What endosseous surface is appropriate for dental zirconia implants?

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INTRODUCTION: Dental implants are a valuable treatment option to replace missing teeth. Titanium is currently the material of choice. However, a general dispute on the biocompatibility of metals induced the development of metal-free options. Today, zirconia implants are rated a viable alternative to titanium implants in dentistry.

It is generally accepted that the surface roughness of the endosseous part of dental implants is a crucial parameter for osseointegration, meaning the direct structural and functional connection between living bone and surface of the load-bearing implant. The current dogma states that implants should exhibit a moderately rough surface of R_a = 1-2 µm to ensure a fast and long-term osseointegration [1].

However, data of a two-center clinical trial with a zirconia implant (ceramic.implant, Vita, Bad Säckingen, Germany) implies that a smooth surface may be as attractive to living bone as a rough surface because the bone level around the implants was equally distributed on the moderately rough endosseous and the smooth transmucosal part [2].

Aim of the study was to assess osteoblast and fibroblast behavior on smooth and moderately rough surfaces in comparison to biofilm formation.

METHODS: Cell culture experiments with osteoblasts (*MG-63*), fibroblasts (*HGF-1*) and a three-species biofilm (*S. sanguinis, F. nucleatum, P. gingivalis*) on zirconia specimens were performed. Zirconia discs (Ø 13 mm) with surface characteristics identical to those of the zirconia implant ceramic.implant (Vita) were used (R_a[rough surface] = 1.35±0.07 µm; R_a[smooth surface] = 0.10±0.00 µm).

Cell viability of both cell types was assessed. With osteoblasts cell spreading and gene expression of alkaline phosphatase, collagen type I, and osteocalcin were measured. Biofilm formation was quantified using safranin staining.

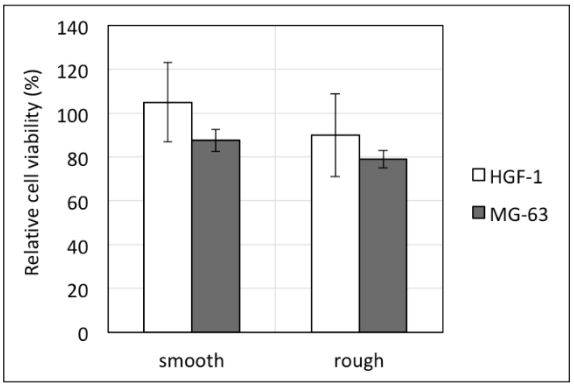

Fig. 1: Mean relative cell viability of fibroblasts and human osteoblasts after cultivation for 24 h.

RESULTS: Gene expression of osteoblasts was similar on moderately rough and smooth surfaces. Cell spreading of osteoblasts was significantly increased on the smooth surface by a factor of 1.65. Cell viability was significantly increased on smooth surfaces for osteoblasts and fibroblasts. (Fig. 1). Biofilm formation was significantly less on smooth compared to moderately rough surfaces.

DISCUSSION & CONCLUSIONS: Cell cultures revealed no benefit of the moderately rough over the smooth surface, suggesting that for zirconia a smooth surface might be at least as attractive to osteoblasts and fibroblasts and additionally reduces biofilm formation. In regard to production costs a smooth surface would be advantageous. However, the present results do not provide any information on how primary stability and time to osseointegration is affected by a smooth surface. Hence, a prospective controlled clinical trial with a smooth endosseous surface is of high interest.

REFERENCES

[1]Albrektsson T, Wennerberg A. On osseointegration in relation to implant surfaces. Clin Implant Dent Relat Res 2019;21:4-7. [2]Rohr N, Balmer M, Jung RE, Kohal RJ, Spies BC, Hämmerle CHF, Fischer J. Influence of zirconia implant surface topography on first bone implant contact within a prospective cohort study. Clin Oral Impl Res, revised manuscript submitted.

Multifuncional Properties of Quercitrin Coated Porous Ti-6Al-4V Implants for Orthopaedic Applications

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INTRODUCTION: One strategy to improve the outcome of orthopaedic implants is to use porous implants with the addition of a coating with an antibacterial biomolecule. In previous studies, a coating method by wet chemistry using the flavonoid quercitrin was developed [1]. We demonstrated that quercitrin coated surfaces were bioactive, presenting osteogenic, osteopromotive, antifibrotic and antibacterial properties [2, 3]. In this study we aimed to produce and test the biocompatibility and bioactivity of quercitrin coated porous Ti-6Al-4V implants on osteoblastic cells and S. epidermidis to demonstrate multifunctional properties of the coating.

METHODS: Porous Ti-6Al-4V implant were produced by 3D printing and further functionalized with quercitrin by wet chemistry. Implants were characterized in terms of porosity and mechanical testing, and the coating with quercitrin by fluorescence staining. Implant cytocompatibility and bioactivity was tested using MC3T3-E1 preosteoblasts by analyzing cytotoxicity, cell adhesion, osteocalcin production and alkaline phosphatase (ALP) activity under control and under bacterial challenging conditions using lipopolysaccharide (LPS). Finally, the antibacterial properties of the implants were studied using Staphylococcus epidermidis by measuring bacterial viability and adhesion.

RESULTS: Porous implants showed a pore size of about 500 µm and a porosity of 52 %. The coating was homogeneous over all the 3D surface and did not alter its mechanical properties of the Young modulus. Quercitrin coated implants showed higher cytocompatibility, cell adhesion and osteocalcin production compared to control implants. Moreover, higher ALP activity was observed for the quercitrin group under both, normal and bacterial challenging conditions. Finally, S. epidermidis live/dead ratio and adhesion after 4 hours of incubation was lower on quercitrin implants compared to the control.

DISCUSSION & CONCLUSIONS: Quercitrin functionalized porous Ti-6Al-4V implants present a great potential as an orthopaedic porous implant that decreases bacterial adhesion and viability while promoting bone cell growth and differentiation.

ACKNOWLEDGEMENTS: This work was supported by "Direcció General d'Innovació i Recerca del Govern de les Illes Balears" co-funded ERDF European Regional Development Fund, (Fondos FEDER) (PROCOE15/2017), the Ministerio de Educación Cultura y Deporte (contract to M.A. L.G; FPU15/03412) by the Instituto de Salud Carlos III, Ministerio de Economía y Competividad, co-funded by the ESF European Social Fund and the ERDF European Regional Development Fund (MS16/00124; IEDI-2017-00941).

REFERENCES: [1]Córdoba, A.; *et al.* Bioinspired Quercitrin Nanocoatings: A Fluorescence-Based Method for Their Surface Quantification, and Their Effect on Stem Cell Adhesion and Differentiation to the Osteoblastic Lineage. ACS Appl. Mater. Interfaces 2015, 7, 16857–16864. [2]Córdoba, A.; *et al.* Flavonoid-Modified Surfaces: Multifunctional Bioactive Biomaterials with Osteopromotive, Anti-Inflammatory, and Anti-Fibrotic Potential. Adv. Healthc. Mater. 2015, 4, 540–549. [3]Gomez-Florit, M.; *et al...* Quercitrin-nanocoated titanium surfaces favour gingival cells against oral bacteria. Sci. Rep. 2016, 6, 22444.

