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Facilitating industry translation of custom 3d printed bone prostheses and scaffolds through Quality by Design

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Abstract

The new generation of patient-specific 3D printed bone implants require the integration of diverse emergent technologies that control material and product characteristics to imitate patients' bone geometrical features. Despite the significant market opportunities, the emerging nature of the 3D printing manufacturing industry as well as the complexity and variability in product characteristics is posing a serious challenge to regulatory bodies tasked with managing and assuring product quality and safety. Therefore, this study explores quality control technologies and activities throw a case of study of a European firm to disseminate industry best practices. The outcomes of this study are: a comprehensive quality control workflow process map; lessons learned in industry to guide medical regulatory bodies to standardize these products, and researchers and industry for the development of new medical technologies for industry translation in this domain.

Keywords: Quality by Desing; Quality Control; 3D Printing; Bone Implants.

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1. Introduction

3D printing is rapidly growing in popularity in the biomedical field for the development and design of customized bone prostheses and scaffolds [1-4]. The great advantage of this technology is that is capable of fabricating complex shapes and manipulating material properties that are impossible with traditional manufacturing methods. However, in order to produce customized bone implants that can resemble the 3D geometrical features of the patients' region of interest it is necessary to obtain a three dimensional representation using Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) [5, 6]. With the use of 3D medical imaging, also virtual surgeries can be planned in collaboration between the surgeon, the orthopaedic engineering professional and the biomedical design engineer to study and manipulate in a virtual environment patient's bone defect to find the optimal solution to restore it to its normal condition. Virtual surgery planning allows the identification of the limitations, constraints, and risk of the surgery [7]. The virtual planning improves technical performance, gives confidence, and pays dividends on the day of the actual procedure [7]

As a result of the integration of these technologies a high degree of complexity and variability in product characteristics are introduced into these products, posing a serious challenge to regulatory bodies tasked with managing and assuring product quality and safety. Moreover, the traditional quality frameworks that have ensured the fabrication of reliable medical devices in the past, are limited to standardized manufacturing methods, which base their quality control activities on lot sampling and statistical quality control techniques. However, these approaches are limited for customized products based on 3D printing manufacturing where the manufacturing environment is reduced to a fraction of traditional manufacturing activities. As result, low production lots and high design requirements lead to the creation of more inspection activities that increase the system lead time, where more maintenance of resources results in quality improvement, but affecting the overall production by decreasing machines' operational time [8].

To date the quality assurance of 3D printed bone implants has been carried out in the medical device industry without specific standards for this technology [9]. Taking all this into consideration, the purpose of this study is to disseminate industry best quality control practices for custom 3D printed bone implants.

2. Methodology

This section provides a brief summary of the results obtained in our previous work which is a key component for this present study, for more details refer to [10]. Moreover, a description of the industrial company used as a case study is provided. To the authors knowledge there is no empirical research on how companies in the sector of 3D printed bone implants deal with product quality. Therefore, an qualitative exploratory investigation based on the results of our previous work [10] was performed following the consolidated criteria for reporting qualitative research (COREQ) [11] with a constructive research approach aimed to produce innovative solutions to practical problems in a heuristic manner [12].

2.1. Adaptation of the QbD system

The QbD system was created by the US Food and Drug Administration (FDA) in 2004, which aims to carefully design products, services and processes considering all aspects of their life cycle [13]**.** The result is a flexible regulatory framework designed to improve pharmaceutical manufacturing processes and enhance product quality [13]. QbD focuses on acquiring process control through a deep understanding of products and processes using science, engineering and quality risk management [14]. Moreover, QbD accelerates research timelines and reduces development costs, by avoiding trial-and-error studies, and focusing on testing methods towards product development [15-17].

