appendix B shows the risk evaluation criteria.

Table 6: Comparison Grid between FormLabs SLS and SLA

Category	Risk description	FormLabs Fuse (SLS)				FormLabs 3B (SLA/DLP)			
		Sev.	Prob.	Det.	Priority	Sev.	Prob.	Det.	Priority
Manufacturing	Poor mechanical or geometrical quality of the parts	5	3	1	15	5	3	1	15
Cleaning/post-treatment	Loss of a part in the unpacking	3	3	1	9	3	1	1	3
	Material contamination	3	1	10	30	3	1	10	30
	Break parts/ crack parts	5	5	1	25	1	1	10	10
	Material residues	5	3	1	15	5	3	1	15
	Cleaning agent residues	1	1	10	10	1	3	10	30
	Unclean printer	1	5	1	5	1	1	1	1
Raw Material Receiving	Alteration of the cleanliness of the MD at the opening	3	1	3	9	3	1	5	15
	Alteration of the quality of the material	3	1	1	3	3	3	1	9
Total Priority Risk		121				128			

The difference in total risk is very minor. However, the actual benefits for a project like POC3DP are key consideration as well. SLS printer involves higher initial costs, more intricate operation and maintenance, and greater operational expenses. On the other hand, SLA/DLP printers offer a more user-friendly and cost-effective material.

SLS printers have thicker layers than SLA/DLP printers, which can affect the surface finish. Additionally, SLA/DLP printers are generally more accurate and have higher resolution than SLS printers, making them more suitable for detailed models for medical applications. While SLS printers boast larger build volumes than SLA/DLP printers, a POC3DP lab typically deals with smaller volumes, making this advantage less relevant.

Finally, considering affordability, user-friendliness, and handling moderately complex geometries for medical purposes, FormLabs 3B SLA/DLP printers are generally more preferred compared to SLS technology. This makes them a better fit for smaller hospital labs with potentially limited budgets and technical expertise. So that SLA risks are furtherly mitigated through control measures as explained in the following section.

3.2.3. Risk Analysis and Control Measures

ISO 10933 serves as a critical standard that covers the framework of how to asses the biocompatibility, what can go wrong with the medical device and how to mitigate the risk. If a change happens, e.g., in the supply chain, it explains how one can evaluate that the medical device continuous to have a good biocompatibility profile for its intended use. The goal of manufacturing medical devices is to enhance patient quality of life, but good intentions must be translated into the best possible outcomes.

A risk analysis for the selected technology is developed, particularly for the manufacturing of surgical guides where the possibility of deformation is a major concern. Table 7 provides a comprehensive risk analysis and control measures for FormLabs SLA/DLP technology during. It identifies potential failure modes, their effects, and causes, categorizing them under the batch production phases.

The table includes design controls to mitigate these risks, ensuring the reliability and quality of the printing process. The identified risks range from handling issues to external factors. Each risk is accompanied by specific control measures, such as built-in monitoring systems and maintenance procedures, to address and mitigate potential failures.