Rapid Active, Non-releasing Antibacterial Coatings Based on Ag Nano Islets Deposited on TiOx Films

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INTRODUCTION: Healthcare acquired infections (HAI) are a major burden for patients and healthcare costs. A large part of HAI is associated with percutaneous medical devices such as venous and urinary catheters as well as respiratory support devices [1]. To reduce HAI, critical devices are equipped with antibacterial properties, e.g. by addition of silver based on the antibacterial effect of Ag^+ ions.

To avoid possible issues related to metal release, photo-generated catalytically active oxygen vacancy sites in TiO_2 can also be considered as antibacterial surfaces. Most of all, stabilized O vacancies can be obtained by doping with a dissimilar metal generating electron-hole pairs with narrow band gaps [2]. Here, plasma technology is investigated to deposit Ag nano islets on TiOx films, making use of deposition conditions that directly generate O vacancies [3].

METHODS: For plasma deposition, a low pressure pilot-scale reactor was used allowing plasma cleaning/activation and magnetron sputtering from Ti and Ag targets in a one-step process. Thus, Ag nano islets with 4 nm average thickness have been deposited on TiOx films as catalytically active antibacterial surfaces as well as substoichiometric TiOx thin films and Ag 4 nm islands as references. Various substrate materials have been selected such as Si wafers and glass slides for characterization as well as medical grade thermoplastic polyurethane (TPU) and silicone materials as used for ureteral devices and catheters. All coatings showed excellent adhesion following an appropriate cleaning method.

Antibacterial efficacy was assessed with a modified method similar to ASTM E2180 but using a bacterial suspension instead of an agar slurry to detect volume activity over 10-60 min. Furthermore, an agar touch assay with 1, 10, and 30 min sample contact and diffusion assay with overnight incubation have been applied to observe contact killing and exclude leaching effects. *E. coli* DSMZ30083 and *S. aureus* MRSA were used as bacterial strains. Cytotoxicity of the plasma coatings was investigated according to ISO-norm 10993-5 showing no cytotoxic effects. Generation of reactive oxygen species (ROS) was detected using a fluorescent dye.

RESULTS: The non-releasing TiOx/Ag 4 nm plasma coatings and references have been investigated for ROS generation and related antibacterial activity (Figure 1) when stored in the dark, simulating implants or inserted catheters.

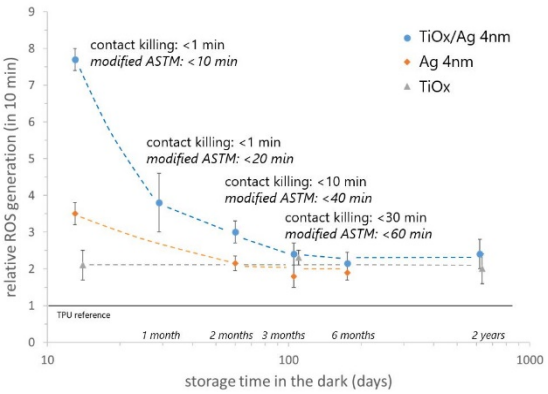

Fig. 1: ROS generation relative to uncoated TPU. For TiOx/Ag 4 nm coatings the time is indicated to show antibacterial activity yielding a reduction of more than 10^3 CFU ml^{-1}.

Initially high ROS generation enables rapid active surfaces by contact killing. Lowered ROS levels over time still yield a levelled antibacterial efficacy demonstrating stabilized O vacancies. The coatings can be reactivated by light exposure or plasma activation.

DISCUSSION & CONCLUSIONS: Plasma coating of Ag nano islets on TiOx yield non-releasing antibacterial surfaces suited for implants due to adjusted ROS generation.

ACKNOWLEDGEMENTS: Funding by Innosuisse, CH, is acknowledged (project no. 30078.1 IP-LS).

REFERENCES: [1]P.W. Stone et al. 2009 *Expert Rev. Pharmacoecon. Outcomes Res.* 9 417. [2]X. Pan et al. 2013 *Nanoscale* 5 3601. [3]M. Amberg et al. 2015 *Nanomed. Nanotechnol. Bio. Med.* 11 845.

European Medical Device Regulation (MDR 2017/745) – MedTech in EU beyond May 2021

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INTRODUCTION: The European Medical Device Regulation (MDR) will fully apply to the entire medical device industry as of 26th of May 2021. While this regulation aims at increasing safety, and transparency for the EU population, the impact on innovation and access to the state-of-the-art medical devices remains uncertain.
The new European Medical Device Regulation replaces the exiting Medical device directive which has been in place since 1993. The new regulation brings more restrictive requirements for sufficient clinical data, higher focus on active post-market surveillance, higher transparency via Eudamed database and higher scrutiny of the notified bodies among other changes.

DISCUSSION: High profile cases such as the P.I.P scandal, had led to a political pressure to make the regulation stricter to protect patients.

Disappearing notified bodies: In the EU, the surveillance of medical device manufacturers and approval of medical devices relies on a system of private notified bodies as opposed to a central or governmental function as seen in most other countries (e.g. FDA in US). Under MDR the scrutiny of these notified bodies has been increased significantly, leading to disappearance of some notified bodies. Despite the decline in the absolute number of the notified bodies, it should be noted that some of the gap will be complemented by the increase in size of the surviving ones. However, until full implementation of MDR in 2025, notified bodies will have to continue their surveillance activities under MDD in parallel to MDR, leading to a system overload in the next four years. This can cause delays in review processes, leading to delays in supply of medical devices in the EU.

Focus on Implants: Uncertainty about long-term effects of implants and implantable materials has translated to a much higher level of requirements for implantable medical devices. More specific and detailed requirements for sufficient clinical data and limitations in the use of equivalency with existing products on the market, may push manufactures to select other markets (e.g. USA) as their initial market prior to entering EU.

Catching up with technology: Medical devices cover a wide range of products and technologies that have developed greatly in the course of the past 20 years. Therefore, the introduction of MDR also allowed the commission to expand/include requirements to address the need for new generations of the devices including devices that contain nano materials and software. Due to high scientific uncertainty about the risks and benefits of nanomaterials, MDR requires such products to be assessed with highest scrutiny. As software becomes more and more integral part of our lives, MDR extends the requirements for devices that are or contain software. While previously most software would be self-declared, under MDR almost all software devices require notified body conformity assessment.

As a result, the increase in cost and efforts to bring new devices into the EU may cause a shift in the industry focus to; a) reduce risk by focusing on established technologies and minor modifications of legacy products, instead of investing in innovation or b) first enter other markets (e.g. USA) prior to entering EU. Either of those would reduce/delay access of EU patients to innovative medical devices but at the same time also protect EU patients from unknown long-term risks of such technologies.

REFERENCES: Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices.

