

# Implementation of risk management activities within a quality management system. An osseous adhesive as case study

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**Abstract**— Medical device regulatory agencies have adopted quality and risk management approaches to demonstrate compliance with the essential principles of safety and performance. For this reason, specific standards are established in the medical device sector for the quality management system by regulatory purposes and a systematic process, in order to minimize risks throughout the life-cycle of the product. The objectives of this paper are to show how the risk management process can be inserted into the product design/development strategy within a quality management system and to apply such strategy to an osseous adhesive as a case study. Integration of a risk management system within a QMS can be an advantage for manufacturers of medical devices in order to comply with regulatory requirements. At the design and development stages the risk management principles should be applied and used to identify and address safety issues and to plan risk control activities. The risk assessment conducted shows that the Wollastonite / n-butyl-2-cyanoacrylate adhesive composite is safe by design. Adequate labeling and operating instructions have to be incorporated to the final product to minimize the risks or improper usage and storage outside prescribed environmental conditions. In addition, validation and control measures of the sterilization process and packaging have to be taken to maintain the acceptable levels for all identified risks.

**Keywords**— risk management, quality management, osseous adhesive, Wollastonite, butylcyanoacrylate.

## I. INTRODUCTION

The development of medical devices involves several activities for maximizing the benefit and minimizing risks in its intended use. Designers, manufacturers and testing services have to provide the required evidence of the safety and efficacy of the developed products. Quality and risk management approaches through the whole life cycle of the medical products have to be integrated to demonstrate compliance with the *Essential Principles of Safety and Performance of Medical Devices* [1]. In this context, a safe product is the one that has acceptable risks, in comparison with the benefit expected and the alternatives available [2]. For these reasons in the medical device industry there are

specific standards, harmonized guides and regulations that establish a systematic process to minimize risks throughout the life-cycle of the product. Medical device regulations required that manufacturer implements a quality management system (QMS) and also a system for managing device related risks. The integration of the QMS and the risk management system may be advantageous because of reducing costs, the elimination of redundancies, and more effective management [3].

These international trends are incorporated in the medical devices regulations in Cuba [4] and Brazil [5], and despite the fact that these countries have different quality system regulations for medical products [6, 7] both explicitly include the requirement for risk management by the manufacturers. The objectives of this paper are to show how the risk management process can be inserted into the product design/development strategy within a QMS strategy and to analyze a case study of an osseous adhesive product.

## II. MATERIALS AND METHODS

### A. Medical device risk management

Risk is the combination of the probability of occurrence of harm and the severity of that harm, meanwhile risk management is a systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk [8]. Risk management should be applied throughout the life cycle of medical devices and the international standard ISO 14971 *specifies a procedure by which a manufacturer can identify the hazards associated with medical devices and their accessories, including in vitro diagnostic medical devices, estimate and evaluate the risks, control these risks, and monitor the effectiveness of the control*.

The risk management process includes the following steps: risk analysis, risk assessment, risk control, production and postproduction information (Fig. 1). The requirements of the ISO 14971 standard can be certainly incorporated into an ISO 13485 QMS as shown in Table 1.

Table 1 Compatibility between high level requirement clauses of ISO 13485 and ISO 14071

ISO 13485:2003	ISO 14971:2007
4 Quality management system	3 General requirements for risk management 3.1 National or regional regulatory requirements 3.2 Risk management process 3.6 Risk management file 8 Risk management report
5 Management	3.3 Management responsibilities
6 Resource management	3.4 Qualification of personnel
7 Product realization	3.5 Risk management plan 4 Risk analysis 5 Risk evaluation 6 Risk control 7 Overall residual risk evaluation
8. Measurement, analysis and improvement	9 Post-production Information

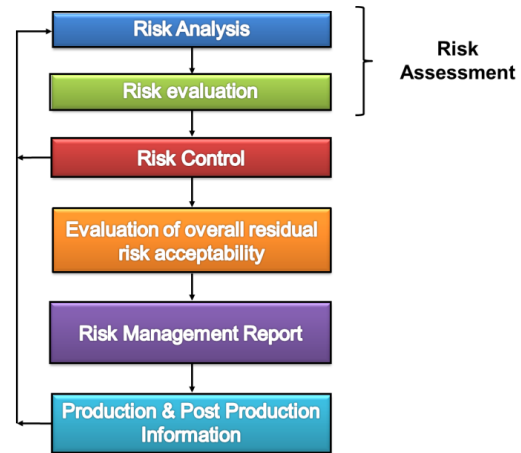


Fig. 1 Risk management process

The scope of the risk management plan developed in this study comprises the design and development stage of an experimental osseous adhesive. An overview of the relationships between risk management activities and design and development activities are shown in Figure 2. The risk management team was constituted by two professors in dentistry with expertise in maxillofacial surgery and dental materials, and two researchers in the field of biomaterials with knowledge and experience of the product, medical device regulations and risk management techniques.