Table 7: Risk Analysis and Control Measures for FormLabs SLA/DLP Technology

Category	Risk ID	Potential Failure Mode (s)	Potential Effect(s) of Failure	Sev.	Potential Cause (s)	Prob.	Design Controls	Det.	Priority	Acceptance
Printing batch	1	Not enough resin	Print failed, print geometry not reached	5	The printing process is interrupted	1	Built-in cartridge monitoring	1	5	5
	2	Expired resin cartridge	Print failed, physical and chemical properties not met	8	-Resin cartridge is outdated or incorrectly stored. -Resin polymerisation process is altered	1	Track expiration date and storage conditions provided by the supplier + built-in expiration-date monitoring	1	8	8
	3	Expired resin in tank	Print failed, physical and chemical properties not met	8	Resin tank is outdated or incorrectly stored. -Resin polymerisation process is altered	1	Instructions sheet according to manufacturer's storage condition e.g. temperature & humidity + built-in expiration-date monitoring	1	8	8
	4	Incompatibility between resin in cartridge vs tank	Print failed, physical and chemical properties not met	8	Resins of cartridge and tank differ (type, age, storage) -Resin polymerisation process is altered	1	Unique identification labels or tags to both the resin tank and cartridges to ensure consistency in expiry date & storage conditions	1	8	8
	5	Worn build platform	Print failed, physical and chemical properties not met	3	Aging of the build platform, bad cleaning of the platform -Adherence of the print is not reached	3	Maintenance procedure for the build platform and regular inspection for of wear, scratches, dents, uneven surfaces	1	9	9
	6	Printing polymerisation process altered	Print failed, physical properties not met	8	Intense UV light in the room, UV shield not closed, dirty optical system, printer not stable, room temp. not stable	3	Implement environmental control in the printing area with -printer is placed on stable surface without disrupt - built-in UV shield state monitoring	1	24	24
	7	Power outage	Print failed, print geometry not reached	3	The printing process is interrupted by design	1	Incident report + Verification of the batch by the QA	1	3	3
	8	Supports and minima loosening	Print failed, resin tank corrupted	3	Poor or inadequate printing design -polymerised resin fall in the resin tank	1	Verification via 3d-printing checklist for PSI or BM before printing	1	3	3
Print removal	9	Build plate print adherence is high	Printed part is broken or damaged	3	Worn building platform, inadequate support base design -Manipulations require forceful handling potentially unprecise	1	Maintenance procedure for the build platform -Cleaning the build plate with >=98% IPA before each print	1	3	3
	10	Not adequate tools (or damaged)	Printed part is broken or damaged	3	Tools rip from the support base into the print body	1	Operator training on using tools to remove prints	1	3	3
	11	Not adequate tools (or damaged)	Printed building plate is damaged	1	Tools scratch the building platform	3	Maintenance procedure for the build platform and regular inspection for of wear, scratches, dents, uneven surfaces	1	3	3
	12	Unsecure print removal workspace	Printed part is broken, damaged or biocompatibility properties are compromised	5	Printed part is ejected out of the print removal zone	1	Quilted/confined workspace	1	5	5

Category	Risk ID	Potential Failure Mode (s)	Potential Effect(s) of Failure	Sev.	Potential Cause (s)	Prob.	Design Controls	Det.	Priority	Acceptance
Washing print	13	Worker hands injured	Worker hands are injured	1	Tools rip into the hands of the worker -Manipulations require forceful handling potentially unprecise	1	Operator wear cut-resistant gloves	1	1	1
Washing print	14	Batch piece fall	Printed part is broken, damaged or biocompatibility properties are compromised	5	Fall on the ground when manipulated	1	Verification of the global functionality of the MD before sending (functional release procedure)	1	5	5
Washing print	15	Uncured resin residues	Biocompatibility not reached	5	IPA source not clean enough, very long hollow sections or high concavity, support density too high, or even bad device presets	3	Incident report + Verification of the design via 3d-printing checklist for PSI or BM before printing	1	15	15
Washing print	16	Isopropanol (IPA) residues	Biocompatibility not reached	8	Too fast usage of the piece or concave geometry does not allow all the IPA to evaporate properly	1	Compressed air drying to ensure IPA evaporation	3	24	8
Support removal	17	Batch piece fall	Printed part is broken, damaged or biocompatibility properties are compromised	5	Fall on the ground when manipulated	1	Verification of the global functionality of the MD before sending (functional release procedure)	1	5	5
Support removal	18	Supports adherence to print is high	Printed part is broken or damaged	3	Support removal breaks a delicate section of the print	1	Verification of the design via 3d-printing checklist for PSI or BM before printing - support removal is made aside a .stl visualisation	1	3	3
Support removal	19	Human error	Printed part is broken or damaged	5	Worker is confused between the print and its support - he removes a part of the print	1	Operator training form	1	5	5
Support removal	20	Human error	Print geometry not reached	5	Worker is confused between the print and its support - some supports residues remain	1	Operator training form	1	5	5
Curing print	21	Uncured resin residues	Biocompatibility not reached	8	Curing protocol cannot prevent any washing failure	1	UV light treatment and multiple exposure angles regarding the part design	1	8	8
Curing print	22	Batch piece fall	Printed part is broken, damaged or biocompatibility properties are compromised	5	Fall on the ground when manipulated	1	Verification of the global functionality of the MD before sending (functional release procedure)	1	5	5
Curing print	23	Bad device parametrization	Cure failed, physical/biocomp properties not met	8	Wrong parameters setting of the curing device	1	Verify the input parameters checklist before initiating the curing process	1	8	8