Challenges for implants under the MDR

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INTRODUCTION: The application of the European Medical Device Regulation (MDR) impacts the development, CE-marking, and maintenance of implantable medical devices.

METHODS: The MDR places more emphasis on a life-cycle approach compared to the Medical Devices Directive. In addition to re-classifying some medical devices, it introduces new procedures within the conformity assessment process, provides more prescriptive guidance on the technical documentation, enhances supply chain oversight, and increases clinical data requirements. With the introduction of a new Unique Device Identification (UDI) System and implant cards, as well as establishing the Eudamed database, the MDR increases transparency and enhances the effectiveness of post-market surveillance. As a result of these increased requirements, to ensure MDR compliance, medical device manufacturers need to devote more resources to quality assurance, preparation of the device documentation, and, in certain situations, conducting clinical investigations to generate additional clinical data.

The MDR's risk-based classification depends largely on the intended purpose of the device as stated by the manufacturer. However, the classification of an entire device can be affected due to e.g., technological changes in the device components or the addition of new software-based functionalities. For instance, using nanomaterials to increase implant biocompatibility can influence device classification under the newly established Annex VIII Rule 19, which states that devices incorporating or consisting of nanomaterials should be classified based on the potential for internal exposure of the body to the nanomaterial.

Changes affecting device components can impact the conformity assessment pathway as well. New materials (e.g., substances, nanomaterials) for implants need to be compliant with the General Safety and Performance Requirements (GSPRs, MDR Annex I). The MDR introduces major changes to several GSPRs including the need for increased information on the chemical, physical and biological properties of the materials used in the device (GSPR 10), changes in the evaluation of the adsorption of substances (GSPR12.2), as well as specific requirements regarding nanomaterials (GSPR 10.6) and the information on materials for implants (GSPR 23.4u). The MDR also introduces a clinical evaluation consultation by an expert panel as a mandatory procedure during the conformity assessment process of Class III implantable devices.

CONCLUSIONS: Identification and implementation of changes mandated by the MDR require the involvement of almost all functions and a well-coordinated adaption of internal processes. Accordingly, manufacturers must subject their portfolio, documentation, and development process to a stringent gap analysis and implement a remediation plan to ensure timely MDR compliance and secure business continuity.

This presentation will provide details about MDR requirements and their implementation, putting emphasis on those requirements specific to implantable medical devices.

Additive Manufacturing of custom made and mass production of implants – Overview of regulatory and quality challenges posed by the MDR

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INTRODUCTION: The Medical Device Regulation 2017/745 (MDR) changes the definition of custom-made devices by specifying that 'devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of an authorized person shall not be considered to be a custom-made'.
Since 3D printers are industrial manufacturing processes, this means that manufacturers need to identify specific criteria to define when a device is "mass-produced".
This work provides a proposed approach for defining a 3D printed custom-made device based on the current status of interpretation of the MDR.

DISCUSSION: Technological progress has allowed easier access and implementation of personalized medical devices. In the orthopedic industry it is now possible to produce implants and instruments that are individualized, for example, using additive manufacturing (3D printing) methods based on patient CT scans.
In parallel, the regulatory framework for custom made devices and in general for high-risk devices was found to be inadequate to prevent big scandals and the MDR was introduced with the aim of improving patient safety by increasing the regulatory requirements and the level of scrutiny.
In the case of custom made, the MDR introduced specific restrictions around devices that 'mass-produced by means of industrial manufacturing processes'. The MDCG 2021-03 0 clarifies that state-of-the-art industrial processes can be used to manufacture a custom made as soon as this is not mass-produced.
According to IMDRF 0 a mass-produced device is *based on standardized dimensions/designs*; is *not designed for a particular individual*; and is typically *produced in a continuous production run or homogenous batch*.
If the second criteria can be self-explanatory, the other two need more discussion.
A typical characteristic of a custom made is that it is not produced in batches, however companies typically produce more than one part to compensate for potential errors during production. Furthermore, it is a good practice to provide the surgeon with at least two devices to reduce potential risks during surgery (e.g. device falls on the floor). Moreover, in some instances, to treat particular cases, different devices are designed and produced to enable the surgeon to delay the choice of the best one at the time of surgery.
Companies need to establish specific criteria to define when a device is mass-produced, such as limit the number of a batch (e.g. to 5 pieces as proposed by FDA 0) and allow different designs or sizes to treat a specific case by including this requirement in the written prescription by the surgeon.
Custom made are in part based on standard designs, but they need specific characteristics that standard devices to not have. In such cases it is important to argue why the custom made is not a 'patient-matched medical device' or an 'adaptable medical device'.

CONCLUSIONS: Additive manufacturing techniques are not automatically qualifying a device as a custom made as these are nowadays used more and more also for standard production. Therefore, custom made manufacturers must identify appropriate criteria to define when a device is meeting the definition of custom made and rule out any doubts that these devices are mass-produced by means of industrial manufacturing processes.

REFERENCES: [1]MDGC 2021-3 - Questions and Answers on Custom-Made Devices - March 2021. [2]IMDRF/PMD WG/N49 FINAL: 2018 - Definitions for Personalized Medical Devices - October 2018. [3]FDA guidance - Custom Device Exemption – September 2014.

Lean PMCF studies using real-world data

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INTRODUCTION: Real-world data (RWD) are a possible source of clinical information manufacturers can use to meet Post-Market Clinical Follow-Up (PMCF) requirements under the MDR. Recognized advantages of RWD over clinical trials are a larger and more heterogenous patient population, broader range of end-users and the provision of long-term information about device performance and safety. However, RWD only come into their own if the underlying study designs adhere to the same scientific standards as clinical trials.

METHODS: RWD may be derived from electronic health records, surgery reports, registries, administrative claims data, collected from mobile devices or are patient-generated.
PMCF studies based on RWD should only use anonymized patient data and not interfere with a health care provider's (HCP) standard protocol for routine application of the device. Choice of an appropriate endpoint, e.g., a rate (failure, success, specific event) is crucial in that respect. The selection of HCPs should be representative of the end-users of a device, e.g., not be restricted to high-volume surgeons or to clinicians involved in the product development.
Sample sizes must be statistically justified. This implies that manufacturers have an expectation regarding the real-world performance of their device, which is benchmarked against a reference value derived from the literature or from a competitor device.

STATE OF AFFAIRS: Regulators consider RWD a valid component of the clinical information used in regulatory decision-making, provided the data are acquired and analysed in line with scientific principles. RWD are as well part of the External Evidence (EE) used in clinical studies to reduce their length and bring new safe and effective technologies to market sooner. Whether HCPs can handle an increasing demand for supply of RWD remains to be seen. If the use of RWD is to be promoted, device manufacturers need more direct access to the sources of RWD, which is in conflict with current data protection regulations.

REFERENCES:

MDCG 2020-6. Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies, April 2020.

MDCG 2020-8. Post-market clinical follow-up (PMCF) Plan Template. A guide for manufacturers and notified bodies, April 2020.

