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THE ROLE OF BIOMECHANICAL ENGINEERING LABORATORY (LEBM/HU-UFSC) IN THE PRE-CLINICAL EVALUATION OF SURGICAL IMPLANTS TECHNOLOGIES IN THE HEALTH-INDUSTRIAL COMPLEX

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Abstract
The Biomechanics Engineering Laboratory (LEBm/HU-UFSC) is a reference center in education and research as well as in the technological development of the health field including pre-clinical testing of biomedical devices. The critical assessment of safety and effectiveness of biomedical devices requires a definition of clinically relevant metrics that allow quantifying the risks associated with their use. In Brazil, the National Health Surveillance Agency (ANVISA) controls the regulatory affairs and permission for commercialization of medical devices upon demonstration that the product is free from unacceptable risks. Therefore, achieve the minimum requirements for commercialization of products developed in Brazil are of utmost importance to the national industry and can positively impact on the trade balance of the Brazilian medical devices companies. In this paper the work of LEBm/HU-UFSC in the development of the medical devices field and in the formation of human resources for the pre-clinical evaluation of surgical implant technologies manufactured in Brazil is described.
Key words: Orthopedic implants. Pre-clinical Testing. Safety and Effectiveness. Technological Development.

A ATUAÇÃO DO LABORATÓRIO DE ENGENHARIA BIOMECÂNICA (LEBm/HU-UFSC) NA AVALIAÇÃO PRÉ-CLÍNICA DE TECNOLOGIAS DE IMPLANTES CIRÚRGICOS NO ÂMBITO DO COMPLEXO INDUSTRIAL DA SAÚDE

Resumo
O Laboratório de Engenharia Biomecânica (LEBm/ HU-UFSC) é um centro de ensino, pesquisa e desenvolvimento tecnológico na área da saúde com foco no projeto e na avaliação pré-clínica da segurança e eficácia de implantes cirúrgicos. A referida avaliação requer a definição de métricas clinicamente relevantes que permitam quantificar os riscos associados ao uso da tecnologia. No Brasil, a permissão para a comercialização de produtos médicos é fornecida pela Agência Nacional de Vigilância Sanitária (ANVISA) após a demonstração de que o produto é livre de riscos não aceitáveis. Portanto, a superação das barreiras técnicas para a comercialização dos produtos desenvolvidos no Brasil é de suma importância para a indústria nacional e pode impactar positivamente na balança comercial do setor odonto-médico-hospitalar. No presente artigo, é descrita a atuação extensionista do LEBm do Hospital Universitário da UFSC no desenvolvimento da área de dispositivos médicos e na capacitação de recursos humanos para a avaliação pré-clínica de tecnologias de implantes cirúrgicos fabricados no Brasil.
Palavras-chave: Implantes Ortopédicos. Ensaios Pré-clínicos. Segurança e Eficácia. Desenvolvimento Tecnológico.

LA ACTUACIÓN DEL LABORATORIO DE INGENIERÍA BIOMECÁNICA (LEBm / HU-UFSC) EN LA EVALUACIÓN PRÉ-CLÍNICA DE TECNOLOGÍAS DE IMPLANTES QUIRÚRGICOS EN EL ÁMBITO DEL COMPLEJO INDUSTRIAL DE LA SALUD

Resumen
El Laboratorio de Ingeniería Biomecánica (LEBm) de la Universidad Federal de *Santa Catarina* (UFSC) es un centro académico de investigación y desarrollo tecnológico en el área de la salud con enfoque en las áreas de proyecto y evaluación preclínica de implantes quirúrgicos, principalmente en lo que se refiere a su seguridad y eficiencia. Dicha evaluación requiere de la definición de aspectos clínicamente relevantes que permitan cuantificar los riesgos asociados al uso de tecnologías. En el Brasil, la autorización para la comercialización de los productos médicos es otorgada por la ANVISA, después de que, los fabricantes demuestran que el producto es libre de riesgos para los pacientes. Por lo tanto, la superación de barreras técnicas para la comercialización de los productos desarrollados en el Brasil es importante para la industria nacional y puede impactar positivamente la balanza comercial del sector Odonto-*médico-hospitalario.* En este artículo, se describe la actuación en el área de extensión universitaria del Laboratorio de Ingeniería Biomecánica (LEBm) en el desarrollo del área de dispositivos médicos y en la capacitación de recursos humanos para la evaluación preclínica de tecnologías de implantes quirúrgicos fabricados en el Brasil.
Palabras clave: Implantes Ortopédicos. Ensayos Preclínicos. Seguridad y Eficiencia. Desarrollo Tecnológico.