In our previous work an adaptation of the first five steps of the Quality by Design (QbD) system for 3D printed bone prostheses and scaffolds, was developed. The aimed of this adaptation, is to help to reduce a regulatory burden that forces many product engineers to purposely design their products to fit within existing approved thresholds in order to avoid seeking further time consuming approvals for minor variations. The results where: A comprehensive workflow map composed of twenty-seven activities; Identification of sixteen critical process parameters (CPP) and

eleven critical material attributes (CMA); A total of 86 risks and 178 effects were identified and categorized using a breakdown structure.

The data collection and validation to adapt the first five steps of the QbD system for 3D printed bone prostheses and scaffolds involved three systematic searches in two scientific databases, an online survey, and face to face interviews with pertinent researchers, industry experts, and medical practitioners from different fields related to medical device development, 3D bone printed implants, motion capture, bone biology, tissue engineering, orthopaedic surgery, bone biomechanics, computational neuromuscular modelling, and nano engineered implants following the consolidated criteria for reporting qualitative research (COREQ) [36].

A total of 231 studies related to 3D printed bone implants and six interviews with industry experts, researchers, and medical practitioners were performed and qualitative analysed to tailor and validate the QbD system for custom 3D printed bone implants.

2.2. Case of study

The main objective of this case of study was to explore the quality control of patient specific implants at the industry level, including the identification of critical processes and technologies used for this purpose. The study was conducted in a Western European company that produces primary, revision and tumor endoprosthesis, and was focused on a specific area: the production of patient specific implants. This study concentrated on a variety of aspects of these products in the company: design, manufacturing processes and methods, raw materials, and quality assurance. The company operates in the fields of product development, manufacturing, sterile packaging as well as sales and distribution of standard and patient specific orthopaedic implants to more than 65 countries worldwide. The headquarters this company is in the same place where this work was developed.

The company's department of additive manufacturing was stablished 5 years ago to produce patient-specific implants. This company produces approximately 10 patient-specific implants per week with a total of 500 implants per year, representing just a fraction of the total production of standard implants. From the total annual production approximately two implants are discharged due to non-fulfillment of quality specifications. However, since the last 5 years there were no registered recalls of their patient-specific implants.

The production and design of patient-specific implants are carried out with specialized employees in additive manufacturing and product design in a separate area from the rest of the company's standard products. However, most of the quality assurance activities and dispatch of merchandise are shared.

Table 1. Summary of company profile

Research method	Experts interviewed	Location	Age	Number of employees	Number of years in the market of 3D printed products	Type of products produced	Total number of products produced per year
Personal visit to the company's headquarters and face to face interviews	• The director of R&D • The head of additive manufacturing • Product development staff	Western Europe	30 years	600	5 years	Primary, revision and tumor endoprosthesis	820,000

3. Results

During the visit to this company the company's products, technologies, and quality control activities were presented by the director of R&D, the head of additive manufacturing, and product development staff, including a

guide through the company's headquarters. According to the company staff comments there is a lack of regulatory requirements for 3D printed medical devices. Therefore, 3D printed medical devices follow the same regulatory requirements and submission expectations as traditional manufactured medical devices. Moreover, the engineering staff feel that there is a need to bridge the current knowledge of industry in 3D printing with medical device authorities.

Following the company staff presentations a presentation of the previous research results was provided to staff [10]. According to their engineering and product development staff the QbD system is aligned with the company's objectives and they believe that the adaptation of the QbD approach for custom 3D printed bone implants can provide clearer direction for the product development process. This would aid them to obtain an in-depth understanding of the numerous factors involved in this process, including a better definition of product boundaries, targets, and potential modifications.

3.1. Quality control

In regards to the quality control of 3D printed products, the company established rigorous quality management systems in accordance with ISO 13485 and Council Directive 93/42/EEC that was applied through the whole process chain, which empowers their staff to actively monitor the quality of each process and activity, in a similar way to Total Quality Management (TQM). The overall quality control methods comprise of a mixture of real-time monitoring, Go/No-go control tests, checklists, and control charts performed internally at the company headquarters. With these quality control methods, this company established six main quality control checkpoints for the most critical areas of the product design and manufacturing supply chain (see Fig 2).