FDA. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Guidance for Industry and Food and Drug Administration Staff, August 2017.

Medical Device Innovation Consortium (MDIC). External Evidence Methods (EEM) Framework. Draft, January 2021.

SMART Devices – Implants 4.0

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INTRODUCTION: This keynote lecture discusses the evolution of medical implants from mere inert "hardware" that primarily functions to bear mechanical loads to the future of sensing and measuring implants and implants as theranostic (therapy and diagnosis) devices. Goal is to highlight that the next generation of medical implants will incorporate sensor technology leading to new clinical workflows and business models and ample opportunities for collaboration between traditional device manufacturers, sensor technology and software / data management companies.

DEFINITION AND EXAMPLES OF SMART DEVICES: We provide a definition of SMART (Sensing Measuring and Advanced Reporting Technologies) devices including examples of some past and recent developments and a vision of how SMART devices may (continue to) enter and revolutionize traditional implantology. This is followed by a review on key trends and drivers creating (unmet) needs that may be addressed using SMART devices such as evidence based medicine, patient compliance and engagement and theranostics. Moreover, advances in both sensor technology and data processing / data management are highlighted that may allow unobtrusive continuous sensing combined with diverse technologies to reshape the clinical workflow for both acute and chronic disease management. We discuss examples of SMART devices applied both in orthopaedics and dentistry. Finally, we discuss the opportunities of strategic partnerships and open innovation to bring together traditional device manufacturers, sensor technology and software and data management companies in order to join forces and co-develop the implants of the future.

FUTURE TRENDS: Technical advances have supported the evolution of medical implants to SMART implants, i.e. from inert hardware towards preventative, predictive, personalised and participatory devices. The sensing technologies discussed in this keynote lecture and their future evolution will play a key role in realising the goal of unobtrusive continuous sensing for earlier diagnosis of diseases and improved monitoring of therapy success. Moreover, clinical workflows for both acute and chronic disease management will be reshaped due to the new "role" of SMART implants as (continuous) sensors of patient health and disease state. Finally, due to the interdisciplinary nature of SMART devices, ample opportunities exist for collaboration and open innovation. Most traditional device makers do not possess the required expertise on sensor technology and/or data processing / management. Vice versa, most software and sensor technology companies are not experts in medical implants and therefore joining forces and developing SMART devices together may be an attractive way forward to mitigate risks and benefit from the respective expertise of the development partners.

Highly porous Ti as bone substitute: triboelectrochemical characterization of highly porous Ti under fretting-corrosion conditions

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INTRODUCTION: Implants require long-term stability and rapid healing however, the existing Ti-based implant materials do not meet completely the current expectation. Lack of bioactivity, wear debris, and the biomechanical mismatch between the implant and the bone are still the major problems in the prostheses field and can cause aseptic loosening, fibrous encapsulation and osteolysis [1]. Macro-porosity in the Ti implant was presented as a beneficial way to reduce the biomechanical mismatch, in order to approach the value of Young's modulus of the implant to the one found in the bone [2]. It also allowed the possibility of ingrowth of new bone tissue inside of the pores [3]. The study of simultaneous wear and corrosion (tribocorrosion) is one of the most important aspects of the biomedical industry. There are micro-motions in the points of the implant fixation, leading to debris and ion release by fretting corrosion. This work aimed to investigate fretting corrosion behaviour of highly-porous Ti intended for orthopaedic applications.

METHODS: Highly-porous Ti samples (Ø = 12 mm) were processed by powder metallurgy with space holder technique. Characterization of the macro-porosity was performed. Fretting corrosion tests on highly-porous Ti, during 16 hours, were performed with a substantial range of loads. Electrochemical data was continuously monitored with a potentiostat connected to the fretting corrosion device where linear voltage displacement transducer sensors on the device were in charge of controlling a displacement of ± 40 µm sinusoidal displacement.

RESULTS: Concerning highly-porous Ti/Ti alloy contacts, several mechanical responses were obtained, from gross slip under low normal load until partial slip under high load. The threshold was highlighted.Friction (COF) decreased with increasing normal load. In addition, the same trend was assessed for dissipated energy, and that was not in accordance with dense/dense materials contacts behaviour. Despite the high amount of metal area exposed to the electrolyte (due to porosity), a decrease in the potential was observed, especially for the extreme loads, even if stick phenomenon was occurring.

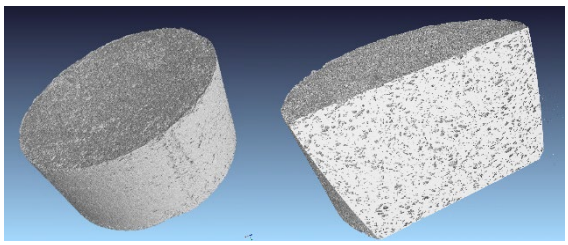

Fig. 1: Three-dimensional tomographic reconstructions of highly-porous Ti sample.

DISCUSSION & CONCLUSIONS: The surface morphology of the highly porous Ti was mostly preserved after 16 hours of fretting-corrosion solicitations. The benefits of porous titanium seem promising for replacing some metallic parts well used in dentistry and implants field.

REFERENCES: [1]Geetha *et al.*, Prog. Mater. Sci. 54 (2009) 397–425. [2]Bansiddhi *et al.*, Woodhead Publishing Limited, 2014. [3]Alves *et al.*, J. Biomed. Mater. Res. Part B - Appl. Biomater. 107 (2019) 73–85.

ACKNOWLEDGEMENTS: This work was a result of the project Operation NORTE-08-5369-FSE-000051 supported by NORTE 2020, under the PORTUGAL 2020 Partnership Agreement, through the European Social Fund (ESF), and M-ERA-NET/0001/2015 project supported by FCT.

Zeta potential of implant surfaces – correlation with hydrophilicity and porosity

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INTRODUCTION: The zeta potential is driving the electrostatic interaction at the material-water interface. The attraction of proteins by an implant surface as a precursor for cell growth, or the repulsion of bacteria to prevent inflammation, may be predicted if knowing the zeta potential.

Surface functional groups, which introduce charge depending on their nature and the pH of the aqueous surroundings of an implant, are also determining the surface hydrophilicity. A correlation between the zeta potential and the water contact angle, which is commonly used to describe material hydrophilicity, seems feasible and is indeed observed for a series of alike materials.

Sample porosity contributes to the zeta potential analysis by means of ionic conductance, which is introduced by water (and water-borne ions) inside pores. The zeta potential indicates the effect of surface porosity even of thin-film coatings, which is otherwise difficult to assess.

Here we report on the assessment of the interfacial charge at titanium (oxide) surfaces and their interaction with proteins by the surface zeta potential. We attempt to derive qualitative information about surface hydrophilicity and sample porosity from the obtained zeta potential results.

METHODS: The zeta potential at the solid-water interface is calculated from the measurement of the streaming potential (SurPASS, Anton Paar, Austria). The principle of the streaming potential is based on the flow of a test solution through a capillary channel created between material surfaces.

