

[MEET THE EXPERT]

IMPLANTS

Technologies - Markets - Trends

28 - 29 April 2014

Congress Centre Kursaal Interlaken
CH-3800 Interlaken

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Conference Documentation

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General Information

How to get to the Congress Centre Kursaal Interlaken (CKI)

The Congress Centre Kursaal Interlaken is easily accessible by car and by train. For directions please visit <http://www.congress-interlaken.ch/en/>

Please use the north entrance at the Strandbadstrasse 44 (Riverside, see arrow). You can find the reception and registration desk directly at this entrance.

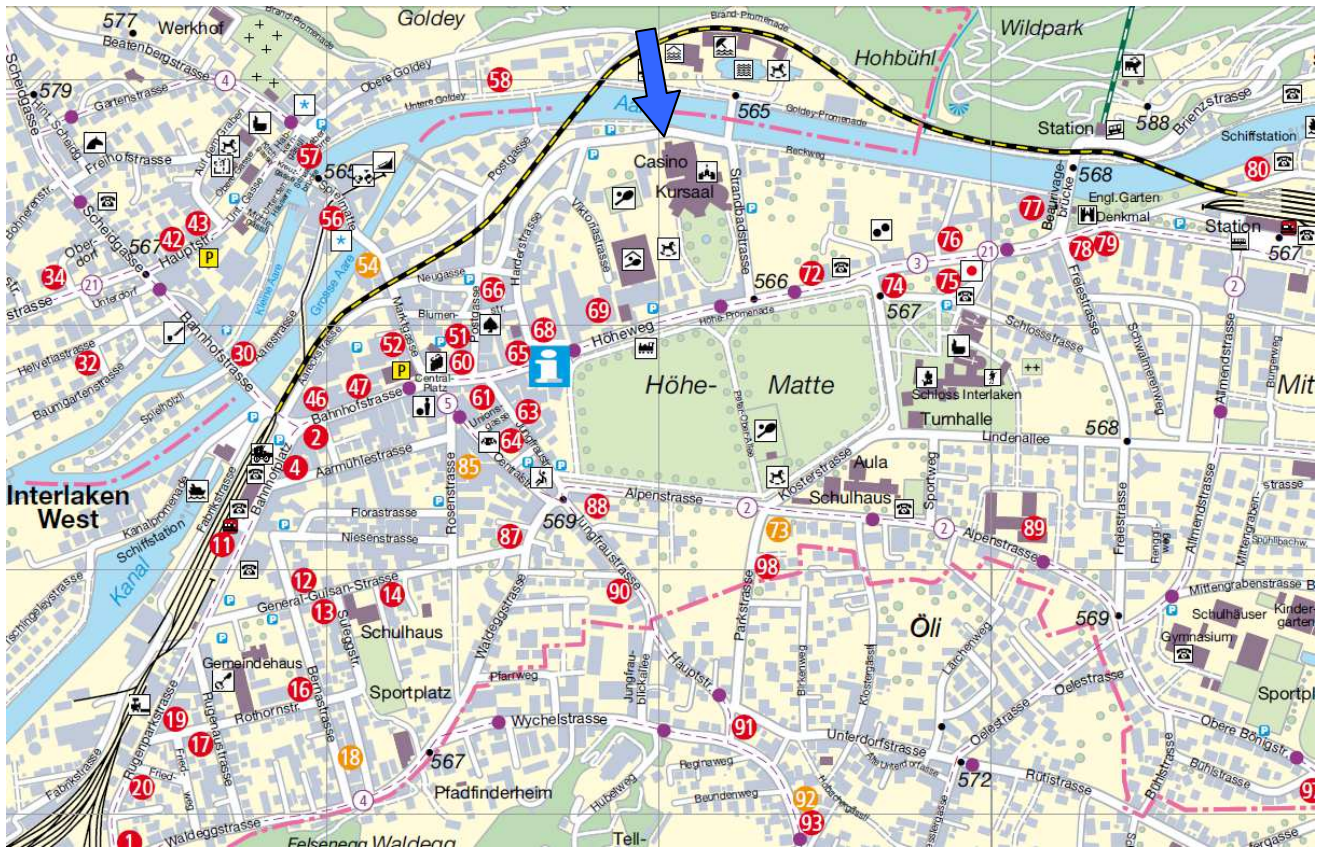
Parking

The parking lot of the Congress Centre Kursaal can be used. Congress-Tickets for CHF 6.00 per day are available at the reception desk of the CKI.

Wardrobe

An unattended cloakroom is next to the reception of CKI in the basement (no liability).

Site map



68 Hotel Metropole (Conference Dinner)

Conference Session of the Swiss Contamination Control Society (Swiss CCS)



The Swiss CCS is holding its Spring Meeting on Monday 28th April as a parallel program to the [MEET THE EXPERT] Conference. The participation in the sessions of Swiss CCS is possible for all attendees. The full program is listed on page 8 of this conference documentation. Please note that all presentations of the Swiss CCS session will be in German without translation to English.

Aperitif

The Aperitif in the poster and exhibition area (Monday 17:10 – 18:30 h) is kindly supported by the municipality of Interlaken.



Dinner

The Conference Dinner will be held on **Monday 28th April 19:00 h** at the **Hotel Metropole**. The Hotel Metropole is located close to the Congress Centre Kursaal at Höhweg 37.

Conference Secretariat

The conference secretariat is managed by Mrs Doris Loretan.

Availability during the meeting: phone +41 76 324 31 15

doris.loretan@medical-cluster.ch

Powerpoint Presentations

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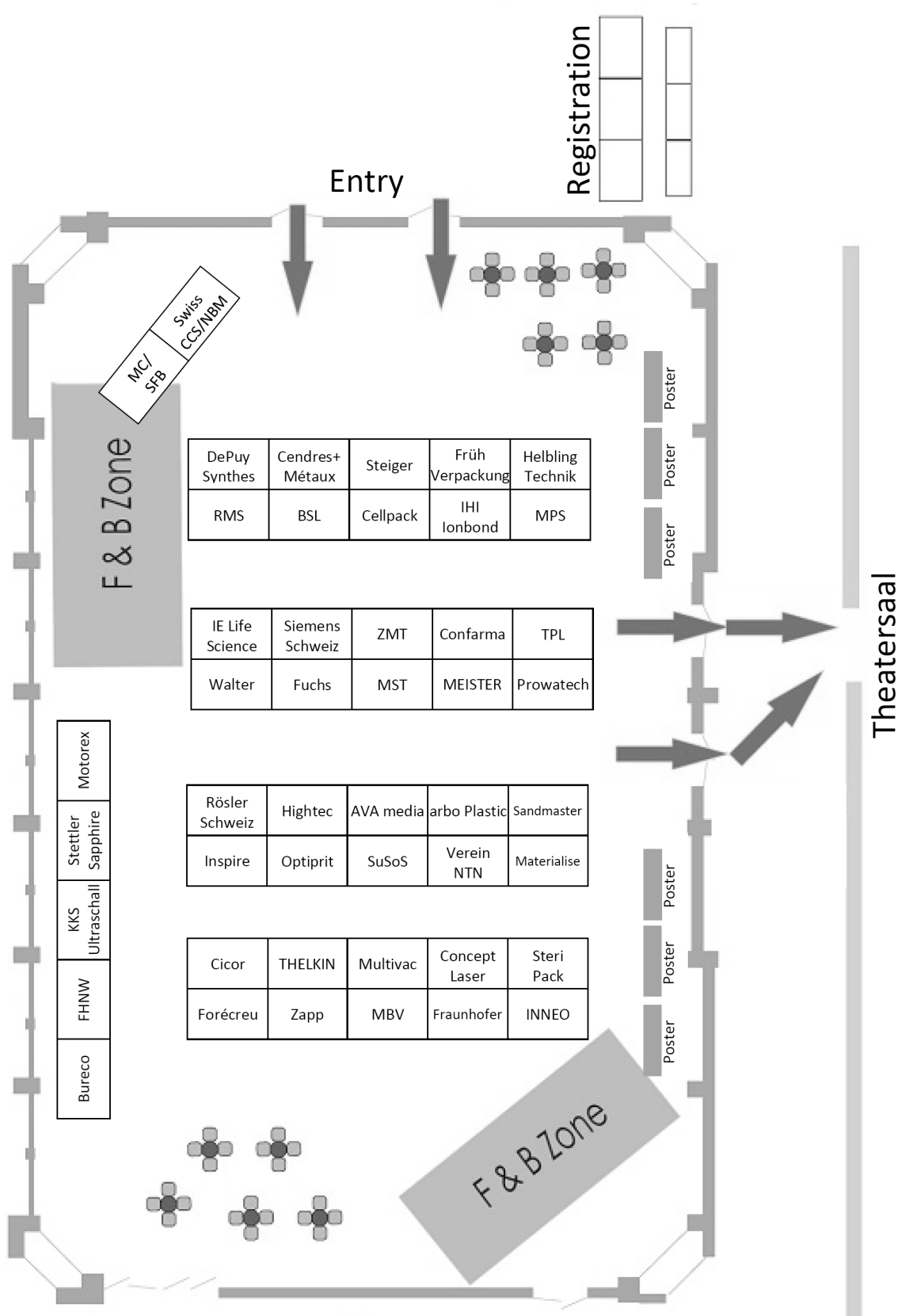
Publication

All abstracts that qualify will be published online in a Supplement volume of the open access Journal eCells & Materials (eCM): www.ecmjournal.org

Please register on the eCM site for paper notification.



Exhibition Area



Meeting Program

Monday 28th April 2014

From 09:30	Registration	
10:00 - 10:15	Welcome	
	Session 1	
	Chair: Dr. Lukas Eschbach	
10:15 - 11:00	<i>«The new innovator's dilemma» - delivering value through innovation (EN)</i>	Douglas Bireley, DePuy Synthes, CH
11:00 - 11:30	<i>Keynote 1: Deep brain stimulation - clinical aspects and perspectives (DE)</i>	Prof. Dr. Volker Sturm, International Neuroscience Institute Hannover, Germany
11:30 - 12:00	Flash presentations exhibitors	
12:00 - 13:15	Lunch (Exhibition and Posters)	
	Session 2	
	Chair: Dr. Lukas Eschbach	
13:15 - 13:45	<i>Keynote 2: Advanced manufacturing - challenges and trends (DE)</i>	Prof. Dr.-Ing. Konrad Wegener, Institut für Werkzeugmaschinen und Fertigung IWF, ETH Zürich, CH
13:45 - 14:15	<i>Keynote 3: Coating-free bioactive surface for coronary stents (DE)</i>	Dipl. Phys. Arik Zucker, Qvanteq AG, CH
14:15 - 14:45	<i>Keynote 4: Active ophthalmic implants (DE)</i>	Dr. Lukas Scheibler, Alcon Laboratories, Inc, USA
14:45 - 15:05	Flash presentations posters	
15:05 - 15:30	Break (Exhibition and Posters)	
	Session 3a: Surfaces and Coatings	Session 3b: Electro-Active Implants
	Chair: PD Dr. Christiane Jung	Chair: Dr. Urban Schnell
15:30 - 15:50	<i>Trends in surface treatments of implantable devices (DE)</i>	<i>Sim4Life: A simulation platform for life sciences and medtech applications (EN)</i>
	Helge Luesbrink, PVA Tepla America, Inc, USA	Maria Del Mar Miñana Maiques, ZMT Zurich MedTech, CH
15:50 - 16:10	<i>Innovative antibacterial and osseointegrative treatment for endosseous implants (EN)</i>	<i>Sending implant data to the cloud (EN)</i>
	Dr. Luca Facchini, Eurocoating s.p.a., Italy	Albrecht Lepple-Wienhues, Valtronic, USA
16:10 - 16:30	<i>Innovative coatings on PEEK substrate for orthopaedic implants (EN)</i>	<i>Humidity management in active implantable medical devices (DE)</i>
	Céline Harnisch, Alhenia AG, CH	Dr. Hans Bernhard, Helbling Technik Bern AG, CH
16:30 - 16:50	<i>Improved tribological performance of PEEK polymers by application of diamond-like carbon coatings (EN)</i>	<i>It's all about value: MST's EMS+ concept for manufacturing of complex active implants (DE)</i>
	Pawel Tomaszewski, Orthopaedic Research Lab, the Netherlands	Michael Fink, Micro Systems Technologies Management AG, CH
16:50 - 17:10	<i>A microporous ceramic implant surface - In Vitro and In Vivo experiences (DE)</i>	<i>MR safety evaluation of implantable medical devices: RF-induced heating (EN)</i>
	Franz Berghänel, Metoxit AG, CH	Prof. Dr. Niels Kuster, IT'IS Foundation, CH
17:10 - 18:30	Aperitif / Exhibition / Posters	
From 19:00	Dinner at Hotel Metropole	

Meeting Program

Tuesday 29th April 2014

Session 4

Chair: Prof. Dr. Michael de Wild

- 08:30 - 09:00 *Keynote 5: Passive implants in orthopaedics - what can be improved ? (DE)*
Dr. med. Claudio Rosso, Universitätsspital Basel, CH
- 09:00 - 09:30 *Keynote 6: Challenges in electro-mechanical implants (DE)*
Dr. Marco Wieland, Myopowers SA, CH
- 09:30 - 10:00 *Keynote 7: Medtech startup in Switzerland - a model for the future? (DE)*
Dipl. Ing. Ralf Schumacher, Mimedis AG, CH
- 10:00 - 10:30 Break (Exhibition and Posters)

Session 5a: Implant Requirements & Biocompatibility

Chair: Lukas Märklin

- 10:30 - 10:50 *The interaction of blood components with titanium implant surfaces is a decisive marker for osseointegration of bone implants (DE)*
Angela Schipanski, EMPA St. Gallen, CH
- 10:50 - 11:10 *Usability-results through human centered design and test models (DE)*
Raimund Erdmann, Erdmann Design AG, CH
- 11:10 - 11:30 *New requirements for registration and biocompatibility of implants (DE)*
Dr. Anja Fritsch, CONFARMA France SARL, France
- 11:30 - 11:50 *Biological evaluation according to ISO 10993-1: Methods and obstacles (DE)*
Dr. Reto Luginbühl, RMS Foundation, CH
- 11:50 - 12:10 *Biological safety assessment of medical device implant sets (DE)*
Dr. Frank Wirsching, BSL BIOSERVICE Scientific Laboratories GmbH, Germany

Session 5b: Implant Materials

Chair: Prof. Dr. Michael de Wild

- High strength titanium: a new candidate for implant materials (DE)*
Dr. Florian Dalla Torre, Institut Straumann AG, CH
- Numerical simulation of a transcatheter aortic valve (DE)*
Joël Grognez, CADFEM (Suisse) AG, CH
- Development of a test model to evaluate the pre-load of screw-retained dental implant systems (DE)*
Thomas Vizer, Nobel Biocare Services AG, CH
- Applications of atomic layer deposition in implant dentistry (EN)*
Anatoly Solovyev, MIPT, Russia
- Design optimization of a ceramic hip cup (DE)*
Sebastian Valet, EMPA Dübendorf, CH

12:10 - 13:30 Lunch (Exhibition and Posters)

Session 6: Markets and Trends

Chair: PD Dr. Christiane Jung

- 13:30 - 14:00 *Keynote 8: The way how products come to market - biomechanical testing of an intramedullary nail as an example (DE)*
Andy E. Schwammberger, Zimmer Trauma, CH
- 14:00 - 14:20 *The orthopaedics market in transition (DE)*
Dr. Martin Schmidt, Jossi Orthopedics AG, CH
- 14:20 - 14:40 *Bringing new spinal implants to market: fundamentals and evolutions in development techniques (EN)*
Dr. Henri Defossez / Ralf Klabunde, DePuy Synthes Spine, CH
- 14:40 - 15:00 *ZfW 102 / Magnezix® the successful way to magnesium based biodegradable implants (DE)*
Prof. Dr. Volkmar Neubert, Institut für Materialprüfung und Werkstofftechnik, Germany
- 15:00 - 15:20 *Short dental implants: clinical and technical challenges (DE)*
Dr. Christian Frei, Institut Straumann AG, CH
- 15:20 Conference end

Poster Session

- 1 *Production of Micro/Nano structured Materials by Metal Injection Moulding (MIM) and its effect on human bone marrow stromal cells*
Dr. Arie Bruinink, EMPA, CH
- 2 *Post-hot isostatic pressing: A healing treatment for process related defects and laboratory grinding damage of dental zirconia?*
Jakob Kuebler, EMPA, CH
- 3 *A new era for porous tantalum biomaterials thanks to Additive Manufacturing: a clinical proof-of-concept*
Ruben Wauthle, Christian Wiel, LayerWise NV, Belgien
- 4 *Release kinetics of electrochemically deposited antibacterial copper from anodized titanium implant surfaces*
Prof. Dr. Michael de Wild, FHNW, CH
- 5 *Roughness of plasma sprayed HA-ZrSiO₄ composite coatings*
Dr. Hassan Gheisari Dehsheikh, Shahreza University, Iran
- 6 *Population Based Design Validation of a Subcutaneous Bone Conduction Implant System*
Dr. Tobias Wagner, Materialise, Deutschland
- 7 *Aqueous Cleaning of Medical Devices: Characterization of Ultrasound in the Cleaning Bath*
PD Dr. Christiane Jung, KKS Ultraschall AG, CH
- 8 *iPROMEDA: A National and European initiative to reduce the risk of implant associated infection*
Dr. Reto Luginbühl, RMS Foundation, CH
- 9 *Biologische Beurteilung nach ISO 10993-1: Vorgehen und Struktur*
Ursula Rösler, Axxos GmbH, CH
- 10 *Ein experimentelles Modell für das Training von endoskopischen transsphenoidalen Hypophysenchirurgie*
Raphael Schmid, inspire AG, CH
- 11 *Nano-Enabled Smart Dressing For Wound Care*
Shruti Mankar, Indian Institute of Technology, Indien
- 12 *X-Ray Microscopy to determine the surface interaction between osteoplasts and a titanium surface in 3D*
Dr. Antonio Casares, Carl Zeiss AG, CH

Parallel session of the Swiss Contamination Control Society (Monday 28th April)

The participation in the session of Swiss CCS is possible for all attendees.



