

SAFETY AND PERFORMANCE IN ORTHOPAEDIC IMPLANTS DEVELOPMENT

SEGURANÇA E EFICÁCIA NO DESENVOLVIMENTO DE IMPLANTES ORTOPÉDICOS

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Abstract

The safety and efficacy are fundamental requirements for the manufacture of medical devices, to permit the recovery of health, bringing social benefits and welfare for the population. Thus, the implants should be designed and developed to meet the biomechanical requirements of each application, covering biological, physical, chemical, physicochemical, mechanical and tribological properties, to be ensured by appropriate choice of material and the definitions of processes and controls that allow the finished product meet such requirements.

The guidelines for providing safe and performance for medical devices are well established and the assurance of these aspects can be achieved in part by compliance with the requirements contained in a broad spectrum of technical and regulatory documents. Here, normative documents available for material selection and qualification of orthopedic products are identified and guidelines for the development of projects of implants are presented. Additionally, the technical requirements for stainless steel are presented and the impacts of processing on the properties of the manufactured products, aspects needed for ensuring the safety and performance of the product, are discussed.

Resumo

A segurança e a eficácia são exigências fundamentais na fabricação de dispositivos médicos, para possibilitar a recuperação da saúde, trazendo benefícios sociais e de bem estar para a população. Desta forma, os implantes devem ser projetados e desenvolvidos para atender os requisitos biomecânicos da cada aplicação, contemplando características biológicas, físicas, químicas, físico-químicas, mecânicas e tribológicas, a serem asseguradas pela escolha apropriada de material e pelas definições de processamentos e controles que possibilitem ao produto acabado cumprir tais requisitos. As diretrizes para prover segurança e eficácia aos produtos encontram-se bem estabelecidas e a garantia desses aspectos pode ser alcançada, em parte, pelo cumprimento das exigências contidas num amplo espectro de documentos técnicos e normativos.

Neste trabalho, são identificados os documentos normativos disponíveis para seleção de materiais e para qualificação de produtos ortopédicos e apresentadas orientações para o desenvolvimento de projetos de implantes. Adicionalmente, são apresentadas exigências técnicas para os aços inoxidáveis e discutidos os impactos do processamento sobre as propriedades dos produtos fabricados, aspectos necessários para garantir da segurança e a eficácia do produto.

Introduction

The use of orthopedic implants has enabled a significant improvement of life of patients whose functional abilities have been altered by traumatic processes or disorders of the skeletal system. However, the occurrence of adverse events show that this benefit, in some cases may not be fully provided, identifying the existence of a void in the health and sanitary controls.

Although other agents may be identified as possible causes for these events – such as improper handling of products (pre-hospital and in-hospital), errors in medical procedures and misuse related to post-operative behavior by the patient – the poor quality of products is still cited as a major determining factor. However, there are no assessments and studies to corroborate this assertion, which was established by the ease of identifying the poor quality of products in the few instances studied and the difficulty in characterizing the incidences and intrinsic causes related to the other aspects.

In Brazil, since 1999, the National Agency for Sanitary Surveillance – ANVISA is the government agency responsible for regulating the sale of implants, for providing records of products and sanitary inspection.

Products for osteosynthesis and arthroplasty are the items of greatest frequency of use and expenditures by the *Sistema Único de Saúde – SUS/MS (Brazilian Unified Health System)* in orthopedic surgery. In 2004, the outlay for these surgeries totaled around one hundred million dollars with about 270,000 surgical procedures. The areas of traumatology and arthroplasty concentrated near 75% of total expenditure, representing 85% of surgical procedures. In arthroplasty, hip and knee surgeries were, respectively, 71% and 24% of expenditures and 82% and 13% of procedures, with the revision surgeries accounted for about 7% of the surgical acts and 18% of expenditures¹.

Quality assurance of orthopedic implants must be guaranteed in the product development projects, for which various technical standards can be employed as support for this goal to establish basic characteristics of quality and the main requirements.

Technical standards, although voluntary instruments for quality, establish guidelines and requirements that represent a consensus of the state of the art and, when related to health products, set recognized standards of quality, which do not require the completion of projects of validation processes, biological and clinical research assessments with regard to their scopes. In this context, stand out the laboratory tests used to validate the quality that can be used both during the process of product development for the validation of the project, and along the manufacturing steps, to control the phase production.