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INTRODUCTION

The Brazilian medical device industry has great relevance considering the national health policy as well as the economic and market perspectives for Brazilian manufacturers. Besides the medical industry being one of the fastest growing sectors worldwide, it is known that development and manufacturing of biomedical devices involves significant investment in research, which contributes to the technological development of the country. In this context, the concept of health-industrial complex aims to understand the regulatory and economic aspects of this sector taking into account the interaction between health and development (Gadelha, 2006). From this logic, instead of having health as an economic burden, this industrial field can be seen as a potential wealth creator for the country.

An important area in medical devices is the development and manufacture of surgical implants, which has high added value due to the inherent complexity of their use. However, a critical step to transfer innovative theoretical concepts into reliable products for use in humans lies in ensuring their safety and efficacy. Currently, there is a wide range of normative documents describing the methods for experimental evaluation of commercially available biomedical devices, such as ISO, ABNT and ASTM technical standards. However, the creation of new products through variations in the geometric features, materials, or manufacturing process requires the development of new test methods. In this context, the Biomechanical Engineering Laboratory (LEBm/HU-UFSC) has greatly contributed to the advance of national technological development, transferring to the society the know-how on the development and regulation of implantable medical devices.

The LEBm/HU-UFSC (Fig. 1) was founded in 2005 through a partnership between researchers from the Surgery and the Mechanical Engineering Departments from UFSC, with the institutional support of the University and its Hospital. The LEBm/HU-UFSC multidisciplinary team consists of Professors from previously mentioned departments as well as other researchers from the technological and health areas of UFSC, which enabled nucleation of the area of Biomechanics Engineering and Biomaterials until then incipient in the country. Currently, LEBm/HU-UFSC is a laboratory of excellence in Brazil and has worked extensively with the health-industrial complex to overcome biomedical problems. In 2011, LEBm/HU-UFSC was nominated as an official laboratory of National Health Surveillance Agency to provide technical-scientific support in the demands involving biomedical devices, and in 2017 the laboratory was accredited by INMETRO.

Figure 1. Partial view of the area of the LEBm/HU-UFSC for testing and analysis of surgical implants (Source: LEBm/HU-UFSC)

The laboratory research and extension projects are developed in partnership with federal agencies and with national industries. During this process the engineering technology is transferred to the health area, resulting in improvements in surgical techniques and the quality of national implantable devices. The know-how transferred to society includes the systematization of activities associated with the evaluation of medical device technologies as well as the development of the experimental and numerical methods required for device evaluation. Therefore, the LEBm/HU-UFSC has been a reference center in medical technologies, playing a leading role in the development of health-industrial complex.

LEBm/HU-UFSC PROPOSAL TO CLASSIFY EXPERIMENTAL APPROACHES FOR ASSESSMENT OF SURGICAL IMPLANTS TECHNOLOGY

According to the experience acquired in the extension projects of the LEBm/HU-UFSC, the evaluation of biomedical devices in the preclinical[1] phase can be performed *in vitro*, *in vivo*, and *in silico*.

In vitro (Latin for within the glass) tests comprise procedures performed in a controlled environment outside of a living organism but simulating physiological conditions. Parameters associated to biocompatibility and mechanical performance may be assessed through *in vitro* tests. The experimental conditions must be carefully selected to replicate the chemical, mechanical, and electrical environments as close as possible to the intended clinical use. To evaluate the mechanical properties, the device may be tested with the aid of positioning fixtures or using parts obtained from animals or human cadavers. The former is usually employed to reproduce the geometric configuration required for the experimental test. On the other hand, when the use of anatomical parts is chosen, expert surgeons should perform the surgical technique to ensure that

[1] The pre-clinical phase is defined as the entire period of development and validation of a medical product that precedes the clinical use in humans.

the relationship between the device and the anatomical host piece matches the *in vivo* condition. Select experimental model and its limitations must be considered during the interpretation of results and generation of reports. For example, the evaluation of mechanical properties of an isolated medical device is denominated as mechanical test while the evaluation using anatomical pieces system is considered a biomechanical test. The *in vitro* approach allows, through controlled trials, to quantify the level of performance of the medical device contemplating *in vivo* demands. The major limitation of these tests is the lack of the biological response of the living tissues interfacing the device, making the results valid only for immediate postoperative period.