To further mitigate the risks probability of occurrence to the value of 1 identified as ID 6, 15, and 16, the following controls are developed within the QMS:

- Risk ID 6: A checklist form for 3d-printing is developed. This form details all necessary controls mentioned in this category and has to be completed by the operator each printed batch.
- Risk ID 15: Verification of each batch by initially trained lab supervisor is required before release.
- For risk ID 16: Drying time specifications shall be added as a reference for each design application to ensure all IPA (isopropyl alcohol) evaporates completely.

Conclusion

As healthcare facilities expand their capabilities in patient-specific models, adopting and adapting quality assurance methods becomes imperative. The output of this internship establishes the groundwork for a robust and hospital-specific quality management system (QMS) customized to POC3DP project. The ISO 13485-compliant structured QMS prioritizes simplicity, a culture of quality, and adaptability to improve patient safety and operational effectiveness in the manufacturing of medical devices and minimizes the burden on hospital staff. Moving forward, hospitals shall provide feedback to further adjust the system to their specific needs, ensuring successful POC3D implementation within diverse settings in the futre.

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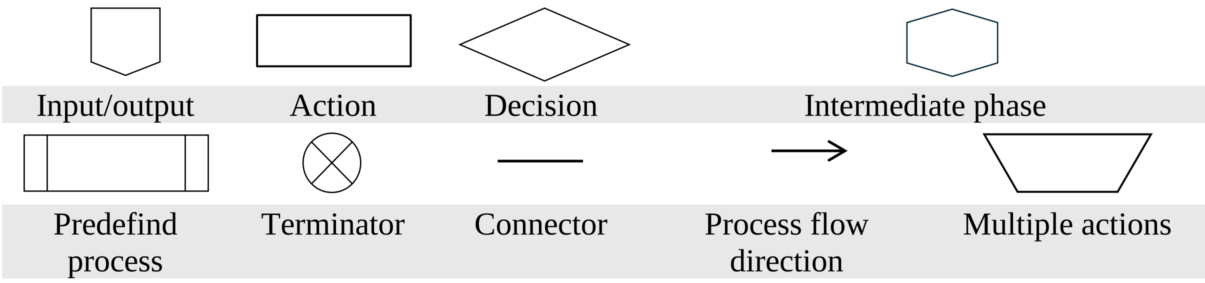
Appendices