08:30	Eintreffen, Kaffee, Gipfeli	
09:00-9:45	Generalversammlung SwissCCS (SRRT) (Gäste und Neumitglieder willkommen)	Hans Zingre Präsident
10:00-12:00	Programm gemäss MTE Meeting Programm	
12:00-13:15	Mittagspause (Ausstellung und Poster)	
	Session 2a: SwissCCS (SRRT) „Contamination Control“ for Medical Devices Saubere Produktion – notwendige Infrastrukturen	
13:15-13:45	1. Übersicht Kontrollierte Bedingungen (DE) - Risikobetrachtung des Herstellungsprozesses - Prozesse ermöglichen - Mitarbeiter- und Umweltschutz sicherstellen	Arnold Brunner Dozent HLK, HSLU Hochschule Luzern, CH
13:45-14:15	2. Reinhaltung im Betrieb (DE) - Hinweise zum Aufbau eines optimalen Reinraumreinigungskonzeptes. - Von der Personal- bis zur Matreialauswahl	Frank Duvernell Reinraum Akademie Wangen a/Aare, CH
14:15-14:45	3. Reine Luft - Die Luftfiltration (DE) - Grundlagen der Partikelfiltration - Filterklassierung nach EN 1822 und ISO 29463 - Filterabstufungen - spezielle Filter-Auslegungen	Andreas Nägeli Leiter Entwickl. UNIFIL Niederlenz, CH
14:45-15:15	4. Medizinische- bzw. pharmazeutische Druckluft (DE) - Regulatorische Anforderungen an die Druckluft / Gase - Messungen von max. zul. Gehalt von Spurengasen - Messung von Wasser u Oeldampfgehalt, Partikelreinheit, Drucktaupunkt und Mikrobiologie.	Norbert Otto Geschäftsführer C-tec Rottenburg a.N., D
15:15-15:30	Pause (Ausstellung und Poster)	
15:30-15:50	5. Wasserqualität in der Medizintechnik (DE) - Wasser Spezifikationen und Ihre Anwendungen - Vom Trinkwasser zum „Medizin“ Wasser - Energie Effiziente Wasser Erzeugung ist das möglich?	Marcel Zehnder Manager Sales BWT AQUA AG Aesch BL, CH
15:50-16:10	6. Fabrikplanung & Raumkonzept (DE) - Material- und Personenflüsse, Dokumentenmanagement - User Requirement Specification URS / Projektpflichtenheft - Prozessequipment, Rauml原因, Infrastruktur - Zonenkonzept, Reinheitskonzept, Lüftungskonzept - Planung der Planung, Realisierung, Qualifizierung, Validierung	Arnold Brunner Dozent HLK, HSLU Hochschule Luzern, CH
16:10-16:30	7. Klima und Reinraumkonzept (DE) - Aussenluft und Umluft inkl FFU Konzept - Druckhaltung, Schleusenkonzept - Energiebetrachtung	Werner Straub Leiter Verkauf Reinraumtechnik Cofely AG, Zürich
16:30-16:50	8. Personal - die Kontaminationsquelle Mensch mit Liveschaltung BodyBox (DE) - Die Partikelabgabe von Mitarbeitern in unterschiedlichen Bekleidungssystemen - Live-Demonstration in einem Test-Reinraum / Body-Box - Was ist bei solchen Untersuchungen zu beachten? - Wie beeinflusst die Reinraumkleidung den gesamten Reinraumprozess	Carsten Moschner Dastex Reinraumzubehör GmbH & Co.KG, Muggensturm, D
16:50-17:10	9. Hybrid-Forschungsprüfstand „LORA“ der Hochschule Luzern (DE) - Projekt angewandte Forschung im Bereich Reinraumtechnik - Welche Vorteile hat eine Beteiligung als Industriepartner - Wie können Produktionsbetrieb davon profitieren	Arnold Brunner Dozent HLK, HSLU Hochschule Luzern, CH
17:10-17:20	10. Diskussionsrunde und Abschluss	Werner Straub

Trends in surface treatments of implantable devices

H Luesebrink¹, M Barden²

¹ PVA Tepla AG, Feldkirchen, DE. ² PVA Tepla America, Corona, CA, USA

INTRODUCTION: The continued evolution of implantable devices includes advances integrating technologies from the pharmaceutical, biomaterials and microelectronics industries. Along with the emphasis on miniaturizing devices to limit invasiveness and improve safety, these “*Combinatorial Products*” present challenges for selective surface modifications. Plasma treatment and deposition processes provide excellent methods to modify the surfaces of biomaterials and enhance their performance in implantable medical devices. Herein we discuss trends in plasma processes which improve precision cleaning, adhesion and bonding, biocompatible nanocoatings and 3d architecture.

METHODS: Eligible case studies on plasma treatment were separated into 4 areas: precision cleaning; improved bonding performance; biocompatible coatings; and surface roughness. Inclusion criteria were set as follows (1) projects had a clear outcome; (2) they included a follow-up study or validation process; (3) minimum samples were 25; and (4) an implant device was involved.

We searched our in-house project database from 2010-2013 searching for “surface implant treatment.” Using the inclusion criteria, we selected 22 of 707 projects.

All precision cleaning, activation and plasma-enhanced chemical vapour deposition (PECVD) experiments were conducted using a multi-shelf parallel plate capacitance electrode in a 40 L aluminium chamber [1]. The plasma was ignited with a 13.56 MHz power supply through an impedance matching network. Gas flow rates and pressure were regulated and controlled by means of electronic mass flow controllers (MFC) and capacitive pressure gauge (Baratron MKS Instruments). The system was pumped down with a rotary pump to a base pressure of 10mtorr. Real-time plasma process parameters (pressure, flow, power, reflected power, etc) were recorded every second and stored in an Access database for future reference.

RESULTS: Selected projects were broken down as follows: plasma cleaning (6); treatments for improved bonding (4); biocompatible coatings (4); cell adhesion coatings (4) lubricious coatings (3); and superhydrophobic coatings (1).

Precision Cleaning: O₂ plasma cleaning still dominates this area. The process usually involves high pressure and low power to minimize physical damage to the surface while maximizing the chemical cleaning aspects. PEEK spinal implants and titanium hip replacements were commonly cleaned in this fashion.

Improved Bonding Treatments: there were 3 common methods to creating low energy surfaces for improved bonding: physical or ablative methods to disrupt surface energy using argon plasma; chemical bond breaking and reorganization using O₂ plasma; and reduction of fluorinated surface using NH₃ plasma.

Biocompatible Coatings: PECVD of sublimed lactic acid and amphiphilic phosphorylcholine are coatings we investigated for use on stents.

Cell Adhesion Coatings: porous substrates such as wound healing membranes, spinal implant rods and stents respond well to pulse plasma coating of amine based cell adhesion coatings.

Lubricious Coatings: flexible tie-layer strategies were used to create hydrophilic or lubricious coatings on bendable devices such as flex circuits, guidewires and catheters.

Superhydrophobic Coatings: micro-nanobinary structured anti-wetting coatings typically used in microelectronics have seen cross-over as antimicrobial coatings on wound healing scaffolds.

DISCUSSION & CONCLUSIONS: The following observations were made as a result of reviewing the process parameters:

- cleaning and surface activation are still major plasma processes for implants;
- trending towards surface coatings for cell binding and compatibility.

REFERENCES: ¹ Ion series tool from PVA Tepla America.

ACKNOWLEDGEMENTS: The authors wish to thank Demetri Chrysostomou, Ray Chen and Luke Turalitsch for useful discussions.

Innovative antibacterial and osseointegrative treatment for endosseous implants

L Facchini¹, F Bucciotti¹, C Della Valle², R Chiesa²

¹ Eurocoating s.p.a., Ciré di Pergine Valsugana, I. ² Department of Chemistry, Materials and Chemical Engineering, Politecnico di Milano, Milano, I.

INTRODUCTION: Titanium and titanium alloys are widely used for dental and orthopaedic implants. Surface modification is often applied to improve osseointegration and to increase clinical performance of the implants. Nevertheless, some complications may arise, and infections are often the reason of implant mobilization and failure.

An innovative biomimetic treatment capable to modify the surface titanium oxide by the insertion of specific ions was developed and tested. The main aim of this treatment was to bring long term antibacterial capabilities to titanium with no detrimental effects on the biocompatibility and also to improve osseointegration.

METHODS: Surface modification of c.p. Ti was performed using the Anodic Spark Deposition (ASD) electrochemical technique. The treatment was aimed to enrich the superficial titanium oxide with Ca, P, Si and Na (selected to improve osseointegration) and with gallium ions (chosen to provide antibacterial properties [1]). Exploiting the chemical similarity of Ga³⁺ with Fe³⁺, gallium ions are capable to interfere on the iron metabolism in many bacteria, without bringing negative side effects on biocompatibility and osseointegration.

Three different surfaces were prepared starting from the same electrolytic solution called SiB [2]. The following ASD surfaces were obtained: (i) GaCis, by adding Ga-nitrate and L-cysteine to the SiB solution; (ii) GaOss, by adding Ga-nitrate and oxalic acid to the SiB solution; and (iii) SiB-Na, obtained by using the starting solution. Specimens treated with SiB were subjected to an alkali treatment in NaOH in order to promote surface Na enrichment and to increase the Ca/P ratio. The resulting samples called SiB-Na were used as control. Ti grade 2 was used as second control.

RESULTS: The GaOss, GaCis and SiB-Na samples are characterized by microporous surface (Fig. 1) enriched with silicon, calcium, phosphorus and sodium elements. EDS and XPS analysis on GaCis and GaOss showed the gallium presence onto surfaces; in particular, the gallium peak resulted higher on GaOss than on GaCis samples. Slightly different micro-morphology was observed for GaOss, in which the pores resulted smaller in diameter and irregularly-sized if compared to other ASD surfaces. Both treatments revealed that Ga is

mainly released in the first 7 days of soaking in D-PBS, reaching a plateau after 21 days.

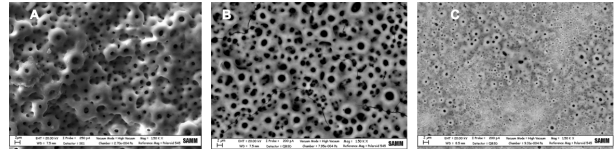


Fig. 1: Surface micro-morphology: SEM images of SiB-Na (A), GaCis (B) and GaOss (C).

The mechanical characterization reported an optimal surface cohesion without any presence of delamination. After 24 h of culture, the SAOS 2 osteoblast-like cells attached onto the ASD surface were fully spread and flattened with a completely branched shape. GaOss treatment showed a significantly higher ALP activity than on all the other ASD antibacterial treatments, also better than the control SiB-Na ($p < 0.05$). Both Ga-based treatments showed a strongly reduced bacterial proliferation against all the bacterial strain analysed even after 21 days, indicating a long lasting antibacterial activity. A strong biofilm inhibition was found against *S. mutans*, *S. epidermidis* and *A. baumannii* bacteria strains.

DISCUSSION & CONCLUSIONS: The developed ASD surfaces are characterized by homogeneous and reproducible morphological and chemical-physical properties suitable to favour osteoblastic cell adhesion and proliferation. The presence of the antibacterial agents together with their kinetics of release is able to confer bacteriostatic and long-lasting bactericidal properties. Gallium-based treatments, in particular GaOss, showed the best properties in stimulating the osteoblastic activity toward the new bone formation and the highest capability in limiting bacteria adhesion and proliferation and biofilm formation for all of the studied bacterial strains and represent the best candidate for future studies.

REFERENCES: ¹ Y. Kaneko et al. (2007) *J Clin Invest* **117**(4):877-88. ² C. Della Valle et al. (2013) *J Appl Biomater and Funct Mater* **11**(2):106-116.

ACKNOWLEDGEMENTS: Authors thank the Provincia Autonoma di Trento that co-funded the project.

Innovative coatings on PEEK substrate for orthopaedic implants

C Harnisch, J Garcia-Forgas, A Salito

Alhenia AG, Baden-Dättwil, CH

INTRODUCTION: Coatings of implants applied with different technologies have been in continuous development in the last fifteen years in order to improve fixation in bones, to protect against wear and for anti-allergy applications.

After many years of research, a new technique to apply porous titanium coatings on PEEK (Polyetheretherketone) medical implants has been developed.

METHODS: Porous titanium coatings were applied on PEEK samples using Vacuum Plasma Spraying (VPS) technology. This technique is performed in a chamber filled with an inert gas at low pressure and enables the creation of a large variety of coating materials, including oxygen-sensitive materials like titanium. Studies have been performed to investigate the PEEK/Titanium interface chemically and physically. Crystallinity of PEEK after coating at the PEEK/Titanium interface and in the bulk area was analysed using Differential Scanning Calorimetry (DSC). PEEK molecular weight was determined with Gel Permeation Chromatography (GPC). In the same way, the structure of the polymer was analysed using Fourier Transform Infrared spectroscopy (FTIR). Finally and in order to check important mechanical properties, tensile, shear strength, and shear fatigue values were measured according to ASTM standards to ensure the compliance with the FDA requirements.

RESULTS: The titanium coating obtained on the PEEK substrate shows a rough surface as well as open porosity. Pictures of the coating are displayed in Figure 1 below. Values of porosity vary between 20 % and 60 %. Roughness R_z of the coating surface is higher than 50 μm .

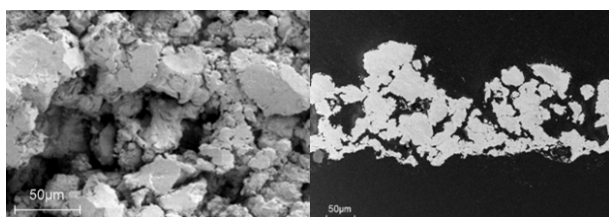


Fig. 1: Top view (Left) and Section view (Right) of the titanium-VPS coating on PEEK substrate.

Presence of oxides during the coating deposition is excluded because coating of the parts is performed in a vacuum chamber filled with inert gas.

Mechanical test results showed high properties which comply fully with FDA requirements.

Table 1. Results of statistical study performed on Titanium-coated PEEK samples.

	Mean	Standard Deviation
Roughness	$50 \mu\text{m} < R_z < 70 \mu\text{m}$	
Porosity	47.2 %	2.1
Thickness	107 μm	30
Bond strength	35.0 MPa	3.4
Shear strength	34.8 MPa	3.3

According to the DSC analysis, PEEK crystallinity remains unchanged after vacuum plasma sprayed titanium coating. Crystallinity in the bulk area was 29.70% and crystallinity at the PEEK/Titanium interface was 29.26%. In addition, GPC and FTIR analyses proved that PEEK is not altered or damaged by the vacuum plasma sprayed titanium coating process.

DISCUSSION & CONCLUSIONS: As bone cells are sensitive to surface topography [1], it is important to control the coating roughness amplitude and porosity. This technique for coating implantable PEEK with vacuum plasma sprayed titanium is unlikely to have a detrimental effect on the polymer substrate.

This particular know-how opens a new horizon to develop the industry with new applications. Moreover, the unique combination of porous titanium on PEEK has a great potential for spine and extremities implants and will enable to substitute some metal substrates used in the orthopaedic field.