In vivo (Latin for "within the living") studies refers to the investigation using a whole, living organism as opposed to a partial or dead organism. *In vivo* tests are performed in a bioterium under controlled conditions. Studies of biomedical devices performance consists in the implantation or placement of the device in animals with characteristics that approximate the conditions that will be found in the human body. These animals are monitored during the entire test and sacrificed at predetermined periods allowing the evaluation of physiological response of the tissue in contact with the medical device. Histological e pathological analyses of the surrounding tissues are the main techniques used to evaluate the *in vivo* response and provide information about the biocompatibility of the material (ISO 10993 series). It should be noted, however, that a series of considerations should be taken when selecting an appropriate animal model for the assessment of biomaterials performance. In orthopedics, the main limitation in the animal models it that the mechanical demand imposed on the product presents a lower magnitude when compared to the intended clinical use in humans. Changes in the product dimensions or even in the product shape are frequently needed to match the animal size.

Increasingly over the last two decades, *in silico* (performed on computer or via computer simulation) tests have been developed to assess devices and drugs, including their potential risk to the public (Geris, 2014). Supported by the Food and Drug Administration (FDA, 2016) from United States, this technology can be used to develop computer models of cells, organs, and systems to better predict product safety and efficacy. In orthopedics and odontology, materials with specific properties and geometries may be evaluated regarding to their mechanical properties, generating data to predict clinical risk-benefit and regulatory decision-making. While it is not possible to conduct entirely simulated clinical trials with current technology, its development should have major benefits over current clinical trials.

CASE STUDIES

To demonstrate the collaborative work between the LEBm/HU-UFSC and the health-industrial complex, three studies conducted through extention projects in the LEBm/ HU-UFSC and of clinical relevance were selected and will be described as follows.

Case Study 1- Safety assessment of silicone breast implants

In 2012 a series of adverse events related to the use of silicone breast implants manufactured by the French company Poly Implant Prothèse (PIP) raised a concern for many health surveillance agencies around the world. Unlike the prostheses submitted for approval during the ANVISA registration process, investigations revealed that the PIP breast implants were being manufactured using industrial-grade silicone instead of the required medical-grade material. Given the problem severity and the duty of ANVISA to regulate, control and supervise products and services involving public health risk, several actions were taken including the creation of a program for Conformity Assessment of Breast Implants (INMETRO Certification) and stricter surveillance measures for breast implants. Both actions had distinguished participation of the LEBm/HU-UFSC, as a member of the technical committee of the conformity program (Ordinance INMETRO 161 of 05/04/2012) as well as performing mechanical tests to inspect the safety and quality of the products commercially available in the national marked.

Breast augmentation using silicone prosthesis remains among the most commonly performed procedures in aesthetic and reconstructive surgery. Breast implants have biomechanical functionality to support their own weight during *in vivo* use, in addition to being resistant to compressive and impact loads. The worst-case scenario expected for these devices is the combination of compression load and alternating movements in the frontal plane of the breast implant, establishing shear stress under compression. Therefore, the characterization of breast implants mechanical properties is essential to guarantee the performance and safety characteristics required by the regulatory agencies.

Considering the intended use for breast implants, the main *in vitro* mechanical assays for assessing the compliance of these medical devices in their finished state (product testing) include the Breast Implant Fatigue Test, and the Impact Test. Both trials have clinical relevance, since the rupture of implants due to fatigue or impact are recognized adverse events. The technical Standard ISO14607 Non-active surgical implants - Particular requirements, describes the

experimental conditions and methodology to determine the mechanical properties of breast implants. However, when the problem with PIP implants came to the light, there was nor national or international manufacturer that could provide the facilities to perform the required tests in Brazil.

The project carried out by LEBm/HU-UFSC consisted of designing and manufacturing the necessary equipment to evaluate the fatigue and impact properties of PIP breast implants collected by ANVISA. In addition to the mechanical tests, the calibration of the equipment and associated sensors was developed and performed. The equipments for fatigue and impact (Fig. 2) testing were patented with the INPI under registration numbers of BR1020150107250 and BR1020130180971, respectively.