Moreover the acceptability of risks is based on the estimation of their probability and consequence levels, codified to obtain a “scoring system”, giving a risk priority “number” ( $RPN = Probability \times Severity$ ) as shown in Table 2. The estimation is performed under normal and fault conditions. After the team work to identify the hazards and the potential harm that they provoke, each expert done estimation and the final level was the mode of the overall values. For all fault conditions the experts were asked to value the probability at least in the level 2.

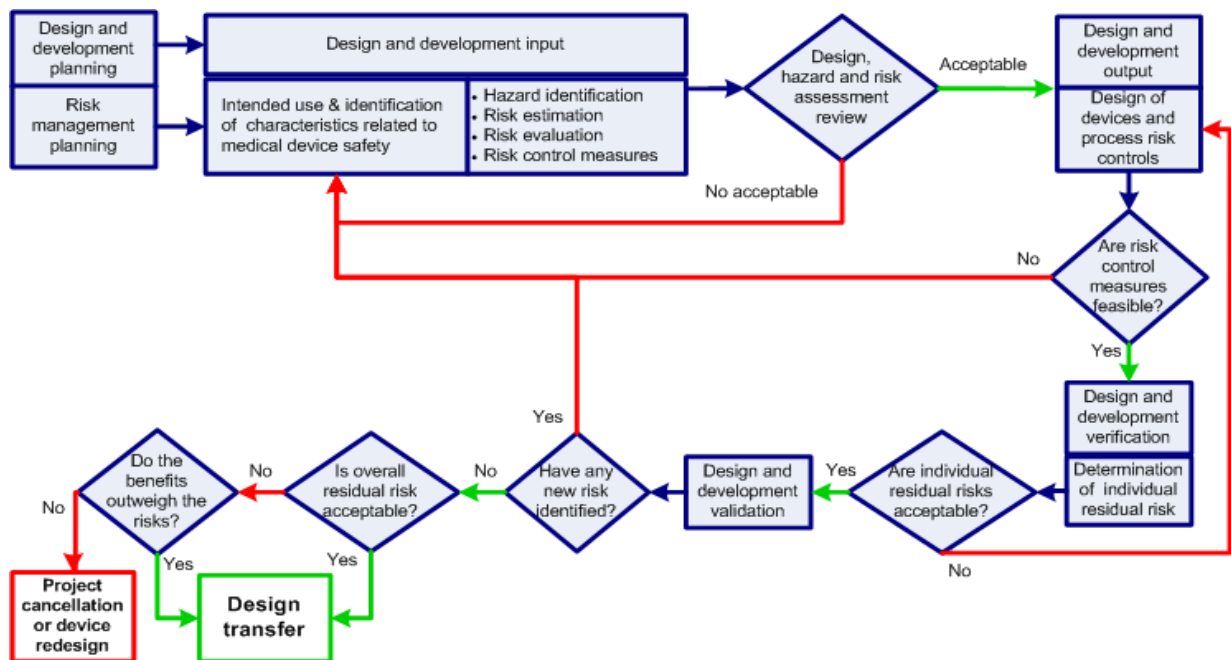


Fig. 2 Risk management activities in design and development.  
Modified from GHTF/SG1/N41, 2005 [1]

### B. The studied osseous adhesive

A composite adhesive made of natural Wollastonite and n-butyl-2-cyanoacrylate (W-BCA) was chosen as case study. The adhesive is intended to be purchased as two-component system. Component I is natural Wollastonite powder with average particle size of 13.2  $\mu\text{m}$  and 1.06 SiO<sub>2</sub>/CaO molar ratio. Component II is n-butyl-2-cyanoacrylate monomer, purity  $\geq 97\%$ . The adhesive is prepared in situ by mixing the two components in 60/40 solid/liquid (Wt/Wt) proportions. The polymerization occurs in less than 30 min.

Table 2 Risk estimation based on the risk priority number

Levels	Codification
Probability levels	1: Improbable
	2: Probable
	3: Frequent
Severity levels	1: Trivial
	2: Moderate
	3: Significant
Risk estimation	1-2: Acceptable
	3-4: Undesirable
	6-9: Inacceptable

### III. RESULTS

Design and development inputs include considerations about the intended use of the medical device, safety and regulatory requirements. The present study is focused on the design and development of a biocompatible adhesive to glue small bone fragments in craniofacial surgery. The bond strength value required to ensure bony healing in such application is still unknown. The fact remains that an adhesive used for bone bonding must possess several properties. It must hold the bone fragments together with adequate bond strength for the time required for the natural tissue healing and degrade at a rate which is consistent with its replacement. It must be accepted by the body, without toxic reactions and the degradation products must be able to be removed by natural processes. Also, the adhesive must be easy to handle and use by the surgeon [9].