REFERENCES: ¹ K. Anselme, *Biomaterials and interface with bone*, Osteoporosis Int (2011) 22:2037-2042.

Improved tribological performance of PEEK polymers by application of diamond-like carbon coatings.

PK Tomaszewski¹, YT Pei^{2,5}, GJ Verkerke^{3,4}, JThM De Hosson²

¹ Orthopaedic Research Lab, Department of Orthopaedics, Radboud University Medical Center Nijmegen, The Netherlands. ² Department of Applied Physics, Materials Innovation Institute, University of Groningen, The Netherlands. ³ Center for Rehabilitation, University of Groningen, University Medical Center Groningen, The Netherlands. ⁴ Department of Biomechanical Engineering, Faculty of Engineering, University of Twente. ⁵ Department of Advanced Production Engineering, Institute for Technology and Management, University of Groningen, The Netherlands

INTRODUCTION: Overall high mechanical strength, an elastic modulus comparable to bone and low cost makes polyetheretherketone (PEEK) an interesting biomaterial. However, high friction coefficient (CoF) and wear [1] restrict its orthopaedic use to non-articulating applications. A solution might be offered by diamond-like carbon (DLC) coatings, which recently were applied to flexible, rubber-like material [2]. This study aimed to examine whether a DLC-coating can improve the tribological performance of the sliding interface between Ti6Al4V alloy and pure and carbon-fibre reinforced PEEK polymers.

METHODS: DLC-films were deposited on pure PEEK and two carbon fibre reinforced PEEK types: CFR-PEEK PAN (with polyacrylonitrile fibres) and CFR-PEEK pitch (with carbon fibers derived from petroleum pitch). Plasma CVD (p-CVD) was used at pulsed-DC bias voltage of 300 V and 400 V, respectively, for 210 min and 120 min to reach the same film thickness of 600±50 nm. Loads of 1 N, 3 N and 5 N were applied to a ø 6 mm Ti6Al4V ball sliding on PEEK discs (Invibio Ltd, UK) at constant humidity of 50±1 %, 10 cm/s velocity and in room temperature using a CSM tribometer (CSM Instruments, Peseux, Switzerland).

RESULTS: Reduction of CoF (average of 1 N, 3 N and 5 N) from 0.31~0.26 for uncoated to 0.09~0.13 for DLC coated PEEK specimens was measured (the CoF of UHMWPE was 0.12~0.13 as a reference). The coating was stable during the tests and showed no measurable wear for all load levels (Fig. 1).

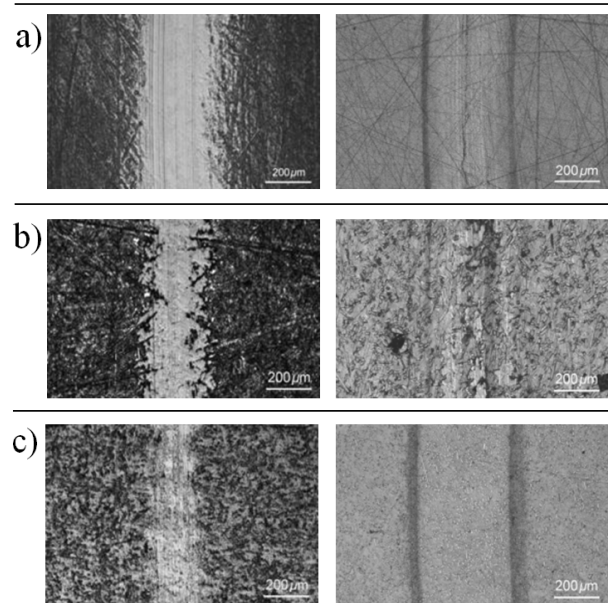


Fig. 1: Micrographs of wear tracks on uncoated (left) and DLC coated (right) PEEK (a), CFR-PEEK pitch (b) and CFR-PEEK PAN (c) surfaces after tests with 3 N load.

DISCUSSION & CONCLUSIONS: Good wear resistance and reduced CoF enable to consider DLC-coated PEEK polymers for articulating orthopaedic implants.

REFERENCES: ¹ S.C. Scholes, A. Unsworth (2009) *Journal of Materials Science-Materials in Medicine* **20**(1): 163-170. ² Y.T. Pei, X.L. Bui, J.Th.M. De Hosson (2010) *Scripta Materialia* **63**(6): 649-652.

ACKNOWLEDGEMENTS: This study was supported by Fonds Nuts-Ohra (Amsterdam, The Netherlands). Invibio Ltd. (Lancashire, UK) provided PEEK materials for testing.

The ceramic ZircaPore[®] implant surface - in vitro / in vivo experiences

F Berghänel, C Strehler
Metoxit AG, Thayngen, CH

INTRODUCTION: Introducing hot isostatically post compacted (HIP) ceramics with their favourable mechanic behaviour into dentistry, the full ceramic implant supported restorations got matter of interest. The ability to osseointegrate was critical endpoint of certain studies. The application of a technically feasible roughness is limited due to the undesired reduction of mechanical strength. Ziraldent[®] Implants (ATZ) with the additive microporous ZircaPore[®] surface (Fig. 1) show beneficial mechanical reliability and favourable tissue friendliness. The 3 years follow up of a prospective cohort study confirms a successful full-ceramic implant treatment so far.

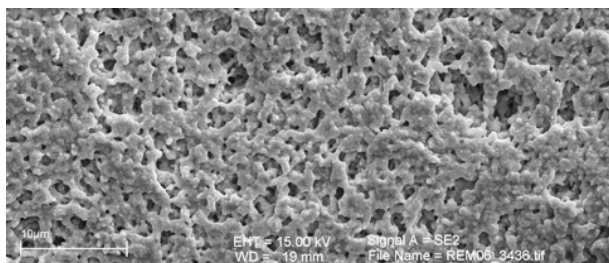


Fig. 1: ZircaPore[®] Surface

METHODS: In preclinical testing, the biological behaviour is compared using osteoblast-like CAL72 cell cultures [1] as well as human osteoblasts [2]. Included in the comparison are different surface modifications of ceramic substrates and SLA[®] versus polystyrene controls.

An animal study compares quantitative and qualitative controls of osseointegration of the modified Zirconia surface versus an anodised titanium surface and machined Ti- and ZrO₂ references. The bone-implant-contact (BIC) is assessed histomorphometrically and the biomechanical strength is indicated by the Push-In forces [3]. 40 patients and 57 implants are included in a 5 years prospective clinical cohort study. Beside the survival rate, the bone level behaviour and gingiva attachment are primary success criteria.

RESULTS: The ZircaPore[®] surface shows a roughness R_a/P_{p-v} of 0.286 μm / 2.73 μm compared with R_a 0.38 μm of the anodised titanium surface. There is no significant difference of proliferation versus the control obvious. The status of gene expression is assessed by RT-PCR during 28 days. Quantity of those genes differencing osteoblasts

increases faster in the titanium group, however at day 28 there is no more a significant difference compared with the control group. The animal study assessing the osseointegration shows 24 % BIC of ZircaPore[®] at day 28 and therefore delayed in difference to the 54.8 % of the anodised titanium implants. However, the biomechanical data of the Push-In-Test comparing ATZ (24.5 N (SD 26.94)) vs. Ti (39.49 N (SD 5.44)) show no statistical significance. The published data of the clinical 3 years follow up reports two implant losses during the early healing period prior to prosthetic restoration. Measurement of gingiva attachment expresses beneficial soft tissue behaviour. Finally, the endpoint bone loss is reported as an increase of the bone level compared with the data of year one p.i. [4].

DISCUSSION & CONCLUSION: Ziraldent[®] implants with ZircaPore[®] surface show promising success and are outstanding related to mechanical safety and biocompatibility. The supposed moderate stimuli for cell proliferation and differentiation demand an implant macro design to ensure necessary primary stability. Concerning that, ZircaPore[®] further development for orthopaedic applications is ongoing.

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Sim4Life: A Simulation Platform for Life Sciences and Medtech Applications

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INTRODUCTION: Sim4Life is a comprehensive simulation platform that has been developed to optimally address computational life sciences applications and especially medical device evaluation, e.g., for safety and efficacy assessment.

METHODS: Sim4Life supports simulations involving detailed anatomical models and is designed to allow modelling based on medical image data. A large set of poseable and morphable anatomical models is available. The high-performance computing-enabled solvers for various physical processes are tuned to the modelling of interactions involving living tissues. They are complemented by a series of specialized biological and physiological solvers. The platform features powerful scripting and visualization functionalities, which seamlessly blend CAD-based data, simulation results, images, and measurement data.

RESULTS: Two implant-related applications serve to demonstrate some of the many capabilities of the Sim4Life platform. Sim4Life has been employed in collaboration with the FDA to develop a high-resolution functionalized head model for implant safety assessment. Diffusion Tensor Imaging (DTI) data is fused with the head model to offer information about brain tissue dielectric anisotropy and help with the embedding of dynamic neuron models. Subsequently, EM-neuron interactions can be modelled to investigate and optimize neuroprosthetic devices and deep brain stimulation. The second application example focuses on the impact of implants on blood flow and the related wall shear stress.

DISCUSSION & CONCLUSIONS: Life sciences and Medtech applications bring along specific requirements that were not sufficiently addressed by existing simulation platforms. By focusing on simulations involving realistic anatomical models, imaging- and measurement-based information, and powerful, validated solvers accounting for the unique behaviour of living tissue, Sim4Life introduces a platform that fills this gap and enables device design and optimization, safety and efficacy assessment, as well as fundamental research with unprecedented realism, detail, and reliability.

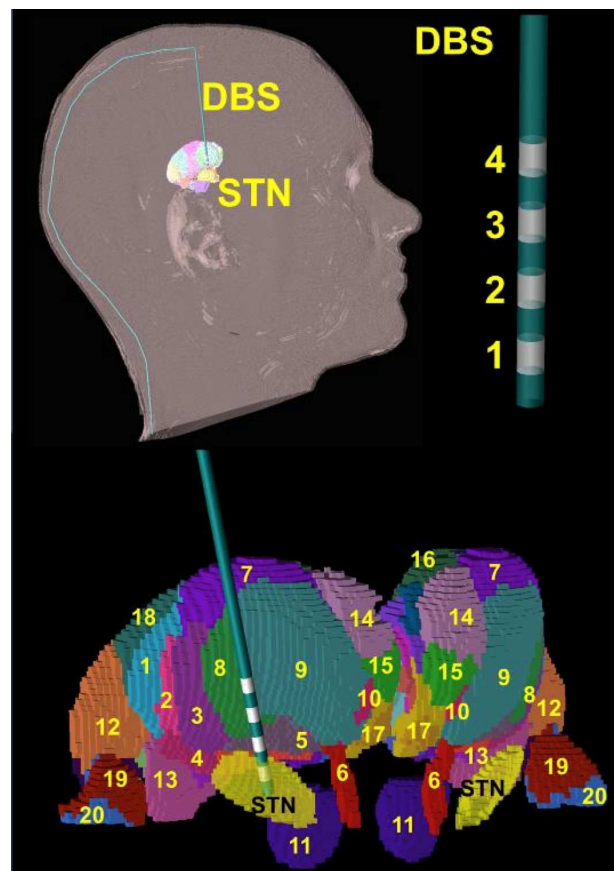


Fig. 1: Head model segmented from multi-modal magnetic resonance image data with an implanted deep brain stimulator (top) and a magnified view of the thalamus and the electrode inserted in the subthalamic nucleus (bottom).

REFERENCES:

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ACKNOWLEDGEMENTS: S4L – CAPITALIS, Commission for Technology and Innovation (CTI), Switzerland, Project No. 148930.1 PFLS-LS.

Sending implant data to the cloud

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INTRODUCTION: Medical devices, including implantable and wearable parts, have become more prevalent over the last several years. These devices have proven benefits for patients who can now return to work earlier and live longer more enriching lives.

A new generation of implantable and personal medical devices, which can be electronic or mechatronic, can sense a person's health condition, save the collected data, transmit it to the cloud and notify a caregiver of a serious condition.

While this cloud based scheme is being widely talked about, the complexity of actually collecting the data from these devices and securing the data transmission, as well as complying with privacy regulations, is considerable. This presentation will discuss how implants are changing to gather and send data wirelessly, show current ways the data is being secured and how privacy considerations may change the way data is collected and sent to a cloud based server. Cutting-edge products currently under development will be shown as well.



Fig. 1: innovative pill for diagnosis of the digestive system

Humidity management in active implantable medical devices

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INTRODUCTION: Nowadays active implantable medical devices become increasingly small allowing for novel placements inside the human body and increasing patient comfort. At the same time, implants become more and more complex by including functions that imply specific encapsulation requirements. This leads to considerable challenges regarding the sealing properties of the device encapsulation and the way to manage moisture ingress in general. Standard leak detection methods and related acceptance criteria may no longer apply because of limited residual gas volumes and mechanical strength of the encapsulation.

METHODS: The presentation summarizes the currently used standard leak detection methods and shows their limits using a calculation example. In a second step, critical aspects that either influence the sealing properties of the encapsulation or that directly influence the moisture level inside the implant are discussed. Possible encapsulation materials and technologies are presented and briefly evaluated based on their main sealing characteristics.

RESULTS: The water leaking into a sealed package from the outside environment is calculated by the following formula [1]:

$$L_{H_2O} = -\frac{V}{t} \left[\ln \left(1 - \frac{Q_{H_2O}}{\Delta p i_{H_2O}} \right) \right] \quad (1)$$

The water leak rate L_{H_2O} depends on the available internal volume V , the time t , the water amount that leaks in Q_{H_2O} , and the initial difference in water partial pressure $\Delta p i_{H_2O}$. L_{H_2O} can finally be converted into a helium (He) leak rate L_{He} by applying the corresponding conversion factor [1]:

$$L_{H_2O} = 0.471 L_{He} \quad (2)$$

Analysing the relationship between leak rate, volume and time shows that acceptable He leak rates are below 10^{-11} atm-cc/s for implant durations longer than one year and internal volumes below 0.1 cc assuming a maximal acceptable water accumulation level of 5'000 ppm (Fig. 1).

Reviewing the proposed fine leak detection methods prosed by MIL-STD-883J [2] reveals that

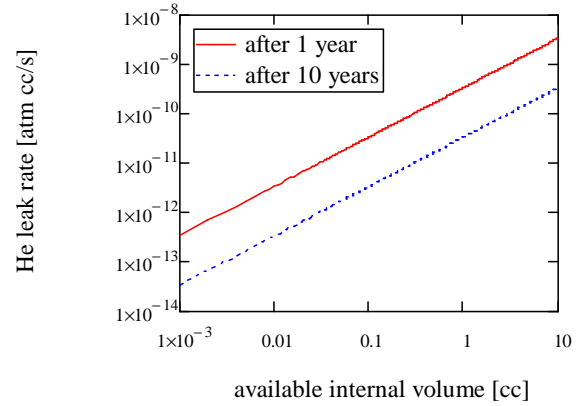


Fig. 1: He leak rate to not exceed a water accumulation level of 5'000 ppm inside the package submerged in water

standard He leak detection does not apply anymore and needs to be replaced by more sensitive methods. At the same time, it is important to consider that the sealing properties of the package have to be improved providing the required level of sealing.

DISCUSSION & CONCLUSIONS: The design of the package of a miniaturized active implant is a challenging task and requires careful selection of appropriate materials and joining processes. Selection criteria should include, amongst others, functional requirements, external interfaces, internal interfaces and, finally, sealing properties.

Depending on the degree of miniaturization, it may be impossible to reach the required sealing level. In this case, the humidity management needs to be extended from passive protection to active measures. One promising option is the integration of water absorbing materials, so-called moisture getters, to maintain an acceptable humidity level within the implant. This measure addresses not only water ingress from the outside but can deal with internal moisture sources as well. Such internal moisture sources are not negligible and have to be considered to successfully manage humidity in active implantable medical devices.

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It's all about value: MST's EMS⁺ concept for manufacturing of complex active implants

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INTRODUCTION: In order to comply with today's quality and reliability requirements at the regulatory level while achieving shortest time to market, fully comprehensive control of the End-to-End-value-chain from design to functional test requires innovative approaches to business, manufacturing and quality assurance processes.

METHODS: An End-to-End value chain starts with the design of a product or, even better, the process that leads to a size and power efficient, highly reliable implantable device. Based upon a structured stage gated New Product Introduction process (NPI), the design inputs must be verified for feasibility and regulatory compliance as well as tested in various simulations. After the project release milestone (RDI), the design work starts and concludes with corresponding components, supplier and process releases, followed by the final design and process freeze prior to validation start (RDO). Upon completed validation, a final milestone (RDT) with all documentation required for regulatory submission concludes the development of the product.