A. Rules of the European Regulation MDR 2017-745

Type	Rule	Class	Comment
Non-invasive	1	Class I	Either don't touch the patient or contact only intact skin
	2	Class I	intended for channelling or storing blood, body liquids, cells or tissues, liquids or gases for The pupose of eventual infusion, administration or introduction into the body
		Class IIa	connected to a class IIa, class IIb or class III active device
		Class IIa	For use with blood, other body fluids, organs , tissues, cells
	3	Class IIa	Only filtration, centrifugation or exchange of gas or heat
	4	Class IIa	in contact with injured skin or mucous membrane (Also for invasive devices into contact with injured mucous membrane)
		Class I	As mechanical barrier, compression or absorbation exudates
		Class IIa	Intended to manage micro-environment of injured skin or mucous membrane
Invasive devices	5	Class I	Transient use
		Class IIa	Short term use
		Class I	If only oral cavity, in ear canal or in nasal cavity
		Class IIa	If ony in oral cavity, in ear canal or in nasal cavity and not liable to be absorbed by the mucous membrane
		Class IIa	Connected to an active medical device in class IIa or higher
	6	Class IIa	surgically invasivetransient use
		Class I	Reusable surgical instrument
	7	Class IIa	Surgically invasive- Short term use
	8	Class IIa	Intended to be placed in teeth
Active devices	9	Class IIa	Active therapeutic devices intended to administer or exchange energy
	10	Class IIa	Active devices for diagnosis and monitoring or suppling energy to be absorbed by the body or to image in vivo distribution of radiopharmaceuticals or allowing direct diagnosis or monitoring of vital physiological processes
		Class I	except for devices intended to illuminate the patient's body, in the visible spectrum
	11	Class I	Software
		Class IIa	intended to provide information used to take decisions with diagnosis or therapeutic purposes,
		Class IIa	monitor physiological processes
	12	Class IIa	Active devices to administer and/or remove medicines & other substances from the body
	13	Class I	All other active devices
Special Rules	16	Class IIa	devices intended specifically to be used for disinfecting or sterilising medical devices
	17	Class IIa	Devices intended for recording of X-Ray diagnostic images
	19	Class IIa	devices incorperating or consisting Nanomaterials: negligible potential for internal exposure
	20	Class IIa	devices invasive in respect to body orifices (not surgical) to administer medicinal products by inhalation
	21	Class IIa	If they applied to the skin or in the nasal or oral cavity as far as the pharynx and achieve their intended purpose on those cavities;

B. Guide to Flowchart Symbols



C. Evaluation Criteria for Risk Analysis

Effect	SEVERITY of Effect	Ranking
Catastrophic	Safety-related catastrophic failures; irreversible harm of patient, maybe mortally	**10**
High	Reversible harm of patient (therapy necessary)	**8**
Moderate	Reversible harm of patient (therapy not necessary)	**5**
Low	Hidden ineffectiveness (partial loss of function), without detraction of health status	**3**
Neglegible	Product operable at similar but slightly lower performances, without detraction of health status	**1**

Probability	Failure PROBABILITY	Ranking
Very High	Failure is almost inevitable; Harm occurs very frequent (≥ 10 %)	**10**
High	Repeated failures; Harm occurs frequent (< 10 %)	**8**
Moderate	Occasional failures; Harm occurs sometimes (< 0,1 %)	**5**
Low	Relatively few failures; Harm occurs seldom (< 0,01 %)	**3**
Remote	Failure is unlikely; Harm occurs improbably (< 0,001 %)	**1**

Detection	Likelihood that the problem will be DETECTED before it reaches the end-user	Ranking
Absolute Uncertainty	Design control **cannot** detect potential cause/mechanism and subsequent failure mode	**10**
Remote	**Remote** chance the design control will detect potential cause/mechanism and subsequent failure mode	**8**
Moderate	**Moderate** chance the design control will detect potential cause/mechanism and subsequent failure mode	**5**
High	**High** chance the design control will detect potential cause/mechanism and subsequent failure mode	**3**

Almost Certain	Design control **will** detect potential cause/mechanism and subsequent failure mode	**1**

Acceptability	Severity * Probability	Ranking
Intolerable	Corrective/Preventive action MUST be carried out	**>30**
Moderate	Tolerable only if its reduction is not realistic in view of the medical benefit	**10-30**
Acceptable	No corrective/Preventive action required.	**<10**

		Severity				
		1	3	5	8	10
Probability	10	10	30	50	80	100
	8	8	24	40	64	80
	5	5	15	25	40	50
	3	3	9	15	24	30
	1	1	3	5	8	10

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