The first quality control activity implemented by this company is used to validate the segmentation and the design processes by checking the geometry and dimensions of the final 3D volumetric model and CAD model directly from the patient's CT images. For this task they use a dedicated software which allowed for the repair and edit of STL files. The second quality control step is performed to control the quality of the raw material for 3D printing. The material used in this company is Ti-6Al-4V powder, which requires a specific chemical composition in order to maintain the mechanical integrity of the 3D printed part. Therefore, the company developed a sealed room for material storage with specific atmospheric conditions to avoid the absorbance of oxygen into the titanium powder. Furthermore, to reduce production costs they use a material recovery system for powder recycling. The recycled powder then is sieved and mixed with new material followed by a chemical test, particle size distribution test, and flowability test to ensure that the particle size, powder flowability, and powder oxygen content are within the required limits.

The 3D printing fabrication process used by this company is an electron beam melting (EBM) system that allows the production of fully dense parts with low residual stresses with predictable mechanical properties similar to casting. As a result, posterior heat treatments and ultrasonic impact treatments are eliminated from the production process, which are required in most laser based 3D printed systems [10]. Moreover, this EBM system includes a real time monitoring validation process, which acts as their third quality control process. The validation process is composed of a high-resolution infrared camera and an X-ray system. The camera provides a frequent high precision calibration for a robust and predictable machine operation to track porosity layer-by-layer and also to report defects in the entire build and in individual components, and the X-ray detection system is used as a material characterization tool.

There are also a variety of important machine settings that have to be taken into account to fabricate consistent parts and batches, such as part orientation and nesting, layer thickness, hatch spacing, bed temperature, beam diameter and temperature, scan speed, bed temperature, and cooling cycle. To identify the best settings for the EBM system and validate the fabrication process this company performed a series of tests to: stablish the link between material properties of test coupons and final device; identify worst case scenarios concerning machine conditions, part placement, and geometry; find the limits of the process.

It is well known that products fabricated in powder based 3D printing systems require the removal of supports structures which is a delicate and time consuming task [18]. Nevertheless, thanks to the EBM system used by this company this task is easily performed due to the fact that parts produced by this system require a smaller number of support structures and their removal is much easier compared to laser-based 3D printing systems.