Risk estimation for the W-BCA studied adhesive composite is based on data reported in the literature for similar products, expert opinions and data generated in chemical, physical and biological evaluation [10,11]. The adhesive composite is non-cytotoxic and have tensile bond strength to bone comparable to the medical n-butyl-2-cyanoacrylate adhesive. Also in vivo study shows that the composite is biocompatible when in contact with osseous and subcutaneous tissue. Table 3 gives the overall risk estimation done for the studied osseous adhesive and the residual risks after

application of the control measures to reduce the probability of the occurrence of the hazard.

### IV. DISCUSSION

The risk assessment shows that W-BCA adhesive composite is inherently safe by design. Only one risk remains undesirable (RPN=3), that is the inflammatory reaction. However, the evaluated composite do not promote an exacerbated inflammatory reaction when in contact with bone [11]. It is not completely degraded after nine weeks of implantation in the femur of Wistar rats, delaying the formation of the new bone. It is important to notice that the biomaterial for osseous fixation has to be slowly biodegradable, to guarantee stability during the healing process. These findings should be confirmed in animal trials under loading patterns. For other identified hazards, adequate labeling and use instructions have to be incorporate to the final product to minimize the risks of improper usage and storage outside prescribed environmental conditions. Validation and control measures of the sterilization process and packaging have also to be taken to maintain the acceptable levels for all identified risks. This control measures are incorporated into the design and development outputs.

Besides ethical and regulatory compliance, medical device manufactures can obtain several benefits from an effective risk management process. This can also reduce operating costs and increase profits by identifying and preventing problems before products are marketed and providing a systematic framework for understanding the causes of problems, which allows more rapid and cost-effective solutions.

### V. CONCLUSIONS

Integration of a risk management within a quality management system can be an advantage for manufacturers of medical devices in order to comply with regulatory requirements. At the design and development stage the risk management principles and activities allow to identify and address safety issues and to plan risk control activities. The risk assessment conducted shows that the Wollastonite / n-butyl-2-cyanoacrylate adhesive composite is safe by design. Adequate product and process control measures have to be taken to maintain the acceptable levels for all identified risks.

### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Table 3 Osseous adhesive risk management summary

Hazard	Harm	Probability	Severity	RPN	Risk control measures	Residual risk
<b>Biological hazards</b>						
Biological Contamination (Fault condition)	Infection	2	2	4	– Validation and control measures of the sterilization process and packaging. – Adequate labeling.	2
Bio-incompatibility /toxicity (Normal condition)	Inflammatory reaction	3	1	3	– Inherent safety by design (biological evaluation - ISO 10993)	3
Incorrect chemical formulation (Fault condition)	No osseous adhesion	2	2	4	– Process control, quality control of the final product.	2
Cross contamination (Normal condition)	Infection	2	2	4	– Adequate labeling (one use product).	2
Degradation (sub- products) (Normal condition)	Inflammatory reaction	3	1	3	– Inherent safety by design (biological evaluation - ISO 10993).	3
<b>Environmental hazards</b>						
Storage outside prescribed environmental conditions (Normal condition)	No osseous adhesion	3	2	6	– Adequate labeling and use instructions.	2
Accidental mechanical damage (Normal condition)	No osseous adhesion	2	2	4	– Adequate packaging.	2
<b>Hazards related to the use of the product</b>						
Reasonably foreseeable misuse (Normal condition)	No adhesion. Infection	2	2	4	– Adequate labeling and use instructions.	2
Inadequate labeling and operating instructions (Fault condition)	No adhesion. Infection	2	2	4	– Control of the labeling and packaging process.	2
Use by untrained personnel. (Normal condition)	No osseous adhesion.	2	2	4	– Adequate labeling and use instructions	2
Insufficient warning of hazards likely the re-use. (Normal cond.)	Infection	2	2	4	– Adequate labeling and use instructions	2
Incompatibility with consumables or other medical devices (Normal cond.)	Adhesion to instruments	2	1	2	– Adequate labeling and use instructions	1
<b>Hazards arising from failure and aging</b>						
Inadequate determination of the validity period (Fault condition)	No osseous adhesion.	2	2	4	Process control, quality control of the final product.	2
Inadequate packaging (contamination and/or deterioration) (Fault condition)	No adhesion. Infection	2	2	4	– Validation and control measures of the sterilization process and packaging. – Control of the labeling and packaging	2

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