Disks (15 mm diameter) of cp titanium were modified by a hydrothermal (HT) growth of anatase nanocrystals [1]. The zeta potential of cp Ti, HT-treated Ti, and Ti after UV exposure was determined using the adjustable gap cell for disks.

RESULTS: Fig. 1 shows the zeta potential of cp Ti and HT-treated Ti after UV exposure in the range between the physiological pH and the materials' isoelectric point. The effects of surface modification and UV activation are clearly visible. Adsorption of albumin (BSA), however, does not distinguish between these surfaces. Only the recording of adsorption kinetics (data not shown) reveals a slightly faster attraction of BSA towards the photochemically activated TiO_2 surface.

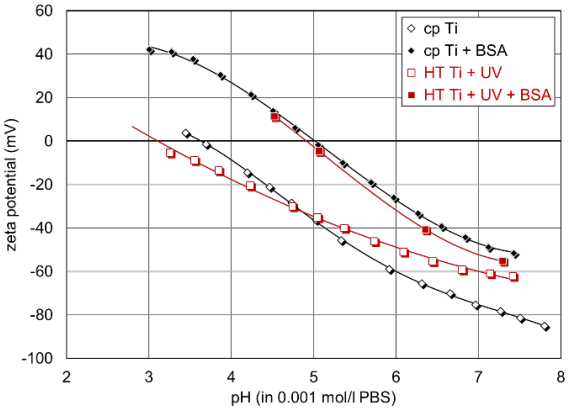

Fig. 1: pH dependence of zeta potential for cp Ti and HT- and UV-treated Ti before and after BSA adsorption.

DISCUSSION & CONCLUSIONS: The streaming potential method enables the analysis of the zeta potential directly at the surface of cp and modified titanium disks, which serve as a model substrate for the study of cell growth and proliferation. Although the net information of the zeta potential reveals only marginal differences between cp and HT-treated Ti, the detailed analysis reveals the transfer from an electrically conductive to a non-conductive surface upon HT growth of a thin-film coating of anatase, and an increase in surface hydrophilicity after UV activation of the TiO_2 top layer. The combination with protein adsorption (kinetics) studies using the zeta potential as an indicator for the increasing surface coverage of Ti and TiO_2 by BSA completes the characterization of the effectiveness of surface treatments.

REFERENCES: [1]Lorenzetti et al., Biomed. Mater. 10, 2015, 045012. [2]Espanol et al., ACS Appl. Mater. Interfaces 8, 2016, 908.

Trends in medical additive manufacturing

D. Seiler

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INTRODUCTION: The Institute for Medical Engineering and Medical Informatics conducts research into diagnostics in living organisms and therapeutic systems. This work focuses on patient-specific solutions and on processing, analysing and communicating medical data. In cooperation with our partners, we address problems from the field of medicine and develop innovative solutions from the initial idea through to a functional model. Our fields of research are implant development, surgical support systems and medical computer sciences. [Ref https://www.fhnw.ch/im2]

The implant development research group has access to outstanding infrastructure and has expertise in developing [1] and testing [2] medical implants, particularly bone replacement materials. Its key competency is designing and producing complex components from polymers, ceramics, metals like titanium and shape-memory alloys [3] in small batches by means of additive manufacturing. Patient-specific implants (Fig. 1) as well as functional implant materials and surfaces [4], e.g. with antibacterial properties, are developed and studied.

SUMMARY: This presentation gives an overview on current trends in medical additive manufacturing and focuses on the different medical applications as well as industry opportunities, challenges and solutions. The latest trends in technology are discussed.

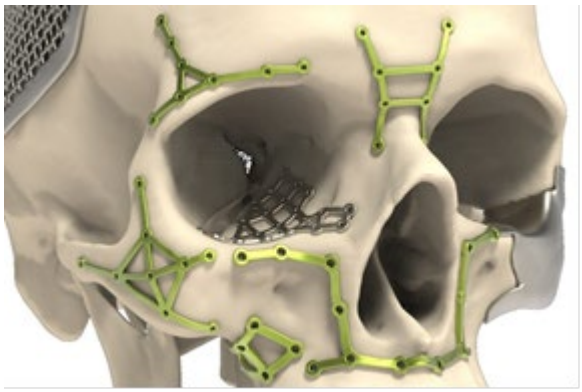

Fig. 1: Additive manufactured patient-specific titanium CMF implants. [Ref www.mimedis.ch]

REFERENCES: [1]S. Zimmermann, M. de Wild, *Density- and Angle-Dependent Stiffness of Titanium 3D Lattice Structures*, BioNanoMat 15 (S1), S35, (2014). [2]R. Schumacher, P. Lamprecht, S. Zimmermann, M. de Wild, A. Spiegel, *Comparison of SLM and conventionally produced implants using dynamic bio-mechanical loading*, RapidTech Erfurt, 2013. [3]Th. Bormann, et al., *Determination of strain fields in porous shape memory alloys using micro computed tomography*, Proc. of SPIE Vol. 7804 78041M-1-9 (2010). [4]M. de Wild, et al., *Surface Modification and In-vitro Investigation of Generatively Produced Implants*, Biomaterialien, 11, 157 (2010).

ZTi-Med®: a potential replacement for Titanium in medical − A dental implant application

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INTRODUCTION: With additive manufacturing (AM) becoming the new production foundry, it is also important to associate new brand of materials to respond to the needs of various industries. New Titanium enhanced powders like ZTi-Powder® have been introduced [1, 2]. ZTi-Powder® can have a role in orthopaedic implants like acetabulum for example.

Titanium alloys such as Ti64 is also widely used in the medical field in dental implants and medical devices manufacturing. However, many studies reported that unsatisfactory loads transfer from the implant devices and the relatively high elastic modulus of implant materials may lead to bone resorption. To overcome these issues, Z3DLAB developed a new dental implant design (DNA implant) and results showed that 84% of the implant's internal volume was colonized by bone cells. These results led to a published research paper in the Helion journal [3]. Also, Z3DLAB developed a new powder family called ZTi-Med® (Figure 1). These powders are called: ZTM35E, TZ10, TNZ14. These powders are characterized by their low elastic modulus (35 GPa compared to 100 GPa found in titanium alloys) and fatigue endurance. This paper shows the different ZTi-Med® materials along with their additive manufactured parts. As an application, a dental implant was manufactured using one of ZTi-Med® powders.

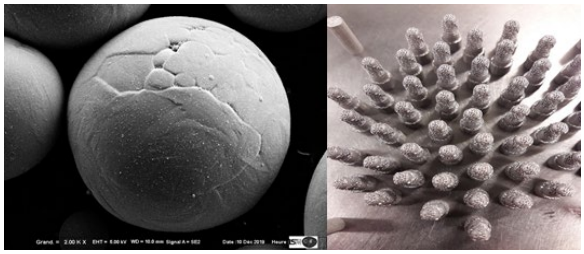

Fig. 1: ZTi-Med® Powder to dental implants, Nano-Zirconia coated on commercially pure Ti particles (left), final dental implant produced by SLM (right).