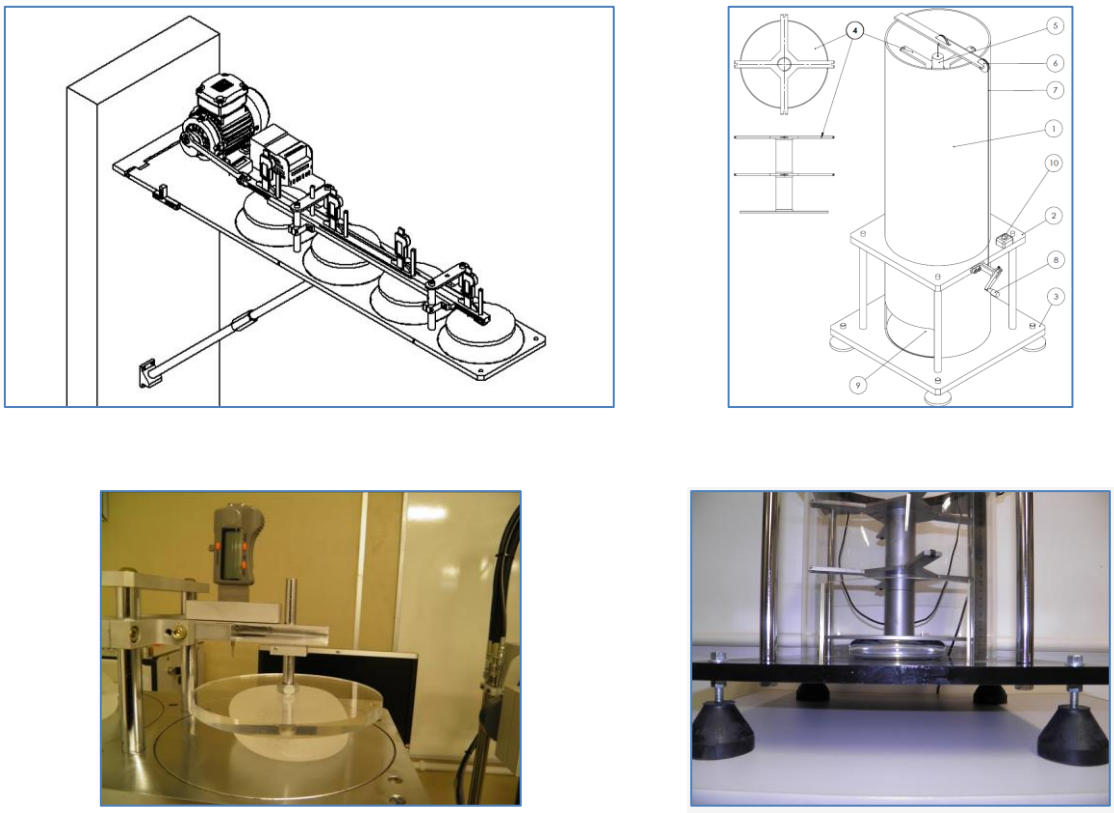


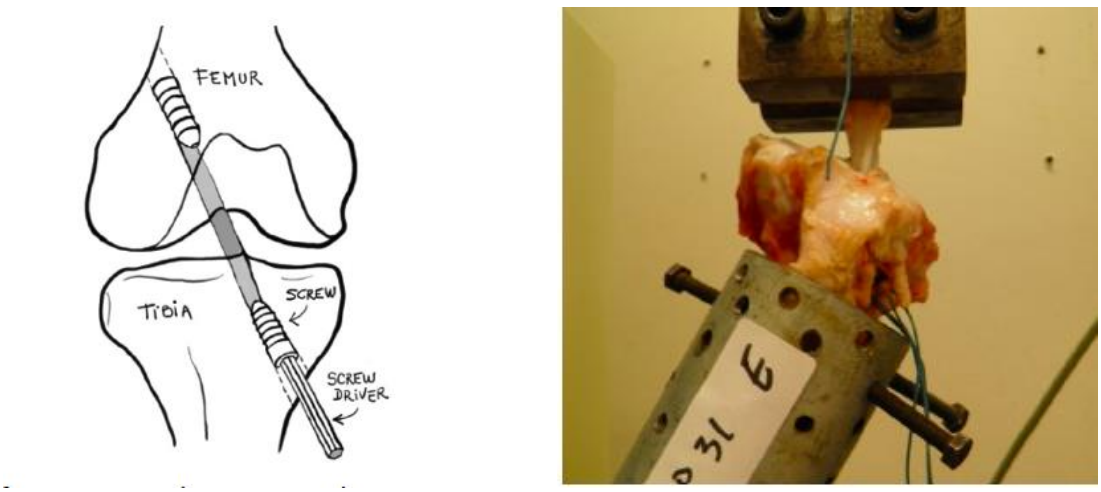
Figure 2. Schematic drawing and manufactured equipment details of fatigue (left) and impact (rigth) equipment developed and patented by the LEBm/HU-UFSC (Source: LEBm/HU-UFSC)

Fatigue and impact tests were carried out in 108 PIP breast implants, and the findings have supported the actions of ANVISA and the Ministry of Health for quality control of these products. The fatigue equipment technology was transferred to local industry. Currently, this equipment is also used at the National Institute of Technology of the MCTI, in the program of Conformity Assessment of Breast Implants.