Within the 2nd phase of the NPI process, components and suppliers have been selected and, if required, validated. However, particular attention has to be paid to the specific requirements of implantable devices, as components characterized by "medical grade" are not necessarily manufactured with specific processes, but rather have undergone a selection by the supplier. Consequently, and for the case of highest grade of component scrutiny, a fully automated internal characterization process has been developed by MST, characterizing 100% of the components such as diodes, capacitors and resistors by visual and electrical specifications. It results an abundant set of data points to judge the individual component performance, and a long term data base, which enables lot-by-lot comparisons to immediately identify non-conformal lot characteristics.

After design and component selection, the product specific manufacturing process validation is the next logical step. From an implantable device perspective, it is absolutely desirable to have the least human interference during manufacturing, which is best accomplished within a fully automated and entirely "digital" factory under complete MES control. It prevents executional or judgemental errors by operators and captures and stores all relevant process parameters in real-time, which assures immediate detection of any deviations.

During functional module test under real operating conditions at 37 °C, all relevant product performance characteristics are verified, including HF communication and optional motion responses, prior to a design dependent fully automated pre-assembly/fold operation.

Due to the fully embedded digital manufacturing environment, an excess of 100 MB of process and product data per module have been stored and are readily available and at any point in time easily retrievable at the end of the completed manufacturing cycle.

DISCUSSION & CONCLUSIONS: Simple stage gate processes and state-of-the-art equipment are not enough to satisfy today's active implants requirements in terms of quality and reliability. Experienced engineers and highly trained operators running leading edge equipment must be embedded into a seamless, fully integrated business and production process and supported by a highly sophisticated IT infrastructure in order to assure real time process capability and traceability in minimized time to market.

ACKNOWLEDGEMENTS: MSE Inc., Lake Oswego / USA, MSE GmbH, Berg / Germany, DYCONEX AG, Bassersdorf / Switzerland.

MR safety evaluation of implantable medical devices: RF-induced heating

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INTRODUCTION: Metallic implants can potentially act as a radio-frequency (RF) receiver and deposit the received power locally in tissue. As relatively large levels of RF fields are induced in the body during magnetic resonance imaging (MRI), the temperature increase in tissue at the vicinity of the implants can reach hazardous levels. Recent progress in computational methods enables the evaluation of passive implants (e.g. hip implants) *in silico*. However, active implantable medical devices (AIMDs) with long leads (e.g. pacemakers) are currently too complex to be handled fully *in silico*. We have developed the methodology, instrumentation, and procedures whereby implant heating is determined from a mixture of numerical and experimental evaluation.

METHODS: Piece-wise excitation (πX) is a robust method that can be used to characterize RF-induced heating of AIMDs. The characterization is based on the technique proposed in [1], where a πX model, $h(l)$, is defined as the relationship between the locally induced electric field around an electrode pole and excitation along length l of the AIMD. Fig. 1 shows a schematic of the method. The tangential component of the local incident electric field, E_{tan} , is coupled with the AIMD at length l and the induced electric field around an electrode of the AIMD at point p_1 is evaluated. The total induced electric field at point p_1 , contributed to E_{tan} coupling along the entire AIMD of length L , can then be calculated.

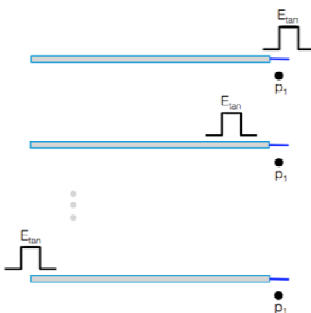


Fig. 1: Schematic of the piece-wise excitation method.

Computational methods may be used to obtain $h(l)$ of a simple AIMD. However, for a complex AIMD structure, the computational burden can be substantial. To overcome the challenges of the numerical implementation associated with a

complex AIMD structure, we have developed an experimental prototype of the πX system. The system is capable of generating a well-controlled local E_{tan} along an extremely elongated AIMD and acquiring the induced electric field at the tip or electrode of the AIMD. The system can be used to obtain the πX model of any AIMD, irrespective of the complexity of its construction. The πX system prototype is illustrated in Fig. 2.

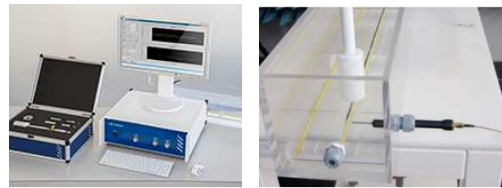


Fig. 2: (Left) The πX system analyzer (signal generator and processor). (Right) Close-up view of the local excitation source antenna and the electric field probe placed near the tip of an AIMD.

RESULTS: Fig. 3 shows a comparison of the phase and amplitude of the πX models obtained experimentally with the πX system and of those obtained numerically. The πX models of three generic AIMDs are illustrated.

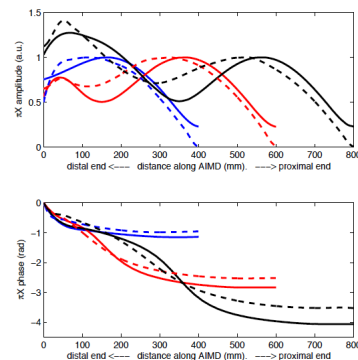


Fig. 3: Comparison of the πX models obtained numerically (solid) vs. experimentally (dashed) with the πX system, respectively.

DISCUSSION & CONCLUSIONS: We have developed the πX system prototype. The system enables RF-heating evaluation of complex AIMDs of which numerical evaluation may not be feasible.

REFERENCES: ¹ S. Park, R. Kamondetdacha, J. Nyenhuis (2007) *J Magn Reson Imag* **26**:1278-85.

Implants in treatment of meniscal tears and shoulder joint lesions – an overview

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BACKGROUND: Meniscal tears and injuries of the shoulder joint including the rotator cuff and labrum are among the most common sports-related injuries requiring surgical intervention. Particularly in young patients, all efforts must be made to avoid extensive surgical resection and to restore the joint function as good as possible [1]. This abstract aims to provide an overview of the commonly used implants in knee and shoulder joint surgery and to present an outlook on possible improvements of these implants.

IMPLANTS IN MENISCAL REPAIR:

Indications for meniscal repairs include acute longitudinal tears in the vascularized peripheral third of the meniscus (red-red to red-white zone) as well as larger bucket-handle tears. To date, inside-out (from inside the knee joint to outside) vertical mattress suture repair techniques are still considered the gold standard for treatment of meniscal tears. However, all-inside repair devices (no need to create an additional incision) experience an increase in popularity because of their lower complication rate (neurovascular damages), decreased morbidity and the easier surgical handling compared to inside-out techniques. The first generation of all-inside repair devices (resorbable, rigid-arrow) provided rigid fixation and good clinical outcomes, but they were associated with high failure rates and damage to the articular cartilage. For this reason, second-generation, flexible suture- and anchor-based repair devices are currently favored in clinical practice (Fig 1).

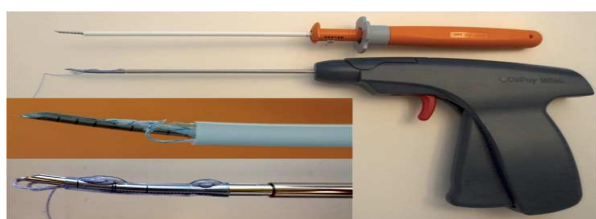


Fig. 1: All-inside meniscal repair devices. Top: Fast-Fix 360 (Ultrabraid® 2-0 suture). Bottom: Omnispan (Orthocord® 2-0 suture).

Traditionally, inside-out repairs were considered biomechanically superior to the all-inside devices. However, a recently published study demonstrated, that all-inside meniscal repair devices showed comparable biomechanical properties compared to

their inside-out suture repairs in initial displacement and cyclic loading, even after 100'000 cycles [2].

IMPLANTS IN SHOULDER JOINT LESIONS:

With the implementation of suture anchors, the transition from open to arthroscopic techniques in shoulder surgery was facilitated. Suture anchors provide a reliable fixation of soft tissue (e.g. tendon or labrum) to bone repair to ensure the healing process. First published studies demonstrated the clinical benefit of metallic anchors with initial pull-out strengths similar to that of transosseous fixation [3]. However, many following studies reported of complications, such as loosening, migration and chondral injury with first generation metallic anchors [4]. Additionally, metal anchors show interference with radiologic studies (MRI in particular) and are often difficult to remove e.g. in revision surgery such as conversion to shoulder prosthesis. For this reason, bioabsorbable polymer anchors were developed and are currently favoured in orthopaedic surgery. More than 40 different types have been developed, but not all of them fit the biomechanical requirements necessary for a secure healing. If the polymer degrades too rapidly, the fixation loses strength and furthermore, foreign body reactions, cyst formation and synovitis may occur. To overcome these complications, the newest available implants contain PEEK (polyetheretherketone) and calcium ceramics (tricalcium phosphate) in an effort to hypothetically create a mechanically stable construct with and improve biocompatibility of the implant [4]. In a summary, bioabsorbable anchors remain a safe, reproducible, and consistent implant to secure soft tissue to bone in and about the shoulder, even if additional biomechanical investigations are desirable.

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The interaction of blood components with titanium implant surfaces is decisive for osseointegration of bone implants

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INTRODUCTION: As blood is most often the first body fluid getting in contact with implant surfaces, it is crucial to understand the mutual interplay specific to this biological interface. Depending on the physico-chemical properties of the implant surface, blood coagulation and protein adsorption are influenced (1). Thereby, the implant is giving a biological identity– a natural matrix that will impact subsequent cellular responses such as adhesion, migration and differentiation (1, 2). In this study we investigated blood coagulation on hydrophobic and hydrophilic micro-roughened titanium (Ti-) surfaces and assessed the osteoconductive potential of the biomaterial-induced natural matrix on primary human bone cells.

METHODS: Material: Sandblasted and acid-etched hydrophobic (SLA[®]) as well as hydrophilic (SLActive[®]) Ti surfaces, which are commercially available, from Institute Straumann AG.

Methods: Primary human bone cells (HBCs) were cultivated on micro roughened Ti surfaces, which were either pre- or non-incubated for 10 min with partially heparinized (0.5 IU/ml) whole human blood from healthy donors (bone cells and blood samples with ethical approval of the local ethics committee). Blood coagulation, as well as proliferation and differentiation potential of HBCs was assessed by immunofluorescent staining and microscopy. Mineralization of HBCs was evaluated after 14 and 21 days qualitatively by Xylenol Orange staining and quantitatively by measurement of calcium deposits.

RESULTS: Early and enhanced blood coagulation was observed on SLActive[®] surfaces when compared to SLA[®] Ti surface 10 min post incubation. Furthermore, HBCs grown on SLActive[®] Ti surfaces, pre-incubated with blood, showed an increased cellular attachment, accelerated differentiation potential and mineralized to a higher extend (Fig. 1), when compared to HBCs on pre-incubated SLA[®] Ti surfaces.

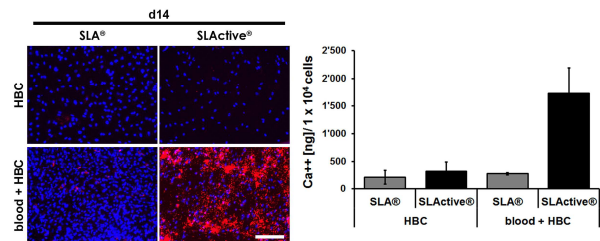


Fig. 1: Assessment of mineralisation (left: Xylenol orange staining or right: Calcium determination) of HBCs cultured for 14 days on SLA[®] and SLActive[®] +/- pre-incubated with blood. Mineral deposition/calcium levels indicative for osteogenic differentiation were increased on SLActive[®] surface pre-incubated with blood (scale bar 200 μ m).

DISCUSSION & CONCLUSIONS: Physico-chemical surface of implants greatly influence blood coagulation, thereby significantly impacting biomaterial-induced natural matrix that harbors pivotal osteoconductive potential for primary human bone cells. Our results underline the reported enhanced osseointegration of SLActive[®] Ti implants as demonstrated in preclinical and clinical investigations (3, 4). Studying the interaction of blood components with implant surfaces might represent a relevant screening tool for novel implant surfaces, thereby providing a simple platform, where questions concerning biomaterial cytotoxicity as well as biocompatibility could be easily addressed.

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Usability results through human centered design and early test models

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Engineering factors dominate the development of most new medtech devices, yet success in the market is often linked to the implementation of user centered design. That begs the question: Can the spark of human centered design develop on demand from within a company or should it be outsourced when needed?

People skilled in pattern recognition

Until fairly recently, many corporations only thought of design as a way to “make things pretty”. It was up to engineers to innovate and add functions. But this approach leads to a pitfall: A new function is only as good as its acceptance by the customer. In order to avoid surprises in the market, product development needs to be started with a preliminary project and requires more intelligence than engineers can bring to the table. Not just individuals but even businesses are prone to information overload these days. In order to make sense of a sea of information and development options, people skilled in pattern recognition and visual communication are needed: This is exactly what designers excel in. Today, essential contributions to successful innovation and corporate strategy are expected from designers. They visualize the world as it could be, even if what they envision is a significant jump from current reality. The designer’s ability to render new ideas tangible serves to drive rapid buy-in and improve the decision-making and iteration processes.

Taking blame gladly

An essential question that defines design driven product development is the characterization of the market. Medical technology companies that outsource the design process enable external partners to get early feedback about new product ideas from the end user - namely medical professionals and patients. This work flow reduces the bias that is generated through existing buyer-seller relationships. By outsourcing design, companies buy themselves the freedom to be wrong (for a little while), in order to find new and better ways to be dead on with the final product. “It is too heavy.” “It is too small.” Such may be the verdict of a first consumer analysis. But “heavy” can also amount to “more stable”. When an end user finds an early mockup “too small”, this may signify that larger, cheaper components can be used for the final version.

The shaping of things to come

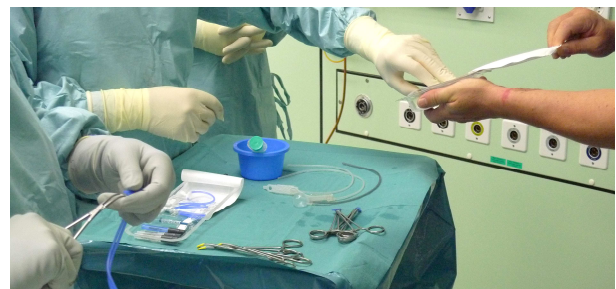
Design as a corporate strategy: Leading businesses who wish to be competitive in tomorrow’s markets must be ready to innovate usability. Human centered design is a new strategic approach that helps to streamline the innovation process. Solution-driven and value-creating, human centered design accelerates product development by conducting different processes in parallel.

Early testing, rapid prototyping

During the initial phase of market research, engineers and designers are already developing ergonomic prototypes. Early testing optimizes further product development. Problems are discovered and solved faster. Designers play a key exploratory role. Their goal is the development of a convincing, smart product which accentuates a positive user experience through intelligent design.



AOT, laser osteotomy, prototype usability study



Myopower, monitored incontinence implant, drylab for operation workflow



Mininavident, Denacam navigated implants functional prototype for early testing.

Biological evaluation according to ISO 10993-1: Methods and pitfalls

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INTRODUCTION: All materials used for medical devices and the finished products have to be evaluated regarding efficacy and safety before they can be marketed. This assessment is done within the frame of international biocompatibility standards, in particular the ISO 10993 series or ASTM F748 and their associated standards. These series consist of standard documents that are on the one hand guidelines, sketching the typical course of action. On the other hand, some documents describe specific test methods or set specifications to be met in material characterization or biological evaluation.

Biocompatibility is defined as *the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy* (Definition ASTM 2011). This definition implies that the end-use application has to be known when carrying out biocompatibility assessments and that the evaluation route has to be adapted each time accordingly. Common and mandatory points to all biocompatibility assessment are a) chemical / physical material characterization of the materials and b) the risk analysis. Biocompatibility can be considered established if the material characterization proves that the product material of the finished is equal to material considered biocompatible and if within the risk analysis enough evidence is found that the own device can be justified by existing data of a predicate device.

A central part in the risk analysis is to assess and review the biological response. This is typically done by reviewing existing data and published literature. Below focus is set on literature review.

LITERATURE REVIEW: The principles of a systematic literature review are outlined in Annex C of ISO 10993-1. It will help to decide whether enough literature is available to perform a complete risk analysis without additional biological tests or studies. Key of any literature review is a systematic search for document in a way that it can be reproduced and validated by a third party, i.e. the notified bodies or administrations.