Over the past ten years, it was observed within the national companies of orthopedic implants awareness of the importance of these tools for quality assurance and a progressive increase in the search for its uses. However, considering the costs associated with necessary infrastructure, the effective use of these instruments is still incipient. Thus, for over a decade, both the lack of domain about the recognized knowledge and the limited laboratory infrastructure for assessment services of orthopedic implants are gaps that have been treated erratically and in isolation, either by the applicant segment (the health system, to search for grants to institutions of health policies and health), or by the issuer segment (local manufacturers, for structuring of projects to ensure the safety and efficacy of products).

Currently, Brazilian society still lacks consolidated laboratory infrastructure that enables the fulfillment of these goals, since the provision of services, which are observed commitments established with metrological traceability of the quantities involved in the tests and the reliability of the results, is restricted, especially in regard to specific assessments, linked to different product families. In this context, on one hand the development projects of the products manufactured in the

country embed a high risk to their safety and efficacy, on the other hand the health assessments of sold implants often become inconclusive, bringing great harm both financial to health system, and social and welfare for the population.

Considerations of risk management for medical devices²

As a general concept, activities that involve an individual may jeopardize the individual himself or other parties, provided that such activities may cause damage or loss of something they value. Risk management is a complex issue because each party places a different value on the likelihood of damage and injury caused by exposure to a hazard. However, it is accepted that the concept of risk has two components: the likelihood of damage (how often the damage can occur) and the consequences of such damage (how severe it might be). The acceptability of a risk to a stakeholder is influenced by these components and by their perception of the risk. These concepts are particularly important in relation to health products, due to the variety of stakeholders including health practitioners, the organizations that provide health care services, government, industry, patients and the general public.

All stakeholders need to understand that the use of a medical device implies some degree of risk. Some of the factors that affect the risk perception of each party are the social-economic and educational background of the society and the actual and perceived patient health state. The way a risk is perceived also takes into account, for example, whether the exposure to risk seems to be involuntary, avoidable, caused by human source, due to negligence, arising from a poorly understood cause, or directed at a vulnerable group within society.

The decision to adopt a clinical procedure using a medical device requires a balance between the residual risks and the anticipated benefits of the procedure. Such trials should consider the intended use, performance and risks associated with the product, as well as the risks and benefits associated with the clinical procedure or the circumstances of use. One aspect of this analysis requires judgments about the safety of the product, including the acceptability of risks, to determine their adequacy likely to be placed on the market. For this to be achieved, procedures are needed through which can be identified hazards associated with the product, estimated and evaluated the risks associated with such hazards, the risks controlled and monitored the effectiveness of such control - in this lies the process of risk management the use of a product to health.

Identification of hazards associated with the orthopedic products implantation

In working out the risk analysis of the use of a product is essential that they be properly identified potential sources of damage. In the case of orthopedic implants can be identified four potential sources of injury-related causes of adverse events in surgery, that are associated to: safety and efficacy of the product handling activity after shipment by the factory; health professionals involved in the deployment, and circumstances of use by the patient.

Regarding the product, these causes can be related to the project or to the manufacture, especially, respectively, to product specifications, materials and processing, or processing of materials and products, production controls and handling. As for handling after shipment, these causes can be related to the pre-hospital environment, and stages of distribution and marketing; and in the hospital context, to stages of storage and processing of pre-operative, as well as the handling pre-and intra-operatively. As for professional health care, specifically to the physician, these causes may be linked to professional qualifications, relating to the surgical indication, choice of product, capacity building and training for surgery etc., related to the surgical procedure itself, property the instruments employed, surgical events etc., and related to guidance to the patient. Finally, regarding the patient may be linked to the ability of understanding and observation of the guidelines provided, the existence of known and unknown co-morbidities, etc.

Control of hazards associated with the manufacture of orthopedic implants

Orthopedic implants are designed to meet the requirements of the intended uses, incorporating relevant and necessary features (biological, physical, chemical, physicochemical, mechanical, tribological, etc.) to guarantee their safety and efficacy. In the development of each project materials, processes and controls that enable to achieve these goals are established, when materials are submitted to respective manufacturing processes.

In order to minimize potential risks, the controls of production shall be established from a risk analysis, which seek to list and define qualitative and quantitative limits for the characteristics that could affect product safety, compiling a list of known or foreseeable hazards associated with use both in normal conditions and in failure conditions. In addition, procedures for quality assurance should be implemented in the company, to ensure continuous improvement of processes associated with both the development of the project, and the product manufacturing.

Evaluation and qualification of orthopedic implants

Orthopedic implants are products with high intrinsic risk, since are invasive surgical products designed to remain inside the human body for long term³. Thus, projects for development of implants should be subjected to strict control procedures that ensure the safety and performance of products manufactured and released for marketing, so that their use does not compromise the patient's clinical status. In this context, the risks must be identified and acceptable in relation to the benefits and should be reduced to a level compatible with the protection to the health and safety patient.