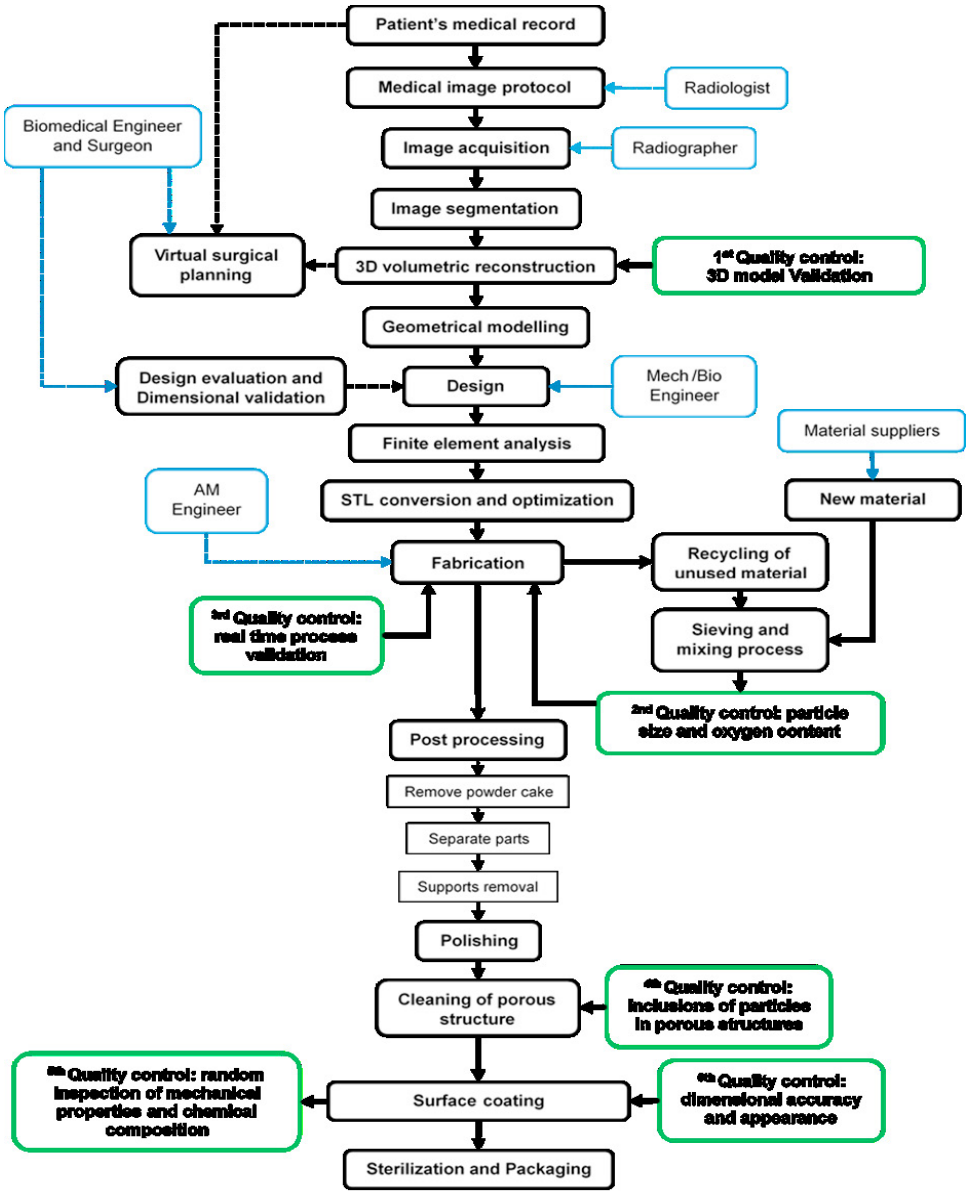

Figure 1. Case of study workflow chart with main quality control activities

Moreover, lattice and trabecular porous structures in bone implants used to improve bone fixation, are frequently affected by imperceptible inclusions of particles inside their pores compromising their biological safety [19]. The removal of particles from the porous structure of bone implants is a current a challenge for most companies in this market. To be ahead of their competitors, this company solved this challenge with their own in-house developed system to extract powder particles up to 60% over the regulatory allowance, acting as their 4th quality control process.

The fifth quality control process is randomly performed in 1% of the total production and compromises several critical activities necessary to meet all relevant testing standards such as mechanical testing (static and dynamic strength, and hardness), porosity measurement, microstructural investigation (grain size, orientation, and phase), and

chemical analysis. The sixth quality control process is aimed to check the dimensional accuracy and appearance of each 3D printed product at the end of the company's production chain. As the last quality control process, this company invests a great number of hours to ensure that the final product fulfils all the necessary requirements before being sterilized and packed. For this purpose, a detailed visual inspection, manual measurements, and an ultra-high precision 3D coordinate measuring system are used to detect defects and micron-sized deviations of implants' geometrical features.

Table 2. Summary of results

Quality control activities	Production per year	3D printing Technology used	Tools and techniques used for quality control
6 quality control processes are performed after and during the main activities of the design and fabrication processes.	A total of 500 custom implants are 3D printed each year.	EBM system Advantages: • Easy nesting of parts • Produces pars with high surface roughness that provides better biological performance • Fully dense parts are produced • Low residual stresses • Easy removal of support structures • Less prost processing • Faster production rates Disadvantages: • Higher downtimes (maintenance) • Low material choice	Material: • Oxygen content test • Particle size distribution test • Flowability test 3D printer machine: • Validation process • Periodic maintenance 3D printed parts: • Tensile test • High cycle fatigue test • Tactile 3D coordinate measuring system • Visual inspection and manual measurements • X-ray for implant geometry control • Porosity measurements • Chemical composition test • Material microstructure