Table 1. Mechanical properties (ZTM35E)

Properties	Values
Young's Modulus (GPa)	35±3
Compressive Yield Strength (MPa)	624±27
Ultimate Compression Strength (Mpa)	1030±32
Ultimate Compression Strain (%)	58±2
Vickers Hardness (HV0,3)	258±11

DISCUSSION & CONCLUSIONS: In this paper, we show the work on powder preparation and additive manufacturing process that resulted in producing high density parts. The next step will be to investigate this material further using mechanical experiments to validate this low Young modulus and its consequences on stress shielding reduction.

ACKNOWLEDGEMENTS: This template was modified with kind permission from eCM conferences Open Access online periodical & eCM annual conferences.

REFERENCES: [1]Amine Hattal, Thierry Chauveau, Madjid Djemai, Jean-Jacques Fouchet, Brigitte Bacroix, Guy Dirras, *Effect of nano-yttria stabilized zirconia addition on the microstructure and mechanical properties of Ti6Al4V parts manufactured by selective laser melting,* Materials & Design 2019, 107909, Elsevier, doi.org/10.1016/j.matdes.2019.107909. [2]A. Hattal, T. Chauveau, M. Djemai, J.J. Fouchet, B. Bacroix, G. Dirras, *Data related to spectrum analyzes for phases identification, microstructure and mechanical properties of additive manufactured Ti6Al4V reinforced with nano Yttria stabilized zirconia,* Data in Brief, 2020, 29, 105249. [3]A-F. Obaton, J. Fain, M. Djemaï, D. Meinel, F. Léonar, E. Mahé, B. Lécuelle, J-J. Fouchet, G. Bruno, *In vivo XCT bone characterization of lattice structured implants fabricated by additive manufacturing,* Helion Volume 3, Issue 8, August 2017, e00374.

The experience of using custom-made implants for gross acetabular defects

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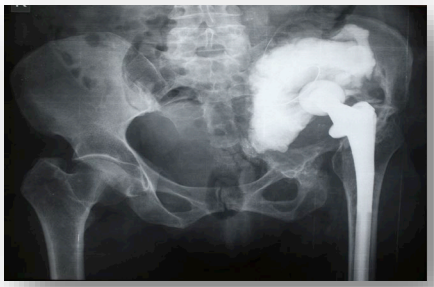
INTRODUCTION: The increasing availability of additive 3D technologies in medicine resulted in the use of individual designs, which minimize bone processing and optimize the fixation possibilities of revision implants. Individual 3D implants, as a rule, are used for the most complex acetabular defects, when the serial implants don't allow to get adequate fixation due to limited contact with host bone.

Purpose — to assess the mid-term results of the custom patient-specific implant for the treatment of severe bone loss in revision total hip arthroplasty.

METHODS: There were 115 acetabular revisions with custom acetabular implants performed from 2016 to 2019 in our hospital. There were 24 augments, 6 hemispherical cup, 2 bilobed cups, 62 triflanged cups and 9 flanged stemmed cups used.

RESULTS: Various patient-reported outcome measures showed in all cases a positive trend in pain, function and quality of life. Migration of the implant with a fracture of the flange was observed in one case (Fig 1).



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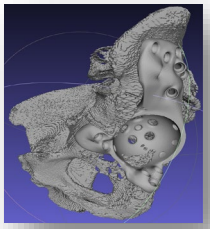

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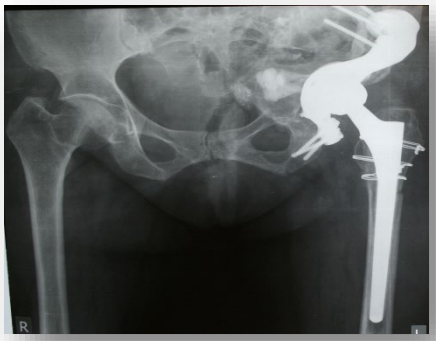

d)

Fig. 1: a) Rg before surgery with gross acetabular defects, b) and c) 3D implant, d) Rg after revision arthroplasty

DISCUSSION & CONCLUSIONS: The use of custom-made implants in the midterm follow-up period significantly improves function of the hip and the quality of life of patients. However, the questions of assessing the strength characteristics of both the developed implants themselves and the implant-bone contact zone remain open, including using finite element analysis, which from our point of view should be an integral stage of the modeling philosophy before printing. In addition, the use of specialized coatings in the area of contact with compromised bone should increase the long-term survival of the developed implants.

REFERENCES:

Kovalenko A.N., Tikhilov R.M., Shubnykov I.I., Bilyk S.S., Denisov A.O., Cherkasov M.A., Ibragimov K.I., *Minimum One-Year Outcomes after Revision Hip Arthroplasty with Custome-Made Implants: Function, Quality of Life and Patients Satisfaction.* Traumatology and Orthopedics of Russia. 2019; 25(1):21-31 (in Russian), https://doi.org/10.21823/2311-2905-2019-25-1-21-31.

4D Printing of Expandable Spinal Cages: Development and Applications

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INTRODUCTION: As the 3D Printing process is maturing, development is now focused on new materials for new applications. Some materials, such as shape memory alloys introduce an additional dimension that leads to a new nomenclature: 4D Printing. In the medical industry, shape memory alloys are typically used for stents and cardiovascular implants. However, shape memory alloys are difficult to process conventionally, and their shapes are limited [1]. Additive manufacturing processes such as laser powder bed fusion allow to overcome these limitations and offer the opportunity to produce new types of implants [2]. In this regard, expandable spinal cages were designed and developed for 4D Printing.

METHODS: Development of the expandable spinal cages was divided in two steps: Material development and design development.

Process development: From bibliography [3], several parameters sets were selected and adapted to a TruPrint1000 (Trumpf, Ditzingen, Germany). A design of experiment (DoE) was conducted, adapting parameters sets while increasing complexity in geometries: from weld seams to medical devices samples. Evaluation criteria thus evolved from visual inspection and ability to produce parts to density and mechanical properties of produced parts.

Design development: Additive manufacturing offers several design advantages, such as lattice structures, improving osseointegration, and design freedom. Moreover, expandable cages allow minimally invasive surgical approaches and a decrease in morbidity [4].

Design was done with CAD software Fusion 360 (Autodesk, USA), and focused on developing a structure that would exploit shape memory properties.

RESULTS: A low laser power, low speed parameter set was found to give the best quality for parts with high density (> 99 %). Surface state has a high influence on mechanical properties. Transformation temperatures are impacted by the thermal history; however, they are difficult to tailor with process parameters due to their connection to the structure and quality of the processed part. From a design point of view, 3D auxetic lattice structures were selected and used for their properties and responses to compression.