To ensure that the characteristics and performance of the products do not change in any degree which could jeopardize this clinical state, the manufacturing projects must add several requirements, particularly biological and biomechanical. In the biological context, must be assured appropriate biological responses to tissue interaction of the materials used in its manufacture, so that all tracks of potential risks, short and long term, may be considered. In the biomechanical context, must be considered a formal and quantitative analysis of the relationship between structures and functions of living tissues, from the evaluation of forces acting and/or generated by the human body and its effects on products implanted in the body. Thus, projects should establish appropriate procedures and include processing of materials to ensure that these biological and biomechanical requirements are met by manufactured products. With regard to materials for surgical implants, although none of them shown to be completely free of adverse reactions in the human body, the clinical trials of prolonged use of standard materials, since correctly processed during the manufacture of products, show that an acceptable level of response can be expected when organic material is used in appropriate applications.

Thus, the development project of implants must initially include steps for qualification of materials to be processed, as well as procedures to ensure the appropriate material processing at various stages of manufacture with regard to the characteristics of both the material (biological) as the product (biomechanical) that are capable of evaluation and / or qualification. In the case of orthopedic implants, besides those for raw materials, there are several normalized requirements and recommendations for development, for material processing and for products themselves, providing assessment and/or qualifications in design and/or in the process. In this context, assessment is a procedure for determination of product characteristics – parameters or properties – without the objective of defining performance levels, while qualification is a procedure for verification of characteristics, with the goal of identifying performance levels or frameworks related to legislative or regulatory requirements specified.

The assessment and qualifications procedures include sets of horizontal tests (chemical, metallographic, coating structures and nondestructive inspections of surface and structure) and of vertical tests (dimensional, mechanical – static and dynamic –, tribological, surface finishing and

corrosion resistance). The universe of products in the orthopedic implant segment and the diversity of applications associated with the osteosynthesis and arthroplasty procedures make the characterization involves a set of over a hundred different specific tests established by the various recognized normative collections.

Development of metallic orthopedic implants

Development of orthopedic implants is an industrial activity that begins at the acceptance of a request of product, internal or external, and ends with the final approval of a project, which must determine, verify and validate all stages of production, from choice of suppliers to the verification of technical requirements on the packaged product approved for marketing through all the procedures and requirements of quality system.

In the absence of technical regulations, the projects are not obliged to implement any standard technique, but such mergers are beneficial both qualitative and quantitative for the process and for the company, that meet the health requirements for the manufacture of the products. The first group includes proper use of resources, production discipline, uniformity of work, record of technological knowledge, improvement of staff training, controls on products and processes, personnel and equipment safety and rationalization of the time. In the second group, the consumption and waste reductions, raw materials specification, standardization of components and equipment, reduced variations in product, procedures for calculations and designs, increased productivity and improved quality of products and services are highlighted. Another important aspect is that biological assessments and clinical trials – time-consuming steps and costly in the project development – can be suppressed by the use of appropriate standards that incorporate the recognized technological domain to be considered.

Standardization is an activity that establishes, in relation to existing or potential problems, requirements for the common and repetitive use in order to obtain the optimum degree in a given context. Normative documents or technical standards are voluntary consensus instruments of quality, which reflect the state of the art. The recognition levels are established by the coverage universe, which can be located as business, industry, national, regional or international. The greater the coverage of a document, the lower the levels of requirements established, once the building is set within a larger universe, so with more restricted common acceptance.

Timely development and periodic revision make medical devices standards effective an efficient tools for supporting project development according regulatory systems, since they represent a consensus on requirements that foster innovation while protecting public health.

The so-called "essential principles" are the general requirements for design and production of medical devices which ensures their safety and performance. The concept was developed by the *Global Harmonization Task Force (GHTF)* to encourage convergence in the evolution of regulatory systems, in order to facilitate trade, while preserving the rights of participating members to address protection of public health by regulatory means considered to be the most suitable. To ensure that the essential principles relevant to a product have been met, a manufacturer may use consensus standards addressing them, as such documents provide a greater of details than can be expressed in these requirements and which, in turn, may be useful or even be recognized in the context of a specific regulatory system. The use of voluntary consensus standards as one means of demonstrating compliance with the essential principles of safety and performance is recognized by regulatory authorities in different countries. When a recognized normative consensus is either not fully implemented or not yet available, it is accepted that an equivalent level of compliance with the essential principles can be achieved and demonstrated through other means. In the absence of international consensus standards, it may be appropriate for the regulatory authorities to accept the use of regional or national standards, or industry standards. In Brazil, the essential principles

regulation is established by Resolution of the Board of the ANVISA⁴, based on the fundamental principles laid down in ABNT ISO/TR 14283⁵.