5. Discussion

It is a common practice to use process capability (PCA) to evaluate the ability of a process to satisfy customer requirements in terms of specification limits. For this purpose the sigma quality level of a process is used to express how well a process performs with respect to specifications [20]. According to the six-sigma principle a process operates with 6σ variation centred between the tolerance limits, only 2-3 parts out of a billion will be unacceptable [20]. Based on this, the process capability of the company studied falls approximately within the range of 2σ variation, which means that 95.45% of the produced parts fall within the tolerance limits.

This is a relative low PCA, however to a obtain a reliable estimate of the process capability large samples are required [20]. Moreover, based on the comments provided in different companies it was found that for the 3D printing industry, up to 50% of the produced products have to be rejected due to quality issues. This suggests that in terms of quality control, this industry is still in its development stages. Additionally, the use of random lot sampling and statistical quality control methods are limited for the 3D printing manufacturing environment which is composed of variable product characteristics, low production lots and high design requirements [8].

To counter these quality control limitations, the studied company adopted a strict quality control process covering the whole production chain and encouraged a staff to proactively manage the quality of their products. Moreover, the adoption of the EBM system to manufacture patient-specific implants was a smart move for this company. This is due to the fact that the EBM system produces fully dense parts with predictable mechanical properties, contrary to what laser based 3D printing systems offer, allowing a reduction of time and costs by completely eliminating posterior heat treatments [21] and ultrasonic impact treatments [22] from the production process.

Nevertheless, the sharing of quality control resources such as staff and technologies between the standard implants and the patient-specific products can be counterproductive in the long term and when the production of customised products is increased. The reason is that this strategy leads to the creation of more inspection activities that increases the system lead time, where more maintenance of resources results in quality improvement, but at the expense of the overall production by decreasing machines' and human resources operational time [8]. Additionally, the use of visual inspections, manual measurements, and tactile 3D coordinate measuring system are not the ideal choice for the metrology of freeform shapes [23]. The reason is that for the metrology of freeform shapes such as the ones present in customized bone implants it is fundamental to measure a large number of points distributed on the surface to be inspected [23]. Optical and scanning probing systems and micro CT scanners are today preferred because they collect much more data in the same or less time, resulting in more correct handling of geometrical imperfections [24, 25]. The main advantages of these systems are to allow a complete automation of the measurements process [23], improve the representation of the real geometrical feature [24], and provide a higher degree of flexibility in measurement settings [26].

5. Conclusion

The work carried out facilitated the identification of the main quality control activities and technologies used for 3D printed products by the studied company. This research method provided a clear picture of the current state of this technology in the medical industry. Moreover, it was possible to capture a detailed understanding on how quality control challenges are overcome by this company.

Overall, there were several key lessons from this case study. Firstly, that traditional process monitoring and control used for mass production are not enough to take the process capability of customized 3D printed bone implants to the six-sigma quality level. This is due to the fact that the 3D printing manufacturing environment is reduced to just a few steps and composed by variable product characteristics, low production lots and high design requirements. Secondly, it is vital to examine the entire product lifecycle of these products, focusing on preventive quality control activities with synergetic efforts across the entire organization, in order to ensure a cost effective product quality strategy. Therefore, quality control activities of such products should take place during and after the most sensible processes and activities. However, this leads to the creation of more inspection activities that increase the system lead-time, where more maintenance of resources results in quality improvement, but reduces the overall production rate. Therefore, the third lesson is that an ideal quality control system for custom 3D printed bone implants, requires a proactive risk identification in combination with adequate quality control technologies to be applied in the product design and fabrication processes. Moreover, all the stakeholders, such as medical doctors, designers and manufacturers, need to have a proactive attitude to identify and control potential risks to product quality, having a clear understanding of the customers, market, process, and the product definition.

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