Any literature review requires good planning and there are three points requiring special attention before a search can be performed. First of all, the aim of the study has to be defined. The aim is typically dependent on the primary mode of action of the device to be reviewed or specific aspects of it. Second, a comprehensive set of keywords and Boolean combinations needs to be defined. The careful selection is essential since the complete search procedure has to be repeated if changes are done at a later stage. And third, the databases on which the search is performed have to be chosen. It is essential to differentiate for reviews on device performance between the scientific literature and the administrative actions since administrative actions, such as field safety action are not found on scientific databases, but on diverse complaint databases of the administrations. For scientific literature there is a good selection of public and behind-paywall databases. It is of utmost importance to know the exact extend of included literature. Often, searches have to be performed on more than one database as the datasets are not complete. For example, PubMed is very popular since it is a free accessible database. However, PubMed does not include for example most of material, chemical, physical information and reviews based on that database can be considered incomplete. Another issue is the use of “Google”-data which is a no-go for systematic reviews as the datasets cannot be reproduced.

In a second phase, results of the literature search have to be reviewed and assessed. A first screening will help to reject papers that are not considered relevant to the aim of the review. All rejections require justification. Next, critical review of each paper will yield the scientific contribution. Often it is most difficult to assess the quality of papers and compare outcomes to other literature as scientific literature does not know any standardization or the quality criteria regarding statistical outcome do virtually not exist. That phase has to be carried out by scientists skilled in the aim of the review.

CONCLUSIONS: While the first phase - literature search - requires a good sense in systematic and structural reflections, the second phase - literature evaluation - entails more soft criteria in assessing the relevant literature. The complete work is assembled and compiled in a literature review document.

Biological safety assessment of medical device implant sets

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INTRODUCTION: Implant devices are often provided together with the respective surgical instrumentation in a set. The biological safety of both, the implant as well as the instrumentation has to be proven according to ISO 10993. Additionally the reusable instruments have to be evaluated for their intended reprocessing procedures.

IN VITRO SAFETY ASSESSMENT: The biological risk of an implant and its instrumentation needs to be evaluated. Evaluation does not necessarily mean testing. If the materials of the devices are already listed as biocompatible and have a demonstrably safe history of use and/or a predecessor product has already been registered, that is comparable to the new device, a so called “bridging concept” can be recommended.

First of all, a thorough literature study has to be performed by the manufacturer, including all material and process specifications. If comparability is given on a theoretical basis, a test for cytotoxicity and physico-chemical tests like e.g. GC/MS Fingerprint and ICP Fingerprint are mandatory. Depending on the invasivity, contact type and contact duration additional biological endpoints as genotoxicity and hemocompatibility should be considered. If no biological hazards can be detected, the results of the tests can be taken for further interpretation in the risk management or an expert statement. If results are of any toxicological concern, further investigations on the product/processes respectively further biological safety testing is considered necessary.

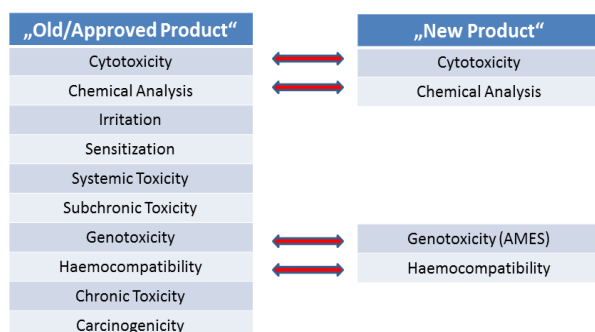


Fig. 1: Bridging study concept

an evaluation of the reprocessing instructions must be performed. In case of submission in the USA, the current FDA requirements [1] are to be observed. For testing the cleanability, the test instruments are contaminated with a suitable test soil. The composition of this contamination solution should be provided and justified by the medical device manufacturer. AAMI TIR 30 [2] lists some commonly used test soils. Before starting the actual test, the test sample should be first subjected to several cycles of simulated use and subsequent reprocessing. During the evaluation study at least 3 complete cleaning cycles each with at least three instruments should be performed to demonstrate the repeatability of the cleaning process. In accordance with the actual FDA requirements, the cleaned instruments should be examined under consideration of two separate cleaning endpoints. As suitable endpoints the total organic carbon (TOC) and the protein content could be examined. In addition, the extraction efficiency of the test instruments should be determined and included in the calculation of the residual contamination. The limit values for the two endpoints must be substantiated by the manufacturer. Here also the AAMI TIR 30 [2] may provide valuable information.

SUMMARY: Evaluation of biological safety is mandatory for each implant device and its instrumentation. Individual testing strategies have to be developed for each device. Comparison of already known to a new product can reduce testing, especially in vivo studies by applying a bridging concept. For the surgical instrumentation a tailor made reprocessing study considering the actual FDA requirements [1] should be conducted.

REFERENCES: ¹FDA, “Draft Guidance for Industry and FDA Staff–Processing/Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling” (Washington, DC: HHS, 2011). ²AAMI TIR30:2011, “A Compendium of Processes, Materials, Test Methods, and Acceptance Criteria for Cleaning Reusable Medical Devices” (Arlington, VA: AAMI).

ASSESSMENT OF REPROCESSING INSTRUCTIONS: For the surgical instrumentation,

High strength titanium: a new candidate for implant materials

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INTRODUCTION: Together with academic partners, Straumann has initiated a program to investigate pure titanium produced via alternative processing methods with a potential to increase the strength while maintaining its ductility and good biocompatibility.

METHODS: Microstructural investigations and mechanical measurements were performed with state of the art analytical techniques, e.g. atom probe, SEM, EBSD, TEM, HRTEM, AFM, nanoindentation, tensile testing, fatigue testing and fracture toughness testing. Biocompatibility on differently treated surfaces (machined, SLA, SLActive) was studied in light of their osseointegration potential, cytotoxicity and protein adsorption.

RESULTS: Figure 1 shows two electron microscopy images (TEM, EBSD) indicating strongly inhomogeneous grain size with most grains of few tens of nanometers and few up to a size of 1-2 micrometers, which is typical for highly cold deformed metals using severe plastic deformation techniques. Such a microstructure is nominated as ultra-fine grained (UFG). Figure 2 (left) shows tensile curves of UFG-Ti and standard cold-worked Ti-grade 4. For UFG-Ti, a strong increase in yield and ultimate tensile strength and a slight reduction in ductility is observed. Fatigue tests (Fig. 2 right) exhibit distinctly higher fatigue strength limits compared to standard Ti-grade 4 samples of conventional grain size, in accordance to [1].

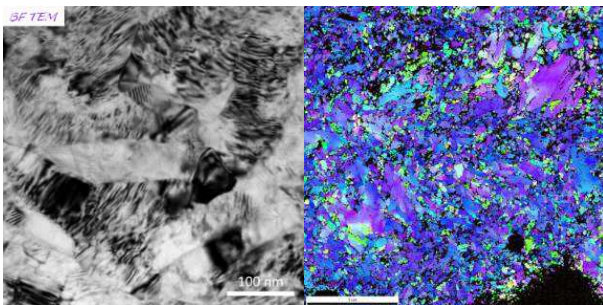


Fig. 1: Bright field TEM image (left) and EBSD image (right) of UFG-Ti.

Biocompatibility measured by the proliferation of human bone cells (HBC) show that UFG-Ti is comparable to micro-crystalline Ti. Mineralization potential of HBCs seems not to be affected by micro- or ultra-fine grained Ti but rather by the

chemical surface of the material (SLActive > SLA). Cytotoxicity (according to ISO 10993) measured by the proliferation of normal dermal human fibroblasts (NHDF) shows no difference between the two material types. In vitro tests with bone cells are in line with the reported enhanced osseointegration of microcrystalline SLActive[®] Ti implant as demonstrated in preclinical and clinical investigations [2-6].

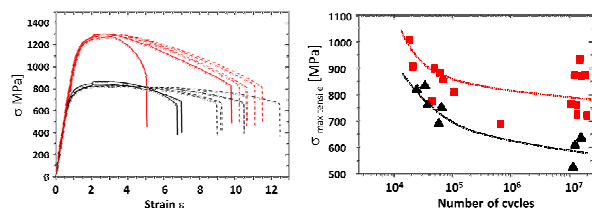


Fig. 2: Left: Tensile curves of UFG-Ti (red) and standard Ti-Grade 4 (black). Right: Fatigue results of various batches of UFG-Ti (red square) and standard Ti-Grade 4 (black triangle).

CONCLUSIONS: Integrity tests of UFG-Ti have proven the material to be flawless and fracture toughness to be similar in range as standard Ti-Grade 4. Mechanical properties have shown high strength values in non-cyclic as well as cyclic loading for UFG-Ti vs. standard Ti-Grade 4. In combination with the positive results deduced by the biocompatibility assessment, results demonstrate that the new titanium is an interesting candidate with high potential as future implant material.

REFERENCES: ¹ Hyun *et al.* (2011) *Rev. Adv. Mater. Sci.* **28**: 69-73. ² Buser *et al.* (2004) *J Dent Res* **83**:529-533. ³ Ferguson *et al.* (2006) *J Biomed Mater Res A* **78**:291-297. ⁴ Schwarz *et al.* (2007) *J Periodontol* **78**:2171-2184. ⁵ Schwarz *et al.* (2008) *J Clin Periodontol*, **35**:64-75. ⁶ Lang *et al.* (2011) *Clin Oral Implants Res*, **22**:349-356.

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Numerical simulation of a transcatheter aortic valve

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INTRODUCTION: In case of transcatheter percutaneous aortic valve implantation (TAVI) [1], the interaction between blood, stent and aorta are of central importance in order to determine implant lifetime.

CADFEM (Suisse) AG and ADMEDES SCHUESSLER GmbH developed together a numerical modeling procedure using commercial software to consider stent crimping and release against the aortic wall followed by a fluid-structure transient simulation during one systolic pulse.

METHODS: In the case of Nitinol self expandable stents, fatigue analyses are based on the determination of accurate stress cycles in the material. The most relevant steps were simulated using both finite elements and finite volumes discretization, for the structural and fluid domains respectively, within the ANSYS Multiphysics Workbench platform. Starting from the stent in the undeformed state (Fig. 1a), a first structural analysis delivered its stress and deformation state after crimping and positioning against a stiff aorta wall (Fig. 1b). The pre-stressed structure was then connected to the pericardium valve leaflets (Fig. 1c). Compressive forces transferred from blood to valve leaflets, stent and aorta wall were then taken into account during a weakly coupled transient fluid-structure interaction analysis (Fig. 1d) over a complete systolic blood pulse.

The following effects were taken into account: frictional contacts between stent and wall, nonlinear material behavior for shape memory alloy (super-elastic model), binding points between valve and stent, pericardium orthotropic properties and non-Newtonian blood properties (Carreau model).

RESULTS: This study delivered preliminary information about the evolution of forces, pressures and stresses during a heart pulse and their effects on working conditions, mechanical integrity and lifetime assessment of the device. Stress-strain curves over a cycle were extracted at the most critical locations in the stent and compared with the fatigue properties of Nitinol.

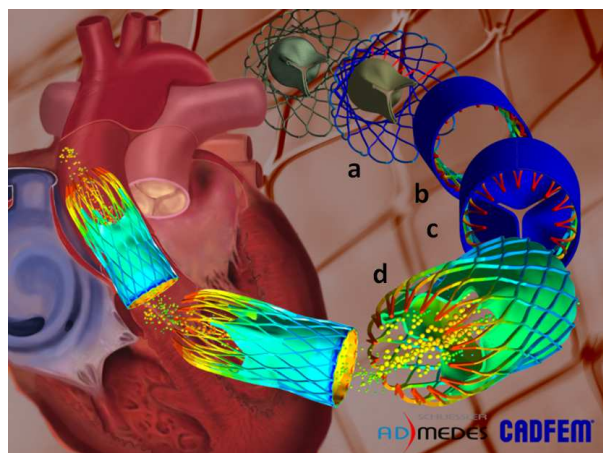


Fig. 1: Representation of the simulation steps; expanded (a), crimping (b), binding with valve (c), fluid-structure interaction over time (d).

DISCUSSION & CONCLUSIONS: The capability to model valve insertion and positioning inside the aorta and interaction with blood flow during a systolic pulse was demonstrated using a state of the art numerical analysis technique provided by the commercial software ANSYS. The results obtained under the assumption of a perfectly stiff aorta wall (strong stenosis) should however be complemented with further simulations using flexible walls.

The ultimate goal of such simulations is the evaluation of patient-specific configurations, due to the possibility to repeat the analysis with different geometric and material parameter sets. Furthermore, this modeling technique could also be applied for other stent percutaneous interventions such as intravascular stenoses [2], atherosclerosis [3] or aneurisms [4-5].

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Development of a test model to evaluate the pre-load of screw-retained dental implant systems

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INTRODUCTION: Pre-load plays a crucial role in the performance of modular screw-retained dental implant systems. Inadequate pre-load can lead to either loosening and/or fracture of the retaining screw. Pre-load is defined as the tensile force generated in the abutment screw as the result of screw tightening. Optimal pre-load condition enables long-term stability of the system because it has – in addition to mechanical strength – a direct influence on the fatigue performance.

This newly developed experimental model allows a real-time evaluation of the pre-load as a function of the tightening torque. Specifically, this model enables an investigation of the influence of various parameters such as different material pairings, seat geometries, environmental conditions as well as screw coating, screw lubrication, and screw design on the pre-load of the system.

METHODS: The test setup consists of a custom-made load frame comprising an implant holder attached to a static tension/compression load cell and an abutment-holding plate assuring a gap of 0.5 mm between the implant and the abutment. The implant system (implant, abutment and screw) is mounted on the load frame. The frame is attached to a torque sensor positioned on a freely axially moving sled of a torsion machine. The screw driver is clamped on the electronic motor of the machine, which allows for controlled rotation (tightening/loosening) of the screw (Figure 1).

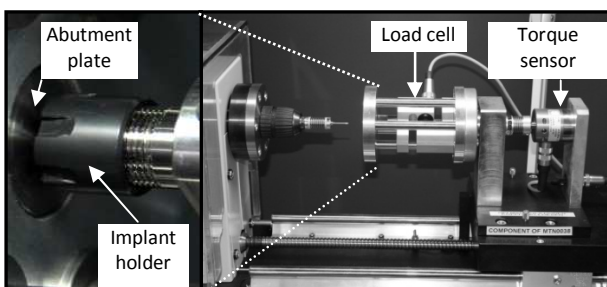


Fig. 1: Rig mounted on torsion/tension machine (TesT GmbH, Germany) used for evaluating pre-load. As the abutment screw is tightened, a load cell is used to measure pre-load.

Preliminary tests were done to verify the feasibility of this test model through an evaluation of the effect of low friction screw coating. The pre-load generated with uncoated titanium (Ti) screws was evaluated in group A (n=4) and compared to

identical but coated screws in group B (n=5). Tests were performed according to standard clinical practice, employing 3 screw tightening cycles. The screw was tightened continuously to 35 Ncm as stated in the manufacturer's IFU, and the resulting pre-load was recorded by the 2 kN tension/compression load cell. Statistical analysis was performed using Minitab 16. Normality was assessed by a Kolmogorov-Smirnov test, and non-parametric tests (Mann-Whitney) at significance level $\alpha=0.05$ were conducted, followed by Bonferroni correction.

RESULTS: The systems in group B showed higher pre-load values compared to group A ($p=0$). Furthermore, while the number of tightening cycles did not affect the pre-load of the standard Ti screws in group A, it resulted in a significant increase ($p=0.01$) in the pre-load values of the coated Ti screws in group B (Figure 2).

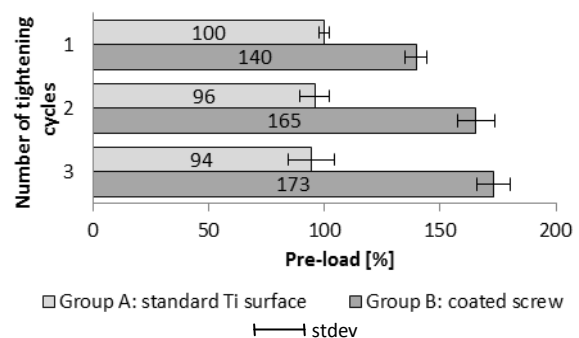


Fig. 2: Pre-load measured at 35 Ncm for coated and uncoated Ti screws.