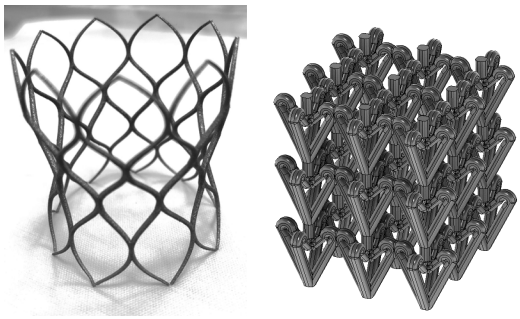

Fig. 1: 3D printed NiTinol aortic valve support (left), auxetic 3D lattice structure (right).

DISCUSSION & CONCLUSIONS: While shape memory alloys can be processed with additive manufacturing, the DoE highlighted some process limitations. Next development will be focused on chemical composition of the alloy, post-process steps, surface treatment and heat treatments, to ensure thermo-mechanical properties of the device, especially with a medical intended use. Design development will be pursued on expandable cages.

REFERENCES: [1]Lagoudas, D.C., Shape Memory Alloys, Springer, 2008, 435p. [2]Dadbakhsh, S., Speirs, M., Van Humbeeck, J., & Kruth, J. (2016), *Laser additive manufacturing of bulk and porous shape-memory NiTi alloys: From processes to potential biomedical applications,* MRS Bulletin, 41(10), 765-774. https://doi:10.1557/mrs.2016.209. [3]Dadbakhsh S., Speirs, M., Kruth J.P., (2014) *Effect of SLM Parameters on Transformation Temperatures of Shape Memory Nickel Titanium Parts: Effect of SLM Parameters on Transformation Temperatures of NiTi,* Advanced Engineering Materials, 16(9): 1140-1146. https://doi.org/10.1002/adem.201300558. [4]Hammad, A., Wirries, A., Ardeshiri, A. et al., *Open versus minimally invasive TLIF: literature review and meta-analysis,* J Orthop Surg Res **14,** 229 (2019). https://doi.org/10.1186/s13018-019-1266-y.

Industrial sterilization methods - an overview

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INTRODUCTION: Sterilisation is a method to reduce living microorganisms on dedicated objects. To reduce microorganisms there are basically two approaches: physical (e.g. irradiation, heat, filtration) and chemical (e.g. ethylene oxide) methods.

METHODS & RESULTS:

Irradiation method:
When focusing on irradiation methods, typically Gamma irradiation is the method of choice for industrial sterilization application. In the last years due to sourcing problem of Co^{60} and stronger regulation requirements, alternative methods are in focus. X-ray seems to be a promising alternative, as no waste is generated, no external source than electrical power is needed and the dose distribution within a pallet seems to be much more even than with a Gamma source. To evaluate the proper sterilisation method not only material properties are to be taken in consideration, but also a proper packaging configuration.
Industrial sterilisation methods are well defined in ISO norms, such as ISO 11137 for Gamma/e-beam/X-ray irradiation:
This norm is separated in 4 parts, which cover the following topics:
1. General requirements for the validation.
2. Dose establishment/monitoring of a proper method.
3. Dose mapping.
4. Dosimetry.

EO (ethylene oxide)
Beside irradiation method, EO treatment is a commonly used method for industrial sterilization. This method is regulated in ISO 11135. The agent is a gas, which inactivates together with humidity the microorganism. For the validation of this process physical (temperature, humidity, pressure) parameters, as well as microbial parameters must be taken in consideration and properly evaluated. Commonly used packaging component, which allows gas penetration but no microbial penetration is the Tyvek material.

DISCUSSION & CONCLUSIONS:

Irradiation method:
Advantage: Treatment at relatively low temperature; penetration of the whole pallet; parametric release possible; fast treatment method.
Disadvantage: Not all materials can be applied due to material property change (e.g. PE); in case of Gamma irradiation: high dependence on external Co^{60} source.

EO (ethylene oxide)
Advantage: Low cost gas; relatively low temperature application; usually no significant material property change.
Disadvantage: Long treatment time (de-gassing); microbial release (no parametric release); high security standard (EO is very well flammable).

REFERENCES:
ISO 11137: *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.*
ISO 11135: *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices.*

Don´t forget to think about family grouping before doing reprocessing validations of medical devices and instruments!

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INTRODUCTION: Validating the cleaning and sterilization processes that occur at healthcare facilities is costly and orthopaedic and surgical implant device manufacturers could be spending a lot more time and money on testing by not considering family grouping when performing these validations. Validating cleaning and sterilization processes is an important and necessary step in ensuring patient safety and minimizing healthcare-acquired infections, corrective actions, and recalls. Family grouping or selecting a worst-case device (or devices) to perform these validations can be used by device manufacturers in many cases except when the device is very unique and specialized. These devices must be individually validated.

METHODS & RESULTS:

Cleaning Validation Family Grouping:

Performing a cleaning validation is a necessary step in order to evaluate the effectiveness of the cleaning process. To save time and money, manufacturers can choose to family group the devices for validation. There are three main approaches to evaluating whether family grouping is appropriate for the medical devices a manufacturer is validating—device use, material type, and device design.

Device Use: If the devices have similar use during surgical procedures, they can be grouped by their function, use, and degree of patient contact. Similarly configured devices or parts used for generally the same purpose and that contact comparable amounts of human tissue, blood, mucus, etc. may be grouped together for validation.

Material Type: If a group of devices are made out of the same metals and soft materials, they could qualify for family grouping. Devices are made from materials ranging from metal to ceramic to polymers, and sometimes, a mix of several materials. Each of these materials holds onto residue differently and, therefore, should be grouped accordingly.

Device design: Medical devices of similar size and challenge features may be grouped together as a family. The considerations that are employed in this type of grouping include the number of components, design challenges for cleaning and surface area.

In addition to considering the devices themselves, reprocessing instructions must be evaluated because only devices that go through the same reprocessing instructions can be divided into family groups.

Steam Sterilization Validation Family Grouping:

Family grouping for steam sterilization validations requires different considerations as compared to family grouping for cleaning. Additionally, whereas family grouping for cleaning validations will mostly consider worst-case devices, family grouping for steam sterilization may include the selection of a worst-case tray configuration (if appropriate). ISO/TS 17665-3:2014/(R) 2016 offers guidance to performing family grouping for steam sterilization validations by evaluating steam penetration resistance, device design, materials, weight as well as packaging.

Knowing the type of packaging is crucial for family groupings and packaging must be a part of the evaluation given that packaging sizes vary and influence volume-to-vent ratios.

DISCUSSION & CONCLUSIONS: Family grouping of medical devices or trays for cleaning or steam sterilization validations is very important. Validating every device or tray is not necessary, but also not preferred due to the cost and time of the validations. On the other hand, choosing worst-case devices and the rationale why other devices and trays would be adopted by these devices must be thoroughly justified and documented. The justifications must also be submitted to the FDA or the appropriate regulatory agency.

REFERENCES: ANSI/AAMI/ISO 17664:2017; AAMI TIR12:2020; FDA 2015/(R)2017. Guidance for Industry and FDA Staff –Processing/Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling; ISO/TS 17665-3:2014/(R) 2016.