In the general principles of ABNT ISO/TR 14283 is established that implants should be designed and manufactured so that, when used under conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. And, the solutions adopted by the manufacturer for the design and construction of the implants should conform to safety principles, taking into account the generally acknowledged state of the art. Thus, before placing a medical device on the market, a manufacturer has to establish that the applicable essential principles of safety and performance have been met in a satisfactory way.

There are several ways to show compliance with essential principles and a significant number of standards that may be appropriate to include certain features associated with this order. In the selection of standards it is important to consider the type of device and process in question. The ABNT ISO/TR 16142⁶ considers and identifies certain significant standards and guides that can be useful in the assessment of conformity of medical devices with recognized essential principles of safety and performance. In this document, are characterized three types of standards: basic standards, which include fundamental concepts, principles and requirements with regard to general aspects applicable to a wide range of products, processes or services; group standards, which include safety and essential performance aspects applicable to several, or a family of similar products, processes or services, or similar, making reference, as far as possible, the basic standards; and product standards, which include all necessary safety and performance aspects of a specific, or a family of products, processes or services, making reference, as far as possible, to basic standards and group standards.

ABNT NBR ISO 14630⁷ provides a means for targeting the fundamental principles outlined in ABNT ISO/TR 14283, when applied to non-active surgical implants. It provides a method to demonstrate compliance with the relevant essential requirements concerning these medical devices, and is characterized as the technical document of the highest level (level 1). There are also two other levels of standards that deal with non-active surgical implants: level 2 standards, with particular requirements for families of non-active surgical implants, and level 3 standards, with specific requirements for types of non-active surgical implants. Regarding the family of orthopedic implants, ABNT NBR ISO 14602⁸ is the standard of level 2. ABNT NBR ISO 21534⁹ is a standard at level 3, applicable to joint implants, which is complemented by ABNT NBR ISO 21535¹⁰, for hip joint replacement implants, and by ABNT NBR ISO 21536¹¹, for knee joint replacement implants^a. These documents provide guidelines and requirements for product development projects, which must add, though, the recognized relevant assessments and qualifications for each type of product.

Among the stainless steels, there is a wide range of alloys known as a biomedical material for implant, identified on the *International Organization for Standardization – ISO* and *ASTM International* standards. These materials include alloys of steel family UNS S31673 (ABNT NBR ISO 5832-1¹², ASTM F 138¹³, ASTM F 139¹⁴) and alloys of the strengthened by nitrogen steel families UNS S20910 (ASTM F 1314¹⁵), UNS S29108 (ASTM F 2229¹⁶), UNS S29225 (ASTM F 2581¹⁷) e UNS S31675 (ABNT NBR ISO 5832-9¹⁸, ASTM F 1586¹⁹)^b. These special chromium steel, not susceptible to intergranular corrosion, are characterized by low

^a Currently, there is not a level 3 technical document for both fixation implants, as for vertebral column implants.

^b The *Unified Numbering System (UNS)* is an alloy designation system comprising a letter and five digits, which designate the composition ranges for the major constituents of the material, where the prefix S indicates the corrosion-resistant alloys and heat (stainless steel) and the iron-based superalloys. A UNS identification alone does not constitute a full material specification because it establishes no requirements for material properties, heat treatment, form, or quality. UNS is managed jointly by the *ASTM International* and *SAE International*.

or extra-low carbon, exhibit no delta ferrite, chi, or sigma phases, limited levels of non-metallic inclusions, limited grain size, and defined mechanical properties for specific forms. ASTM F 1350²⁰ and ASTM F 2257²¹ establish specific requirements for wire and tube steels UNS S31673 family.

Regarding the processing of these steels, the cast components must meet additional requirements to ensure the chemical, metallurgical and mechanical properties of the material (ASTM F 745²², ABNT NBR 15628-1²³) and the absence of internal defects (ASTM F 629²⁴ and ABNT NBR ISO 9584²⁵). For forged components, in addition to material characteristics (ABNT NBR ISO 15374²⁶, ASTM F 621²⁷ and ABNT NBR 15628-528), the absence of surface defects (ABNT NBR ISO 9583²⁹ and ASTM F 601³⁰) is required. Moreover, requirements for surface finishing of the products (ABNT NBR 12932³¹, ABNT NBR 15252³², ASTM F 86³³) are applicable.