Case Study 2 - Performance comparison between metallic interference screws and bioabsorbable screws in the ACL reconstruction surgery of the human knee

In the human knee, a torn ligament can be replaced by a graft through the anterior cruciate ligament (ACL) reconstruction surgery. The reconstruction is performed to restore physiological stability and normal function of the knee joint. However, the implant design and material, as well as the surgical procedure chosen by the clinician may influence the reconstruction outcome. To avoid the reoccurrence of knee instability it is important to determine how different implants and surgical techniques influence in regards to immediate post operatory stability under cyclic loading (Moré et al., 2016a).

Therefore, the goal of the present study was to compare the biomechanical performance of two surgical techniques of the graft fixation to the tibia using different devices. The first technique employed a bioresorbable interference screw. This implant begins to degrade, through hydrolytic degradation, only after the period necessary for the biological fixation of the graft in the host bone. The second technique used a titanium interference screw, which is cheaper material in comparison to the polymer. The biomechanical *in vitro* tests, using parts obtained from animals (Landrace porcine knees), were set up by an experienced orthopedic surgeon. The cyclic biomechanical tests were performed at a frequency of 1.2 Hz that simulates the frequency of human gait. Loads of 50 N to 250 N were employed to simulate the forces measured in the ACL (anterior cruciate ligament) (Fig. 3) (More *et al.,* 2015). The load was repeated for 1000 cycles to simulate a rehabilitation protocol.



(a) (b)

Figure 3 (a) Illustration of ACL reconstruction surgery with tibial and femur interference screw and (b) set-up of biomechanical tests (right) (Source: LEBm/HU-UFSC)

The variation of the length of the graft/fixation/tibia system was the parameter selected to evaluate the reconstruction stability. The results did not indicate a significant difference in the length variation of the graft/fixation/tibia system for the two different surgical techniques (Fig. 4). Besides the mechanical evaluation of the different systems, this project also yielded the design a specific test method for bioabsorbable interference screws (Roesler *et al.,* 2014).

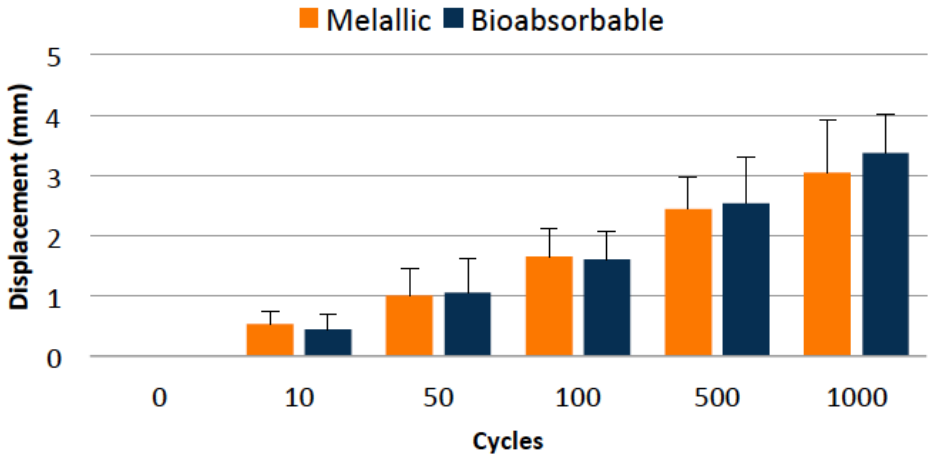


Figure 4. Change in length of the graft system/ fixture/tibia after 1000 cycles for two different implants reviews (surgical techniques) (Source: LEBm/HU-UFSC)

Case Study 3 - Validation of bioabsorbable implants for reconstruction surgery of the anterior cruciate ligament (ACL) of the human knee