Cleaning validation for instrument reprocessing: normative background and the test methods

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[1] *RMS Foundation, Bettlach, CH*, [2] *New affiliation: Stryker GmbH, Selzach, CH*

INTRODUCTION: Surgical instruments are often used during medical device implantation. Once used, the instruments have to be cleaned, disinfected and sterilized in a so-called reprocessing process. It is the responsibility of the companies selling the instruments to inform hospitals how to reprocess the instruments and to make sure that the reprocessing steps meet minimal requirements. The aim of this communication is to briefly review the normative background and the test methods available for cleaning validation of reusable medical devices.

METHODS: Reusable surgical instruments are the devices "*intended for surgical use in cutting, drilling, sawing, scratching, clamping, retracting, clipping or similar procedures, without a connection to an active device and which is intended by the manufacturer to be reused after appropriate procedures such as cleaning, disinfection and sterilization have been carried out*" [1]. According to the Medical Device Regulation (MDR) [1] that is in force since 25 May 2017, reusable surgical instruments are classified as class Ir medical devices ("r" stays for "reusable"). Usually, the conformity assessment of class I medical devices does not involve a notified body. However, for the class Ir medical devices, a notified body is involved in the aspects related to the reuse of the device, such as cleaning, disinfection, sterilization, etc.

RESULTS: Cleaning reusable surgical instruments can be considered one of the most difficult processes to monitor. ISO 17664:2017 [2] specifies that the manufacturers of reusable medical devices shall provide validated cleaning instructions with their products (at least one validated method). Unfortunately, existing standards, recommendations, and guidelines relevant for cleaning validations are inconsistent.

For example, ISO 15883-1:2006 [3] and ISO/TS 15883-5:2005 [4] are two of the key standards relevant to the cleaning validations of reusable surgical instruments. However, these standards do not provide well-described methods for demonstrating cleaning efficacy and clear acceptance limits for the protein contamination. Therefore, they must be taken elsewhere. Both standards are under revision currently.

Depending on the market where the reusable medical surgical instruments are sold, there are different acceptance limits for the residual protein contamination. For example, the FDA uses concentration-based values (certain amount of residues per surface), while the European approach is more amount and geometry based (absolute amount of residues per instrument).

In order to assess the cleaning performance, different protein marker detection methods exist: e.g. BCA assay, OPA-method, ninhydrin method, radionuclide method, etc. Each of these methods has advantages and disadvantages, and interferences are often observed. For example, the BCA assay is one of the most widespread assays used for cleaning validation of reusable surgical instruments. However, Fe cations and organic residues (especially lipids) from the production can interfere with this assay.

DISCUSSION & CONCLUSIONS: The manufacturers of reusable medical devices face a number of challenges due to the existing inconsistent standards, recommendations and guidelines. On the one hand, there are strict regulatory/legal requirements. On the other hand, there are many gaps in the current standards, recommendations, and guidelines regarding the implementation of cleaning validations and their methods.

REFERENCES: [1] Medical Device Regulation (MDR), Annex VIII, Chapter I. [2] ISO 17664:2017, *Processing of health care products – Information to be provided by the medical device manufacturer for the processing of medical devices*. [3] ISO 15883:2006, *Washer-disinfectors – Part 1: General requirements, terms and definitions and tests*. [4] ISO/TS 15883-5:2005, *Washer-disinfectors – Part 5: Test soils and methods for demonstrating cleaning efficacy.*

A novel post-treatment process of medical and pharmaceutical material using $scCO_2$

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INTRODUCTION: Supercritical fluid-based extraction procedures, such as extraction of active compounds and removal of impurities, have been established as important processes since decades. The main advantages of using supercritical fluids resides in the tunable solvation properties based on temperature and pressure, moreover they also possess high diffusivity, low viscosity and absence of surface tension as there is no liquid to gas phase boundary.

METHODS: The use of supercritical carbon dioxide ($scCO_2$) in the post-treatment of medical and bio-material, such as implantable membranes, for final impurities removal or impregnation with active pharmaceutical ingredients (APIs), is becoming very important nowadays. There are several advantages in the use of $scCO_2$ as solvent such as low toxicity, negligible residuals as well as bacterial inactivation. Furthermore, the mild pressure and temperature (73 bar, 31 °C) needed to reach supercritical conditions allows to work with sensitive materials and products without damaging them. Moreover, classical extraction and impregnation methods based on alcohols and hydrocarbons compared to $scCO_2$ method show several drawbacks, such as low diffusion rate, long process time and high temperatures. Furthermore, in many cases hazardous solvents are used which imply increased efforts to remove the solvent or additional installation costs.

RESULTS: However, the implementation of a successful treatment process which can either be applied for impurities removal as well as for APIs impregnations is very challenging. Indeed, homogeneous conditions must be assured through the entire batch volume, in order to achieve the desirable product characteristics and robust reproducibility. The post-treatment process developed by eCO_2 is able to face all those challenges leading to cGMP compliant product purities and characteristics between the production batches.

The innovative nature of the process lies in the horizontally placed process chamber equipped with a special rotatable basket, depicted in Figure 1, which ensure homogeneous conditions throughout the entire process chamber volume. Furthermore, the basket design can be customized according to the material to be treated, thus maximizing the contact area with $scCO_2$. The rotation of the basket enhances mass transfer between $scCO_2$ and treated materials. Simultaneously, the absence of surface tension of the $scCO_2$ improves the penetration inside the material matrix, enhancing the diffusion and thus the mass transfer. These process features are essential for ensuring homogeneous conditions throughout the entire process, which is of paramount importance for the quality of the final product and thus for its reproducibility.

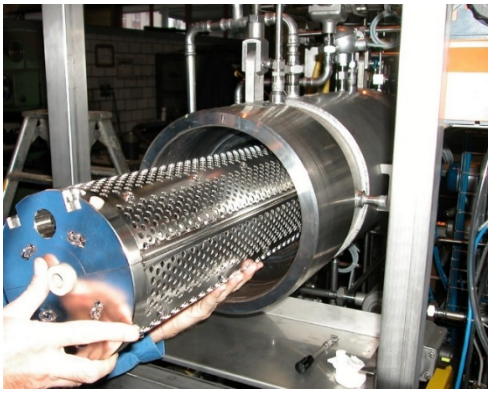

Fig. 1: Picture of the horizontally placed process chamber with the special rotatable basket.

DISCUSSION & CONCLUSIONS: The new proposed post-treatment process has been proved very promising as substitute of standard solvent-base processes. The tunability of the solvation properties by mild temperature and pressure conditions coupled with the rotation of the basket and the horizontal process chamber lead to homogeneous conditions. This involves, for the case of impurity removal treatments, a reduction by factor 10 of both process time and raw material expenses compared to the classical approaches. The homogeneous conditions, the even impurity removal or APIs impregnation and the batch-to-batch reproducibility make the proposed process compliant with the cGMP standards and, thus, can be applied in the pharmaceutical, medical, and food industries.