DISCUSSION & CONCLUSIONS: The reproducibility and small scattering of the initial results underline the feasibility of the test model developed in this study. The higher pre-load obtained for coated screws in comparison to the uncoated screws and the increase of pre-load with number of tightening cycles are both in accordance with the coating manufacturer claims. This model allows versatility, e.g. in operating modes (continuous vs. stepwise tightening, physiological environment, etc.) and has demonstrated feasibility in evaluating the influence of various parameters on the pre-load of screw-retained dental implant systems.

Applications of atomic layer deposition in implant dentistry

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INTRODUCTION: Bioactive materials are of great interest due to a strong bond between bioactive surface and bone material. Materials and techniques used for treatment of implant surfaces have a number of considerable disadvantages. Bioactive thin films grown by Atomic Layer Deposition (ALD) can solve a number of problems of implant treatment and increase the quality and lifetime of implants. ALD is a technique allowing the growth of extremely uniform, conformal and reproducible thin film coatings for various industrial applications [1]. Recently, the bioactive ALD coatings on titanium have been experimentally investigated [2, 3]. This work, however, focuses on ALD application for implant dentistry on an industrial scale.

METHODS: Deposition of thin TiO₂ films was performed using a hot wall low pressure ALD reactor with titanium ethoxide and water as precursors. Commercial pure titanium (cp-Ti) plates, dental implants and silicon plates were used as substrates. The chemical and structural properties of coatings were characterized by X-Ray photoelectron spectroscopy, ellipsometry and X-ray diffractometry. Biological evaluation of samples with bioactive coating was carried out in accordance with ISO 10993-1:2009. The bioactive properties were verified by *in vitro* Simulated Body Fluid tests and *in vivo* tests.

RESULTS: Anatase phase of resulting thin oxide films was examined with X-Ray Diffraction (XRD) with ARL X'TRA (Thermo Scientific) tool. The hydroxyapatite formation on the ALD coated samples soaked in SBF was detected using X-ray diffraction and Scanning Electron Microscopy (SEM, FEI Quanta 200) with element analysis (EPMA). Acquired data confirmed that the coating is non-toxic; these materials have excellent biocompatibility and can be used for dental implant coatings. The histological evaluation in maxilla of mini-pigs showed a direct bone to implant contact (BIC) with no signs of inflammatory or foreign body reaction. The histomorphometric analysis showed high BIC value on implants with TiO₂ coating when compared to non-coated surfaces. Pull-out tests of cylindrical samples showed

average values of 290 N with bioactive coating and 237 N without it.

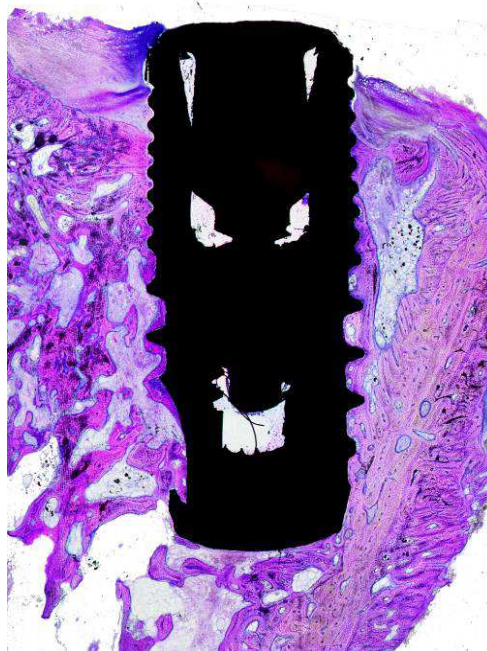


Fig.1: The histologic image of the ALD coated implant after *in vivo* biocompatibility tests.

DISCUSSION & CONCLUSIONS: The present results show bioactivity and osseointegration capacity for the dental implants with anatase covering formed by Atomic Layer Deposition. The batch-type ALD equipment and technology allowing the simultaneous bioactive coating treatment of more than 5000 dental implants per run was developed. An excellent coating uniformity and pinhole free deposition was achieved in this batch ALD process. Serial production of dental implants with bioactive surface have started by CONMET, LLC.

REFERENCES: ¹ N. Pinna et al (2012) Atomic Layer Deposition of Nanostructured Materials. ² I.R. Spears, M. Pfeleiderer, E. Schneider, et al (2000) *J Biomech* **33**:1471-77. ³ A.A. Solovyev et al, *Nanotechnologies in Russia 2013*, Vol. 8, Nos. 5–6, pp. 388–391.

Design optimization of a ceramic acetabular hip prosthesis

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INTRODUCTION: Hip resurfacing has become of increasing interest for hip replacement procedures due to its benefits such as the preservation of bone and the larger degree of motion that can be achieved by larger femoral head diameters. The goal within this project is to develop a thin walled monoblock ceramic cup as counterpart for a femoral resurfacing head implant. Target characteristics of the implant are a) sufficient mechanical strength, b) good stability after insertion (termed as *primary stability*) and c) an optimal anchorage when osseointegration has taken place.

METHODS: 2d / 3d Finite Element Analysis (FEA) was used to calculate mechanical stresses in the cup that occur under insertion and critical loading conditions such as stumbling. The *primary stability* of different cup designs was evaluated by numerical simulation of the press-fit procedure using anonymized CT data of 5 selected anatomical subjects. Furthermore, press-fit experiments acc. to MacDonald et al. [1] were performed (in PU-foam with a density of 0.24 g/cm³). The resulting primary stability was then quantified by three test configurations 1) pull-out, 2) lever-out and 3) torsion-out. Each design was evaluated in terms of the magnitude of load (F_{OUT}) and torque (M_{OUT} for lever-out and torsion-out) to release the press-fit (with respect to F_{IN}). The influence of the outer contour on the anchorage was studied under simplified conditions (geometrical anchorage w/o bone-implant interface adhesion) by pull-out tests on cup-variants that were embedded in gypsum. The cup design was optimized in terms of outer diameter oversize and outer contour (rills, spikes and combination of both).

RESULTS: Experiments showed superior stability for variants fulfilling the following criteria: a) high press-fit contact area in area of densest bone; b) local anchorage through rills and spikes with a depth of 0.5-1.0 mm. A multi-radius contour without rills provided good *primary stability* as long as it fulfilled criterion a). Designs with rills exhibiting a combination of both criteria showed highest potential to assure sufficient *stability*. Depending on the design, F_{OUT}/F_{IN} was in a range of 0.08-0.15 and 0.07-0.20 for press-fit experiments and 3d FEA on a CT-based bone

model, respectively. M_{OUT}/F_{IN} was in range of 2.4-6.5 mNm/N and 0.6-2.1 mNm/m for lever-out and torsion-out, respectively. Experiments and 2d FEA revealed an optimal *stability* for a multi-radius contour with a diameter oversize between 1 and 2 mm.

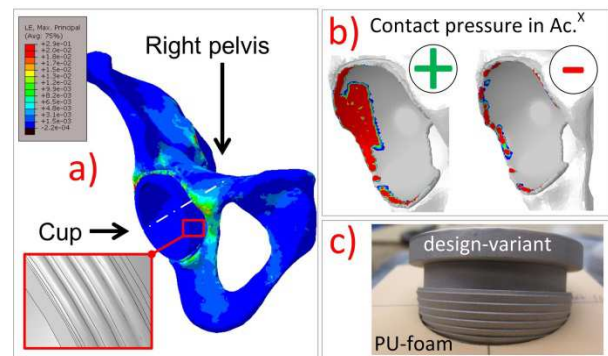


Fig. 1: a) strain distribution in bone during cup insertion, b) contact pressure distribution in acetabulum, c) press-fit test.

DISCUSSION & CONCLUSIONS: To assure long term reliability, implant *stability* is of crucial importance. Schreiner et al. showed that a porous & rough surface revealed osseointegration of bone, but questioned whether a porous surface alone is enough to ensure a safe long term stability of the implant [2]. For an optimal stability, we suggest a combination of an oversized outer-contour with spikes and a rough surface to enhance osseointegration. The adhesion and proliferation of bone cells on a ceramic surface has been investigated within a separate biological study.

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The orthopaedics market in transition

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INTRODUCTION: Single products or groups of products follow so-called product life cycles (PLC). This is an idealised model describing product sales, profits or cash flows as a function of time (Fig. 1, sales, full line). Usually, 4 phases are used to describe the PLC, introduction, growth, maturity and decline. The following explanations might be easier to picture if one imagines the example of desktop PC. *Introduction:* After a new type of product is invented, it is introduced to the market, often by a pioneering company. Investments are high and, as a consequence, prices are high as well, and only a few consumers can afford the new product. *Growth:* If sales reach a certain level, the market penetration is high enough to trigger increasing demand (avalanche effect) and competitors are encouraged to enter the market. Investments are readily amortised, the price level is still relatively high and margins are comfortable. *Maturity:* The products turn into commodities, and, as inexpensive generic products become available, brand awareness weakens. Purchase decisions are mainly based on the price. Growth rates may be small in established markets, but low-cost products may open opportunities in developing countries. Suppliers and manufacturers are forced into concentration, specialisation and process optimisation to keep appropriate margins. *Decline:* New types of products appear replacing the old products, e.g. portable devices instead of a desktop PC, and sales decrease. Eventually, most companies abandon the product.

THE ORTHOPAEDICS MARKET: The term orthopaedics is used as synonym for mainstream joint implants, such as hip, knee, shoulder and elbow endoprostheses. This product group had an introduction phase during the 1960s and 70s, followed by a growth phase, globally ending around 2005 (Fig. 1). Thus, for approximately one decade now, the signs of the maturity phase become increasingly evident:

- only 5 orthopaedic companies, in terms of sales, control approximately 90% of the world market
- single digit global market growth rate
- pressure on consumer prices
- mainstream («generic») product designs
- rather process than product innovation
- efficiency is predominant issue.

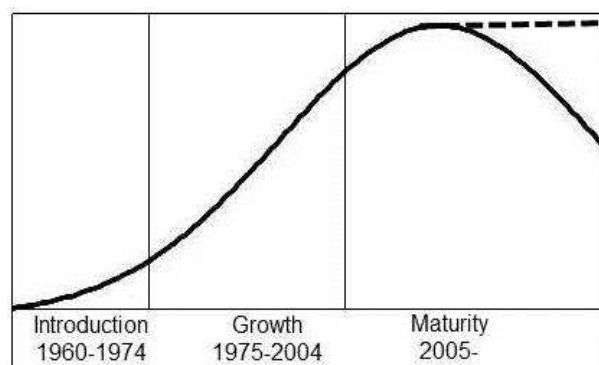


Fig. 1: PLC of joint implants: the phase of maturity was entered around 2005. Since no technology is known to replace these products, there is no sign of decline yet. Instead, the dotted line is the most likely scenario ("stable maturity").

CONSEQUENCES FOR SUPPLIERS: Entering the phase of maturity affects all market participants. Cost reduction is the predominant issue along the logistics chain. Suppliers participating in the production of mainstream implants can only be successful if core competences can be turned into cost leadership, usually related to high volume production. The necessary investments have to be done in a position of strength, before heavy cash drains appear. Due to specialisation, former competitors may become partners; therefore professional networks, such as Medical Cluster, are essential.

Jossi Orthopedics, for example, is in the process of optimising its cold-forming technology, producing acetabular shell blanks from flat discs. A number of design propositions were elaborated and, if possible, IP protected to be able to offer possible solutions to orthopaedic companies from a position of strength. A streamlined high-volume production enables competitive pricing. Strategic partnerships with other suppliers create new business opportunities and may serve as flank protection.

CONCLUSIONS: Orthopaedic joint implants have entered the phase of maturity. The effects become increasingly visible and strongly affect suppliers. Efficiency has become the main driver for process and product innovation. Anticipation of change is the prerequisite to successfully shape the future and to maintain a position of strength.

Bringing spinal implants to market: fundamentals and evolutions in development techniques

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DePuy Synthes Spine, Le Locle, CH

INTRODUCTION: The requirements to bring new medical devices to market have significantly increased through the years. Regulatory bodies have been placing continuous emphasis on the control of the design, manufacturing processes, and post market surveillance. Therefore this study aimed at reviewing the best practices and industry trends.

METHODS: The current Product Development process at DePuy Synthes Spine was used as an underlying roadmap to explain preeminent practices, and was supported by real life examples of commercialized products.

RESULTS: To optimize the control of the entire development process, most companies use today a stage gated process to transfer the product idea over design iterations, into the manufacturing environment, and onto the market. Its major elements cover for how a project starts, where the original idea emerges, who are the stakeholders, how the idea is refined, design concepts generated, how intellectual property challenges are managed. Risk management activities are concurrently being addressed focusing not only on the technical activities, but also onto other business risks such as regulatory and reimbursement complexity, and possible clinical study needs to validate the strength of the business case, resource planning and alignment in matrix organizations. As the project progresses, quality track records are established, from design inputs to outputs with associated verification and validation including transfer to production. Latest ISO and ASTM standards are applied onto the implants, instruments, and entire system and surgical flow through full functional evaluation via simulations, benchwork and labs. Technical activities are substantiated with appropriate statistical significance, and linked to the risk management to ensure safety and efficacy. Additionally, the new product instructions for use provide claims for which equivalence to a predicate is needed; else a clinical study will be required. Launch preparation is completed with product production and inspection, getting appropriate regulatory approvals and country registrations, and finalizing the market introduction and possible professional education. As the product is released and clinically used, feedback will be obtained via

the company complaint handling system, post market surveillance program and eventual clinical study. Major development activities evolved to meet the industry trends are summarized in Table 1.

Table 1. Industry development trends.

Addressing all customer needs (Patients, Physicians, Providers, Policy Makers, and Payors).
Reducing cost during New Product Development, Manufacturing, and Distribution
Generating robust clinical data to substantiate claims, justify price, and reimbursement
Continuing compliance to growing demands in Health Care Compliance, Post Market Surveillance and Quality Documentation
Supporting increasing expectations of single-use and custom products availability
Combining complementary technologies to cover the entire continuum of care
Using latest Product Development procedures, simulations, risk management, verification, validation, and manufacturing methods
Leveraging from Design Excellence [1], Six Sigma and ethnographic studies to optimize development

DISCUSSION & CONCLUSIONS: While performance expectations on newly launched medical device are rising, the pressure on sales price continues as health care providers and payers try to cap health care spending. Since development, commercialization and clinical study costs have rocketed, only companies mastering the art of absorbing the unmet needs of their stakeholders and translating them properly into a product/service will be able to stay successful. In these scenarios, robust processes such as Design for Manufacturing and Design Excellence are paramount to take out risk and thereby cost early in the development process.

REFERENCES: ¹ H. Défossez, H. Serhan (2013) *J Biomech Eng* **135**: 11450601 - 11450611.

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ZfW 102/Magnezix die erfolgreiche Entwicklung eines resorbierbaren Magnesium-Implantatwerkstoffs

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EINLEITUNG: Aufbauend auf der Eigenentwicklung von 20 neuen Magnesiumlegierungen wurde 2007 mit der Entwicklung bioresorbierbarer Implantatwerkstoffe begonnen. Die Grundvoraussetzungen waren: Zugfestigkeit 250 – 350 MPa, Bruchdehnung > 5 %, gute mechanische Bearbeitbarkeit, Korrosionsbeständigkeit in körperähnlichen Flüssigkeiten mindestens 30 % oberhalb von Reinmagnesium, gute Erschmelz- und Vergießbarkeit, niedrige Toxizität, gute Verfügbarkeit, niedriger Preis.

UNTERSUCHUNGEN: Zur Entwicklung des bioresorbierbaren Magnesiumwerkstoffes wurden alle werkstoffkundlichen und physiko-chemischen Untersuchungsmethoden benutzt. Von besonderem Interesse waren die Beeinflussung der Korrosionsgeschwindigkeit durch metallurgische Maßnahmen und zusätzliche physikalische und elektrochemische Oberflächenbehandlungen. Die Verwendung der Sekundärionen-Massenspektrometrie erwies sich als besonders hilfreich. Im Anschluß an diese grundlegenden Vorarbeiten erfolgten dann *in vitro* Auslagerungsversuche in den verschiedensten körperähnlichen Flüssigkeiten - Ringer, Hanks etc. Hierzu verwendeten wir die quantitative Messung des freigesetzten Wasserstoffgases, der gelösten Metallkomponenten mittels ICP und der gebildeten festen Korrosionsprodukte mit der Röntgenfluoreszenzanalyse und Röntgendiffraktometrie. Nach Abschluß der *in vitro*-Versuche erfolgten dann *in vivo* Untersuchungen, Implantation des Zielwerkstoffes in Ratten, und Kaninchen. Auf Grund der erfolgreichen Tierversuche wurde von 2010 bis 2012 die klinische Studie *Hallux Valgus* in Hannover durchgeführt. Im Mai 2013 wurde die CE-Zulassung der Syntellix Magnezix Kompressionsschraube für 30 europäische Länder erteilt. Seit Juni 2013 ist die Magnezix Kompressionsschraube im täglichen Einsatz.