Metallic interference screws, pins or buttons are usually used in ACL reconstruction surgery. However, issues caused by metallic material in imaging techniques are an important disadvantage associated with this technology. The use of bioabsorbable polymers potentially overcomes this limitation, since these implants allow for the graft to be fixed in the bone tunnel during the healing period of the treated tissue. During the degradation process, the mechanical stress is gradually transferred to the surrounding tissue allowing for good integration with the physiological environment. After bone healing, the implant loses its mechanical function and is gradually expelled from the human body through body fluids. Taking into account that there was no manufacturer of bioabsorbable implants in Brazil, the objective of this project was to promote the advancement of national technology through the research, development and biomechanical evaluations of orthopedic implants manufactured with bioabsorbable polymer. A partnership between the LEBm/HU-UFC and a national company was made to achieve the goals proposed in this project. The interference screw was the select design to be developed and validated using in silico (Fig. 5) and *in vitro* (Fig. 5) techniques. Due to the suitable chemical and mechanical

properties, the poly-L/D-lactide (PLDLA) 70/30 was chosen as bioabsorbable polymer to manufacture the device.

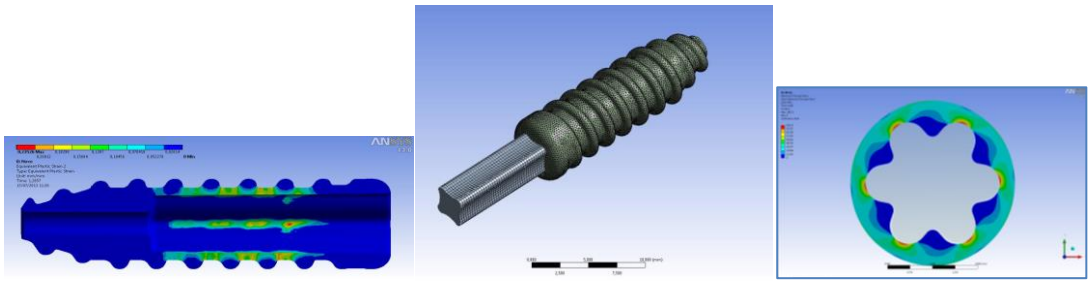


Figure 5. Stages of numerical simulation used in the development of the product and its connection.

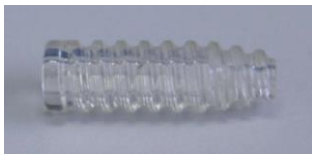


Figure 6. Bioabsorbable interference screw manufactured in Brazil.

A critical step in the product validation was to develop a torsion test method to characterize the mechanical performance of the product, once the available approaches were known to hide the actual performance of cannulated screws (Roesler et al. 2014). Additionally, to guarantee a safe and effective use *in vivo*, these implants must preserve adequate mechanical properties during the healing period, as well as to degrade at a known rate. Therefore, protocols were developed to evaluate the retention rate of mechanical properties of the biosabsorbable screws over time. Fig. 6 demonstrates the image of a failed screw after application of the torsional load limit.

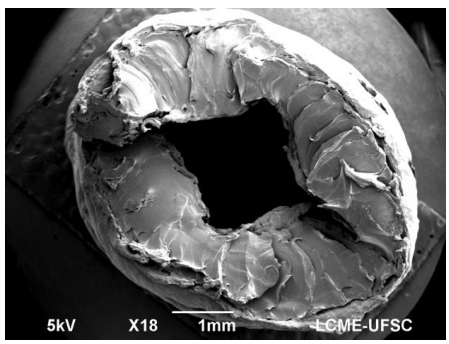


Figure 7. Image of the failed surface obtained using MEV of the PLDLA 70/30 interference screw after torsion test (Source: LEBm/HU-UFSC)

This project provided subsidies for the product regulation in national and international regulatory agencies (ANVISA, CE, FDA Submission). During the device development there was

an intense improvement of human resources especially in injection manufacturing processes and in biomechanical design and analysis of medical devices. This project also advanced in the biomaterials scientific and technological fields in the LEBm/HU-UFSC, as well as strengthened the cooperation between LEBm/HU-UFSC and the medical device company, which accelerated the technology transfer process.

CONCLUSIONS

Extension projects allows for the know-how transfer from the university to the society, which has a great potential to mobilize the scientific knowledge to innovate the products and processes with economical significance to the country. In this sense, the LEBm/HU-UFSC has played a relevant role in the health-industrial complex since it fills a fundamental gap for the biomedical sector, that is, to train and improve personnel as well as developing and validating medical devices. Considering that the domain of technology enables the development of a sustainable economy, since it makes it competitive, the work of LEBm/HU-UFSC has contributed to the development of the health industrial complex in Brazil.

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