While all steels within the specifications of the basic requirements of these standards are suitable for the manufacture of implants, the quality is intrinsically related to the specific processing conditions that are subjected during the manufacturing process, since the various alloys, defined within ranges of values for the chemical compositions, may require specific and distinct processing conditions. It is therefore important that procedures for each stage of material processing are validated for each specific subfamily of each material technical standard. Against this background, fit casting, forging and machining of steels.

Manufacturing steps with thermo-mechanical processing of the material, as forging, involve diffusive processes of components, which are associated with the formation, migration and dissolution of precipitates. Consequently, the metallurgical characteristics and mechanical properties of the materials are defined by thermal and mechanical processing parameters such as temperatures and soaking times, heating and cooling rates, solubilization or annealing temperatures and transformation rates, speed of operation etc.

Definitions of these operational parameters are determined according to the chemical composition of each alloy and are attached to the metallurgical characteristics of the product, such as phase distribution, grain size, concentration and formation of carbides, which in turn define the intergranular resistance and mechanical properties of the product. As the machinability of materials is a function of chemical composition, the manufacturing processes parameters and their control parameters are directly associated with control of chemical composition of raw material.

A practical example may be set by analyzing the composition of both steels identified in Table below. Although they meet the compositional requirements established on ABNT NBR ISO 5832-1 and ASTM F 138, steels A and B have very different characteristics. Steel A, due to higher levels of P and S, has better machinability and, due to lower levels of C, Mn, Cr, Mo and Ni, has less tendency to form carbides – less prone to intergranular corrosion due to the formation and migration of carbides – and, certainly, with very different solubilization temperatures from those of steel B.

Steel	%											PRN*
	C	Mn	P	S	Si	Cr	Ni	Mo	N	Cu	Fe	
A	0,015	0,9	0,020	0,010	1,0	17,5	14,8	2,6	0,02	0,40	bal.	26,08
B	0,030	1,95	0,005	0,002	0,1	18,9	13,1	2,9	0,10	0,30	bal.	28,47

* Pitting resistance number

Thus, meeting the chemical composition of raw material to standard requirements is a necessary but not sufficient condition to ensure the quality of the manufactured implant, since it is necessary also that the product design to establish the various parameters of processing and control associated with the compositional ranges of the materials to be used in their manufacturing processes.

Project must establish the set of requirements – chemical, metallurgical and mechanical – for material for which control criteria to the various stages of the production process were established

and validated, whose parameters are within known and controlled ranges and ensuring that the product meets the quality requirements in the input data, according to the risks taken to guarantee the quality of the product, set for its safety and performance.

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- ⁶ ABNT ISO/TR 16142:2009, Produtos para a saúde – Orientações para a seleção de normas em suporte aos princípios essenciais de segurança e desempenho de produtos para a saúde
- ⁷ ABNT NBR ISO 14630, Implantes cirúrgicos não-ativos — Requisitos gerais
- ⁸ ABNT NBR ISO 14602, Implantes para cirurgia não-ativos – Implantes para osteossíntese - Requisitos particulares
- ⁹ ABNT NBR ISO 21534, Implantes para cirurgia não ativos – Implantes para substituição de articulações – Requisitos particulares
- ¹⁰ ABNT NBR ISO 21535, Implantes cirúrgicos não ativos – Implantes para substituição de articulação – Requisitos específicos para implantes de substituição da articulação do quadril
- ¹¹ ABNT NBR ISO 21536, Implantes cirúrgicos não ativos – Implantes para substituição de articulação – Requisitos específicos para implantes de substituição da articulação do joelho
- ¹² ABNT NBR ISO 5832-1, Implantes Cirúrgicos – Materiais metálicos – Parte 1: Aço inoxidável conformado
- ¹³ ASTM F138, Standard Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)
- ¹⁴ ASTM F139, Standard Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Sheet and Strip for Surgical Implants (UNS S31673)
- ¹⁵ ASTM F1314, Standard Specification for Wrought Nitrogen Strengthened 22Chromium-13Nickel-5Manganese-2.5Molybdenum Stainless Steel Alloy Bar and Wire for Surgical Implants (UNS S20910)
- ¹⁶ ASTM F2229, Standard Specification for Wrought, Nitrogen Strengthened 23Manganese-21Chromium-1Molybdenum Low-Nickel Stainless Steel Alloy Bar and Wire for Surgical Implants (UNS S29108)
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- ³¹ ABNT NBR 12932, Implante para cirurgia – Materiais metálicos – Tratamento superficial
- ³² ABNT NBR 15252, Produtos para a saúde – Passivação de aços inoxidáveis por eletropolimento
- ³³ ASTM F 86, Standard Practice for Surface Preparation and Marking of Metallic Surgical Implants