ERGEBNISSE: Abbildung 1 zeigt exemplarisch den Einfluß einer spezifischen Wasserstoffbehandlung auf das Korrosionsverhalten des Magnezix Werkstoffes. Mit Hilfe der Implantation von Wasserstoffatomen in die Oberfläche des

Substrates kann das freie Korrosionspotential um 500 mV in positiver Richtung verschoben werden.

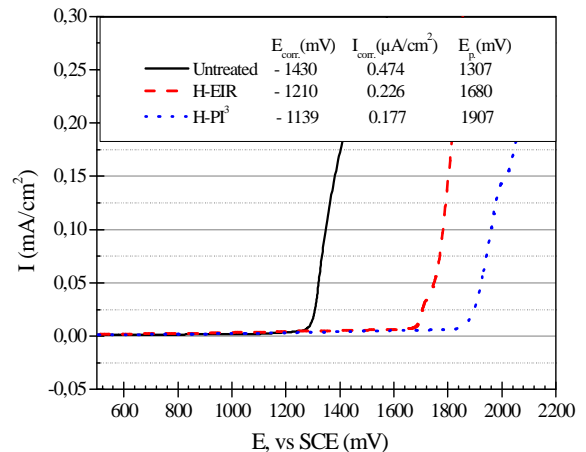


Abb. 1: Freies Korrosionspotential in Abhängigkeit der Oberflächenbehandlung, Ringer Lactatlösung, 37 °C.

SCHLUSSFOLGERUNGEN:

Die erfolgreiche Entwicklung dieses resorbierbaren Magnesium-Implantatwerkstoffes ist ein Beispiel dafür, dass aufbauend auf grundlegenden Ergebnissen einer gezielten Werkstoffforschung neue Wege in der Human- und Tiermedizin beschritten werden können.

SCHRIFTTUM: ¹ V. Neubert et al (2007) Thermal stability and corrosion behavior of Mg-Y-Nd alloys. *Mater. Sci. Eng.A* pp. 329-333. ² J. Kuhlmann et al (2013) *Acta Biomater.* (10) 8714-21.

Short dental implants: technical and clinical challenges

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INTRODUCTION: The rate of elderly edentulous patients with vertically severely resorbed jaw bones is constantly increasing. In such cases, the treatment of standard for implant-borne dental prostheses consists in vertical bone augmentation, often supported with autologous bone, and following placement of long implants. This excludes many patients from the advantage of a fixed dental restoration, due to risk reasons but also due to the patient's treatment fear. Short implants offer a simple, less invasive and little time-consuming alternative therapy, however, the dental surgeon has to observe carefully that mechanical overloading of the bone is avoided.

METHODS: A titanium based implant system with an enossal length of 4 mm, a total length of 7.3 mm and diameters of 4.1 and 4.8 mm, was developed. The enossal part with a narrow thread pitch enhances the surface area. The coronal, supra-crestal part of the implant has a design identical to a commercially available implant line (Institut Straumann AG, Standard Plus implant neck configuration). The enossal surface, after machining is sandblasted, acid-etched and chemically modified to render the surface moderately rough (as defined in [1]) and hydrophilic. Mechanical stability of a 4 mm short implant (4SI) with 4.1 mm diameter was compared in a finite element model (FEM) with a marketed control implant of 10 mm length (CI) in a test setup aligned to ISO 14801 with 1 mm simulated bone resorption. Clinical performance of 4SI was investigated in patients with severely resorbed mandibula [2]. 86 implants were used in splinted restorations (every dental unit supported by one 4SI) and loaded after healing of 10-12 weeks. The patients were followed up to 5 years.

RESULTS: The FEM results (Fig. 1) reveal that at an angulation of the force axis of 30° in a 4SI the maximum van Mises stress is 121 % of the value in the CI (100 %). At a force angle of 10° the maximum van Mises stress is reduced to 53 % for CI and 62 % for 4SI.

In the clinical trial, 24 subjects with 77 4SI were followed up as per protocol for 5 years (Fig. 2), of which five implants were lost and one censored i.e. judged as failures. This yields a 5-year implant survival rate of 92.2% (71 out of 77).

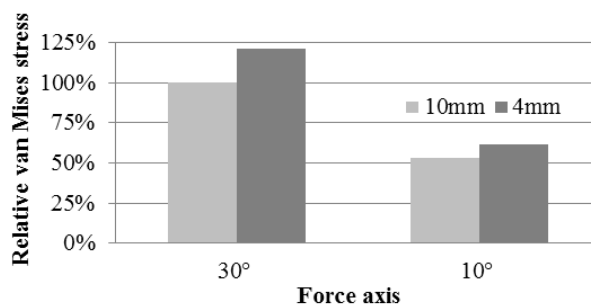


Fig. 1: FEM maximum van Mises stress values at different implant lengths and force axes.



Fig. 2: Clinical trials radiograph of fixed dental reconstruction based on 4 mm short implants

DISCUSSION & CONCLUSIONS: Long implants are designed for lateral forces acting in a 30° angle to the implant axis. In short implants this leads to increased mechanical stress; therefore, the supra-structure should be constructed to minimize lateral forces. Following this principle, clinical data with 4SI reveal a survival rate of 92.2 %, which confirms earlier findings [3,4] that survival rates are comparable to procedures with bone augmentation and longer implants, however, short implants reveal lower complication rates. More clinical investigation is required to determine safe and efficient use of short implants.

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Poster Session

- 1 *Production of Micro/Nano structured Materials by Metal Injection Moulding (MIM) and its effect on human bone marrow stromal cells*
Dr. Arie Bruinink, EMPA, CH
- 2 *Post-hot isostatic pressing: A healing treatment for process related defects and laboratory grinding damage of dental zirconia?*
Jakob Kuebler, EMPA, CH
- 3 *A new era for porous tantalum biomaterials thanks to Additive Manufacturing: a clinical proof-of-concept*
Ruben Wauthle, Christian Wielk, LayerWise NV, Belgien
- 4 *Release kinetics of electrochemically deposited antibacterial copper from anodized titanium implant surfaces*
Prof. Dr. Michael de Wild, FHNW, CH
- 5 *Roughness of plasma sprayed HA-ZrSiO₄ composite coatings*
Dr. Hassan Gheisari Dehsheikh, Shahreza University, Iran
- 6 *Population Based Design Validation of a Subcutaneous Bone Conduction Implant System*
Dr. Tobias Wagner, Materialise, Deutschland
- 7 *Aqueous Cleaning of Medical Devices: Characterization of Ultrasound in the Cleaning Bath*
PD Dr. Christiane Jung, KKS Ultraschall AG, CH
- 8 *iPROMEDA: A National and European initiative to reduce the risk of implant associated infection*
Dr. Reto Luginbühl, RMS Foundation, CH
- 9 *Biologische Beurteilung nach ISO 10993-1: Vorgehen und Struktur*
Ursula Rösler, Axxos GmbH, CH
- 10 *Ein experimentelles Modell für das Training von endoskopischen transsphenoidalen Hypophysenchirurgie*
Raphael Schmid, inspire AG, CH
- 11 *Nano-Enabled Smart Dressing For Wound Care*
Shruti Mankar, Indian Institute of Technology, Indien
- 12 *X-Ray Microscopy to determine the surface interaction between osteoplasts and a titanium surface in 3D*
Dr. Antonio Casares, Carl Zeiss AG, CH

Production of micro/nano structured materials by metal injection moulding (MIM) and its effect on human bone marrow stromal cells

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INTRODUCTION: Micro metal injection moulding (μ -MIM) is a cost effective series production process for shape forming of micro parts and micro-structured surfaces. Material and surface characteristics can be tailored depending on the powder characteristics, surface quality of the mould, and sintering program. In the present study we optimized the μ -MIM process to improve material characteristics and to obtain a well-defined surface micro and sub-micrometer scaled pattern. For instance, small surgical and dental implants featuring improved mechanical performance and defined bioactive surface patterns can be realized in one processing step [1]. Surface structuring is known to affect cells [2].

METHODS: Micro structured stainless steel samples were prepared by blending an iron powder mixture with a master alloy (MA) powder containing 55 % Chromium, 38 % Nickel and 7 % Molybdenum. While the MA powder share was maintained at one third by weight for all experiments, the iron mixture of two thirds by weight was blended from micron-sized carbonyl iron powder and nanoscale iron powder (nanopowder). On the whole, four powder blends were prepared with a total nanopowder share of 0, 16.7, 25.0 and 33.3 wt%, respectively termed I, II, III, IV. To prepare feedstock for injection moulding, these blends were mixed with a wax-polymer based binder. The ratio of powder to binder was 55:35 vol% for all materials. Final homogenization took place at 120 °C for two hours. After cooling to room temperature and granulating, materials I, II, III and IV were obtained with a defined powder : binder ratio and different shares of nanopowders. Cell culture procedures and tests are done as previously described [3, 4].

RESULTS: Using a patented (EP 09708 521 1) MIM process the idea of improving cell adhesion by creating regular micro patterns on biocompatible alloys for medical implants was evaluated. Key points of the process and obtained material are:

- The process allowed selective and reproducible structuring without the need of post-processing steps.
- A precise replication of a surface topography of regular, defined, potentially bioactive surface arrays in the form of micrometer scale hemispheres with 5, 30 and 50 μ m in diameter was produced.
- By using hybrid nano/micro powder mixtures, a very fine microstructure developed during sintering which caused an additional surface roughness on submicroscale.
- Using the current optimized procedure, the very fine microstructure strongly improved mechanical characteristics in comparison to conventional materials in terms of stiffness and stability under mechanical stress.
- Human bone marrow stromal cells were able to colonize the surface and to differentiate towards osteoblasts. It was found that the current evaluated microstructured surfaces affected the cell shape and surface contact, i.e. as a result cells adhered nearly exclusively on the hemispherical structures (Fig. 3).

DISCUSSION & CONCLUSIONS: In this study an optimized μ -MIM process was developed, enabling:

- surfaces with highly replicable predefined micrometer scale topography and with defined sub micrometre-scale sub-structure
- parts with superior density and strength characteristics
- high biocompatibility and suitability for implant applications

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- ³Bitar et al (2012) *Eur Cells Mater* **23**, 333 – 347;
- ⁴Bitar et al (2013) *J Mater Sci: Mater Med* **24**:1285-1292.

Post-hot isostatic pressing: A healing treatment for process related defects and laboratory grinding damage of dental zirconia?

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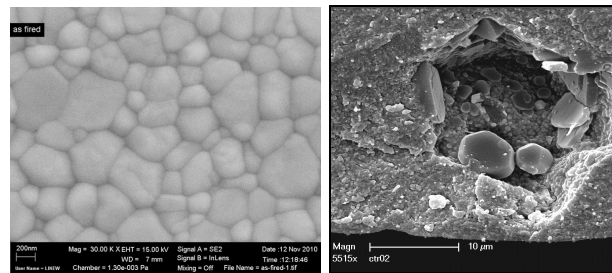
INTRODUCTION: Processing parameters and post-sinter rough or even fine grinding are influencing the final mechanical properties of 3Y-TZP [1-3]. The hypothesis of this study was that post-sinter hot isostatic pressing (post-HIP) would be beneficial for improving reliability and strength of both sintered and coarse ground sintered zirconia by closing or reducing surface and/or small volume defects [4].

METHODS: Sintered bars (3 x 4 x 45 mm³) of an experimental 3Y-TZP with diamond surface finish were provided by a manufacturer and randomly distributed in five groups. One group served as control (G1); one was post-HIPed at 1400 °C (G2) and one at 1350 °C (G3); one was coarse ground with 120 µm diamond disk grain size (G4); one was ground 120 µm and post-HIPed (G5). The specimens were fractured in air in 4-point-bending tests. Weibull characteristic strength, reliability-parameter and confidence intervals are reported. Identification of the critical flaw was performed by SEM on the fractured surface of all specimens and XRD analysis was performed in all groups.

RESULTS & DISCUSSION: G5 had a significantly lower σ_0 than G1. No significant differences were seen in the reliability (m) among the groups. Fractography revealed critical intrinsic

	Weibull (σ_0) + CI (MPa)	m (reliability) + CI
G1	973 (932 - 1016)	10.6 (7.45 - 15.1)
G2	930 (871 - 995)	6.90 (4.87 - 9.9)
G3	898 (848 - 952)	7.94 (5.6 - 11.4)
G4	921 (857 - 991)	6.35 (4.48 - 9.11)
G5	881 (847 - 918)	11.4 (8.03 - 16.3)

subsurface flaws of 10–60 µm present in all groups resulting from the processing parameters. No “healing” resulted after post-HIP. Grinding sintered zirconia with 120 µm diamond disks induced radial cracks of 10–20 µm and an important pseudo-cubic phase transformation that was not completely removed after post-HIP.



Left: SEM images of mirror polished and thermally etched specimen (G1).

Right: Processing flaws (G1).

Post-HIP increased slightly the relative density by 0.1 % but without improving the strength and reliability.

CONCLUSIONS: Post-sinter HIP could not close existing critical processing subsurface flaws in the size range of 10–60 µm. Surface grinding with 120 µm diamond grain sizes introduced radial cracks which were smaller than the processing defects of this experimental ceramic.

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ACKNOWLEDGEMENTS: This research was funded by SSO grant # 240-09. The poster presented is based on SS. Scherrer, et al (2013) *Dental Materials* **29**: e180–e190.

Release kinetics of electrochemically deposited antibacterial copper from anodized titanium implant surfaces

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INTRODUCTION: Functionalizing implant surfaces by antibacterial agents reveals as a promising strategy to reduce infection risk appearing immediately or years after medical implant placement. We have recently established an electrochemical method to deposit antimicrobial copper on anodized titanium samples [1, 2]. First studies indicated that only ~25% of Cu are released into simulated body fluid (SBF) after release time of one year (studies at 37°C and 80°C) [1]. Here we report the release kinetics in more detail. It is observed that calcium present in SBF facilitates apatite formation at the implant surface which reduces copper release.

METHODS: Discs of cpTi were anodized according to the spark-assisted anodizing method [1, 2]. Copper was electrochemically deposited using proprietary electrolyte and process parameters (KKS TioCelTM). The amount of deposited Cu per disc was determined by dissolving Cu in 65% nitric acid at 50°C over night. Cu concentration was determined by atom absorption spectroscopy (AAS, Perkin Elmer, AAnalyst 800, graphite furnace, 324.8 nm) as well as inductively-coupled-plasma mass spectrometry (ICP-MS, Agilent 7500cx). Release studies were performed at 37°C for 14 days followed by an accelerated aging during another 14 days at 80°C (Arrhenius accelerated release, total simulated extraction duration: 289.8 days). Aliquots of SBF (SIGMA, Earl's balanced salt solutions E6267 and E3024) were taken from the incubation vessel after certain time intervals and the amount of Cu was quantified by AAS and ICP-MS.

RESULTS: After 289.8 days in SBF E6267 (no Ca), the cumulated release of Cu from the Ti surface corresponds to the total Cu amount per disc. The release rate decreases with extraction time (Fig. 1). Accordingly, Cu was no more detected on the discs by SEM/EDX after the end of the release experiment (Fig. 2 bottom). Studies with SBF containing calcium (E3024) indicated a qualitatively similar course of the release curve, however with a more pronounced decrease of the rate and lower Cu contents. Interestingly, here SEM after the release experiments revealed dense

apatite formation (molar ratio Ca/P: 1.57), see Fig. 2 top. Cu was still detectable on the surface by EDX. In addition, Cu adsorbed at the surface of the glass vials was observed, however, only in the presence of Ca.

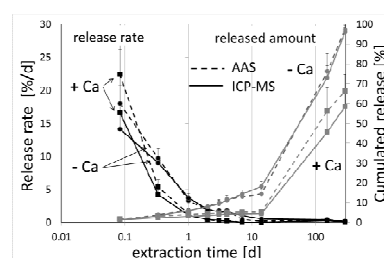


Fig. 1: Mean release rate for Cu ($n = 4$, SBF E6267) and cumulated Cu amount logarithmically plotted against the extraction time.

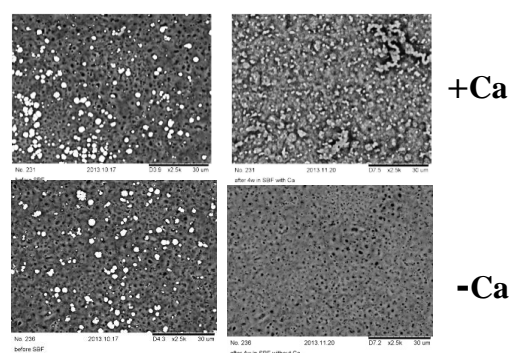


Fig. 2: SEM pictures of copper deposited discs before (left) and after (right) the release experiment in E3024 (top) and E6267 (bottom).

DISCUSSION & CONCLUSIONS: The Cu release rate as function of the extraction time follows known release profiles independently of the presence of calcium. The amount of detectable released Cu is significantly lower in the presence of Ca because (i) apatite growth on the discs hinders Cu leaching and (ii) part of Cu together with Ca is adsorbed at the vial glass.

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ACKNOWLEDGEMENT: CTI funding (N° 14293 2 PFNM-NM) is acknowledged.

Population based design validation of a subcutaneous bone conduction implant system

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INTRODUCTION: The state-of-the-art for bone conduction implant systems is a percutaneous implant. However, especially younger patients often complain about the esthetic aspect of having a visible percutaneous abutment. Recently, a new generation of bone conduction implants is emerging, where a magnet is implanted subcutaneously and the information is passed on to an external magnet through magnetic connection. This study examines a population to validate three aspects of the design: overlaps between magnet and cranium to predict the need for reaming during implantation; bone thickness to validate implant length; soft tissue thickness to validate the strength of the external magnet. As far as we know, this is the first study that yields statistical information of bone and soft tissue thickness in that region.

METHODS: For this study, 50 CT scans of crania were used. The subjects were male (25) and female (25) from US (22) and European (28) nationalities, between ages 16 and 83, with no visible conditions to the cranium. The crania were segmented from the CT scans using Mimics[®]. A cylindrical region of interest (ROI), with a radius of 20 mm, was defined and isolated for each subject using 3-matic[®] (Figure 1). In Matlab[®], a circular magnet with a radius of 13 mm was virtually implanted (Figure 2). The surfaces of magnet, bone and soft tissue in this ROI were sampled and analyzed across the population.

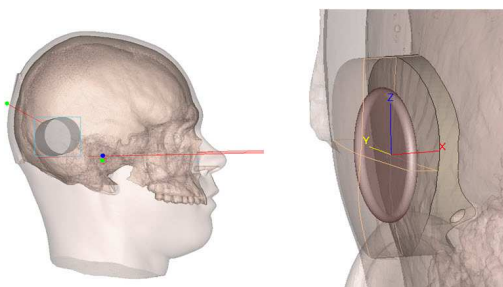


Fig. 1: Region of interest.

RESULTS: There were 11 subjects where overlaps between magnet and cranium took place. All of these overlaps took place over an estimated area of more than 10 mm². When looking at the number of overlaps per sample point, a very clear trend was visible: all overlaps seemed to occur at the top and bottom side of the magnet surface.

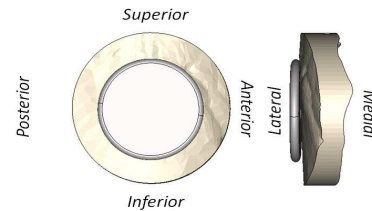


Figure 2: positioning of implant and magnet

This was confirmed by looking at the average magnet distance. This can be explained by the fact that the skull has a higher curvature in the anterior-posterior direction, which gives more clearance to the magnet (Figure 3).

The bone thickness varied between 2.42 mm and 25.13 mm. The average bone thickness in the ROI was 6.8 ± 1.25 mm. Plotting the minimum thickness revealed that bone thickness in the range of 2-3 mm could be found in almost the entire ROI, but certainly in the upper half.

The soft tissue thickness varied between 1.19 mm and 17.88 mm. The average soft tissue thickness was 7.25 ± 1.85 mm. There was a clear gradient towards higher thicknesses in the posterior-inferior direction, which suggests that the soft tissue got thicker towards the neck, as can be expected.

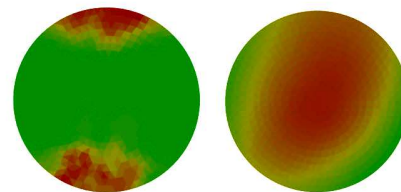


Fig. 3: (left) number of overlaps, between 0 (green) and 6 (red); (right) average magnet distance, between 0 mm (red) and 2 mm (green).

DISCUSSION & CONCLUSIONS: This study validates the design of a subcutaneously implanted magnet for bone conduction implants based on a statistical population analysis. This study suggests that in about 20 % of the cases, minor reaming will need to be performed. The soft tissue thickness distribution validates the strength of the external magnet. Finally, the bone thickness distribution gives valuable information for determining the range of implant lengths.

Cleaning of medical devices: Testing ultrasound in the cleaning bath

A Zwahlen¹, M de Wild¹, C Jung²

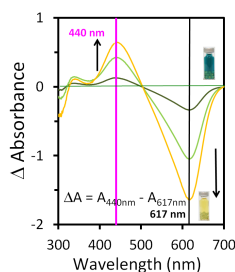
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INTRODUCTION: The cleaning process of medical devices needs to be qualified by monitoring important process parameters. We compare two methods for quantifying ultrasound in the cleaning bath (i) by measuring the cavitation noise level [1] and (ii) by studying the sonochemical reaction used for the color change of the SonoCheck test vials [2].

METHODS: Ultrasound tank: KKS Ultraschall AG; (358 x 358 x 400) mm³; transducers at bottom; neutral cleaner with tensides; 60±2 °C. Tests: at 3 different positions (A, B, C) in the bath; with either 27 kHz or 80 kHz ultrasound frequency. SonoCheck vials (PEREG GmbH) were placed in the cleaning bath using a custom-made holder. The ultrasound-induced color change of SonoCheck vials was quantified by spectral absorbance changes (Fig. 1). The cavitation noise level was determined at 183±0.5 kHz using the KaviMeter (ELMA Hans Schmidbauer GmbH & Co. KG, Singen) [1]. The hydrophone head was placed at exactly the same position as the SonoCheck vial.

Fig. 1: Difference spectra of SonoCheck vials before and after ultrasound application (arrow at 617 nm and 440 nm represent color change from green to yellow, i.e. a change in absorbance).



RESULTS: The absorbance change of SonoChecks increases within the first 15 s of reaction time reaching almost 100% conversion (Δ absorbance ~ 3.1, yellow color) (Fig. 2A). The response of the color change to the increasing ultrasound power is more pronounced at 80 kHz compared to 27 kHz. For longer reaction times, a complete conversion is obtained independently of the value of the ultrasound power and the ultrasound frequency used. During the first 15 s, the absorbance change is linearly related to the ultrasound energy. Again, 80 kHz appears more efficient than 27 kHz (Fig. 2B). The SonoCheck absorbance change plotted versus the level of cavitation noise (origin for cleaning) (Fig. 3) shows different effectivity for 27 kHz and 80 kHz.

A threshold of transient cavitation, an important characteristic of the cavitation noise level and cleaning efficacy [1, 3] is not indicated for the SonoCheck absorbance change (Fig. 3).

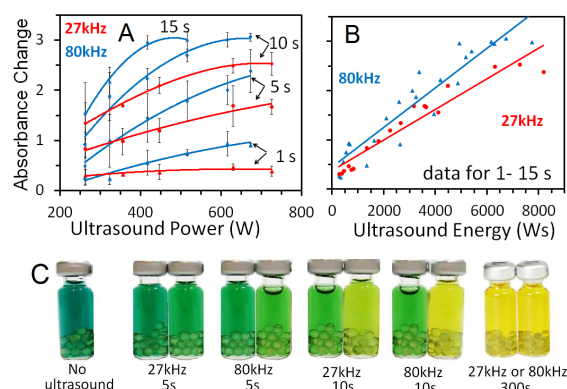
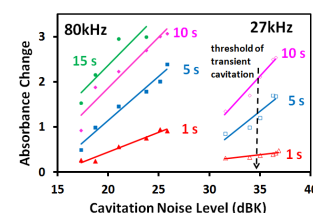


Fig. 2: Absorbance change of SonoCheck at different ultrasound power (A) and ultrasound energy (B). Mean values for positions A, B, C. (C) Color of SonoCheck at ultrasound power of ~750 W (100% power, right vial) and ~375 W (50% power, left vial) for 27 kHz and 80 kHz obtained after different reaction times.

Fig. 3: Absorbance change of SonoCheck as function of the cavitation noise level determined at different ultrasound power. Mean values for positions A, B and C.



DISCUSSION & CONCLUSIONS: The color change of SonoCheck can hardly visually assign if i.e. ultrasound power loss of 50 % occurs (Fig. 1C) neither after short cleaning times of 5-10 s, nor after longer times. Thus just by qualitative visual inspection, SonoCheck is not recommended for validation purposes, in particular for low ultrasound frequencies. Cleaning efficiency cannot be judged from SonoCheck color change because the sonochemical reaction occurs already widely below the threshold of transient cavitation which should be reached for a good cleaning effect [3].

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iPROMEDAI: A national and European initiative to reduce the risk of implant associated infection

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INTRODUCTION: The European medical device industry accounts for more than 11'000 companies with combined annual sales of € 72 billion, representing 33 % of the world market. The majority of such devices serve its purpose in restoring/replacing diseased/damaged body function. Millions of patients worldwide benefit from permanent implants comprising various biomaterials such as prosthetic joints, dental implants, stents, vascular grafts, and pacemakers, or from temporary inserted devices such as intravascular and urinary catheters. However, a non-negligible fraction of **devices fail in practice due to Device-Associated Infections (DAI)**, often with severe consequences for the patient as revision surgeries are required leading to a substantial increase in socioeconomical costs.

DAI is always connected with microbial contamination of an implant or device, either inferred during surgery (e.g. through implant-skin contact) or later through activation of interfacial microbials. The medical profession is aware of the importance of peri-operative hygiene to reduce DAI. Despite substantial, rapidly increasing research efforts on antibacterial strategies, **there is currently no effective clinical solution** although many research projects have been carried out on the topic. The few antimicrobial active compounds (AACs) containing devices rely on delivery of massive amounts of antibiotics, or on release of silver essentially limited to topical applications.

The **Action Improved Protection of Medical Devices Against Infection (IPROMEDAI)** identified device applications with variable established rates of incidence including cardiovascular, orthopaedics, trauma, urinary incontinence and catheters as critical application areas as they account for half of the medical device market. It is the objective of the Action to establish a **network across leading European academic and clinical research groups, and industry** with the aim of providing a scientifically sound, clinically relevant, industrially feasible and timely contribution to these socioeconomic most relevant topics. The issues and problems addressed in the Action are those that are considered to be key for the overall goal of reducing the number of DAIs in general and specifically in the five device

applications identified together with at least five industrial partners who will join the Action once it is accepted.

Based on a matrix of initial performance criteria, novel solutions are discussed and investigated in a comprehensive approach across different scientific disciplines. Potential solutions with the best property profiles will be pre-selected for subsequent advanced and later application-specific investigations. Industry and insurance companies as well as Regulatory Bodies are involved early on in the development ensuring that the **overall technical, societal and economic requirement profiles** for each application are taken into consideration. This helps in finding an efficient strategy for adapting the developed material platforms and for meeting the specific requirements. Working towards different lead applications greatly improves the chances for at least partial **success in the translation to clinical evaluation**.

The COST Action aims at

- (1) investigating the scientific, engineering and clinical issues having been identified as the key challenges in addressing the problem of DAI;
- (2) finding solutions for the unmet needs in the translational process to applications;
- (3) identifying novel designed biomaterials/ surfaces with enhanced antimicrobial device functionality and improved long-term stability;
- (4) documentation of comprehensive sets of standard and novel test methods with appropriate reference materials allowing for comparison of outcomes;
- (5) establishment of structure/property/ function relationships and correlations between *in vitro* and *in vivo* data;
- (6) providing dedicated and integrated training programs across the technical disciplines and socioeconomic aspects of the field.

REFERENCES:

COST Action TD 1305, www.ipromedai.org

Biological Evaluation According to ISO 10993-1: Approach and Structure

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INTRODUCTION: The requirements of the biological safety of medical devices are described in the MDD 93/42. The compatibility of the material used for the medical device to the biological environment must be considered in any case – independently of the classification (I, IIa, IIb and III). Procedures according to harmonized standards shall be applied. For biological evaluation the standard series of ISO 10993-1ff is applicable (Exceptions -2, -8, -10, -19, -20) or ASTM F748 and its associated standards.

METHOD: The biological evaluation of medical devices starts always with chemical analysis of the sterile final product which is compared to the native raw material, together with a toxicological risk assessment. In addition, a systematical literature review (ISO 10993-1 Annex C) from relevant databases is necessary (e.g. PubMed, Scopus, Embase or Cochrane Library, public and internal complaint databases).

For the biological evaluation of the medical device the following topics shall be addressed:

- Original source material;
- intended additives, production agents and residues;
- leachables;
- degradation products;
- other components and their interactions with the final product;
- performance and characteristics of the final product;
- physical characteristics of the final product (e.g. porosity, particle size, shape and surface morphology).

Identification of material chemical composition and consideration of chemical characterization shall precede any biological testing. The chemical characterization is the only mandatory test required by ISO 10993-1. All other tests (*in vitro* and *in vivo*) can be justified by a risk based approach or rationale whether or not they have to be performed, although table A.1 of ISO 10993 mentions these test methods.

Sufficient data is required to support the final considerations and the resultant decision.

OBSTACLES: In general, biological evaluation of the own device can be justified by existing data of a predicate device. Difficulties to demonstrate equivalence in production process and agents used are well known.

The clinical application of a medical device is usually very difficult to simulate under laboratory conditions. Therefore worst-case-scenarios or worst-case-products can be chosen for the tests.

The chemical and biological test evaluation has to be consistent to the following considerations:

- can be measured, what is expected;
- detection limit of the selected test method;
- accuracy of test method.

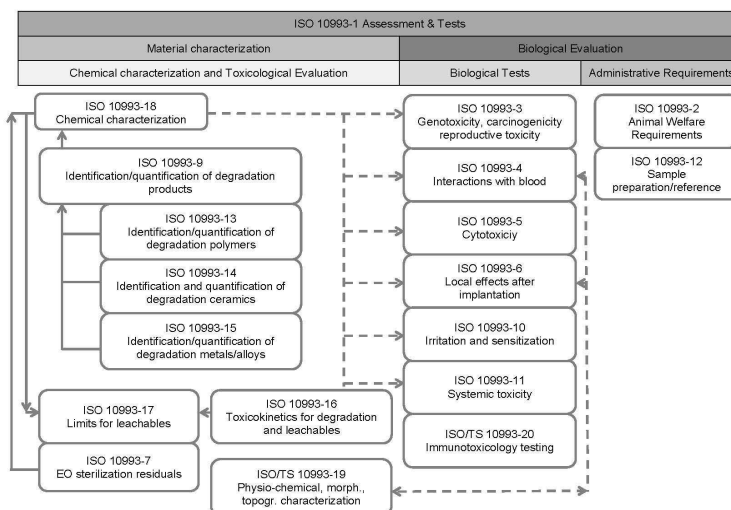


Fig. 1: Interaction of the ISO 10993-Standards

CONCLUSIONS: Planning the process is the key for a straight and successful biological evaluation. It includes at least the following steps:

1. Analysis of all material and production information
2. Selection of the chemical analysis methods to be applied
3. Toxicological assessment of all information obtained under 1. and 2.
4. Analysis of literature (internal/external) in public and internal complaint databases
5. Further biological testing to be performed according to ISO 10993-1 only if final considerations are indicative for additional investigations.

REFERENCES: ISO 10993-Standard-Serie.

X-Ray microscopy to determine the surface interaction between osteoblasts and a titanium surface in 3D

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Whilst X-ray imaging has been used for many decades in imaging biological soft and mineralised tissue, the architecture of the instrumentation has remained largely unchanged. CT imaging systems utilise detectors that are limited to an average energy response for a range of different size and density of sample.

By utilising technology from Synchrotron based X-ray Microscopes, imaging possibilities are enhanced towards higher resolution with much less dependence upon sample size. A series of detectors are employed with energy tuned scintillators, optimizing the absorption contrast over a wide range of samples.

The lens based optics also allow the ability to image propagation based phase contrast further enhancing the imaging capability.

Large differences in Z contrast, typically seen in the interface between mineralised tissue and metal implants, require an efficient contrast transfer function in order to prevent blurring at the critical interface contact points. The presented X-ray microscopy instrumentation provides both spatial and contrast resolution at this critical interface. This can be achieved in both scout mode, to image the whole sample, as well as at high resolution by zooming in to the interface with a high magnification.

In addition to imaging implants and interfaces, with a spatial resolution of 700 nm, there are many voxels within a single osteocyte, allowing for accurate statistical analysis.

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