[MEET THE EXPERT]
IMPLANTS

Technologies and Innovation for Cost Reduction

7 - 8 May 2015

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CH-3800 Interlaken

medical cluster

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General Information

Conference Secretariat

The conference secretariat is managed by Mrs Doris Loretan.

Availability during the meeting: phone +41 79 128 32 99.

doris.loretan@medical-cluster.ch

Parking Tickets

The parking lot of the Congress Centre (CKI) is available for congress attendees. Congress-Tickets for CHF 8.00 per day or day-tickets for public parking spaces for CHF 12.00 are available at the information desk of the CKI.

Wardrobe

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

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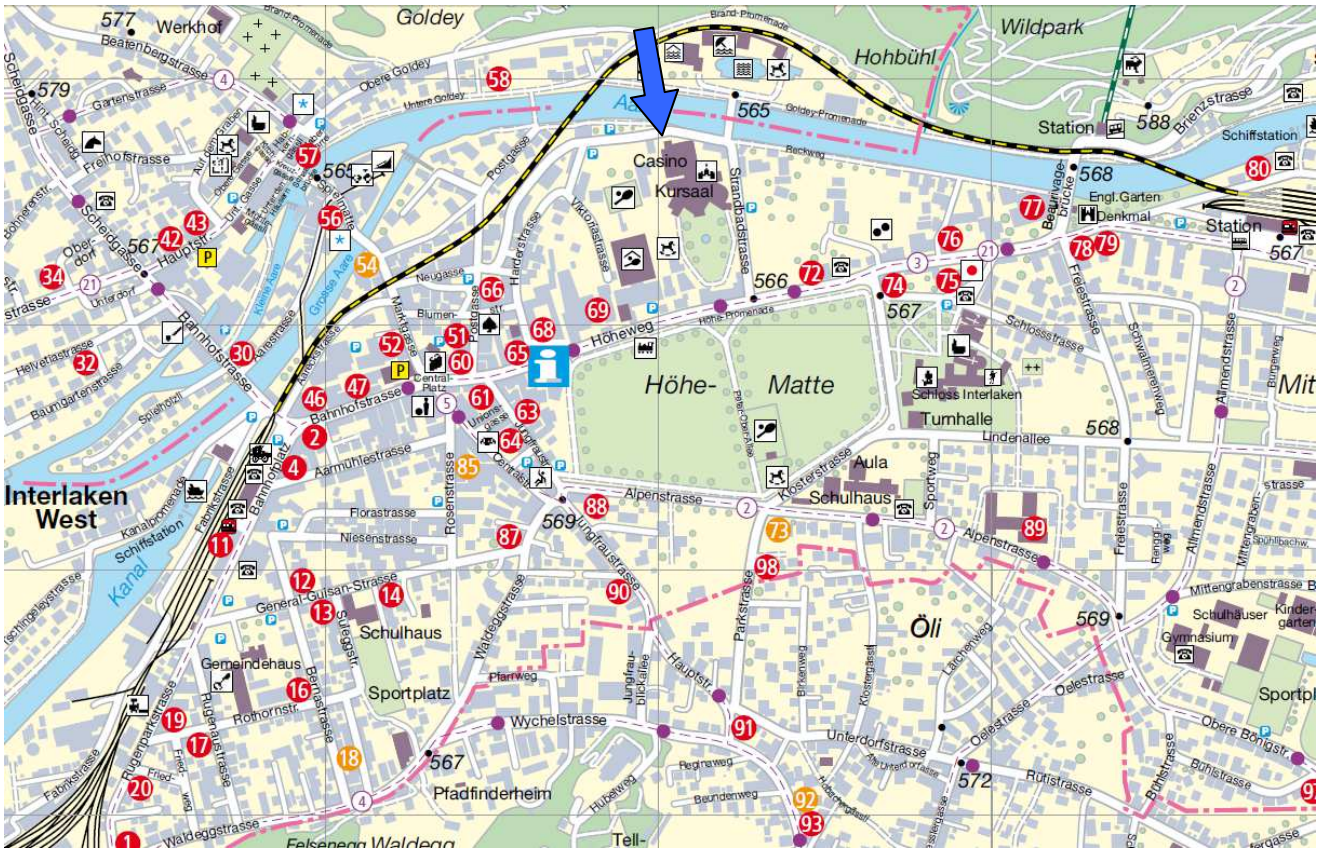
Site map



68 Hotel Metropole (Conference Dinner)

North entrance of the Congress Center Kursaal Interlaken

1to1-Partnering

All matchmaking events will be taking place, on both days, in the conference room.

Every discussion may last up to 15 minutes. By the sound of the bell, you will be asked to move on to your next meeting. All participants registered for a matchmaking event will be receiving their individual meeting schedule at the registration desk.

1to1-partnering timeline:

Thursday:	12:15 – 13:45 & 15:00 – 15:50
Friday:	09:20 – 10:20 & 12:00 – 13:30

Aperitif

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

Dinner

The Conference Dinner will be held on **Thursday 7th May 19:00 h** at the **Hotel Metropole**. The Hotel Metropole is located close to the Congress Centre Kursaal at Höheweg 37.

Powerpoint Presentations

The PowerPoint Presentations shown at this event remain in the property of the authors and presenters. Medical Cluster will not distribute the presentations. Please contact the corresponding author if you wish to receive more information on a specific presentation. E-Mail addresses of the authors can be found on the list of authors at the end of this documentation.

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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
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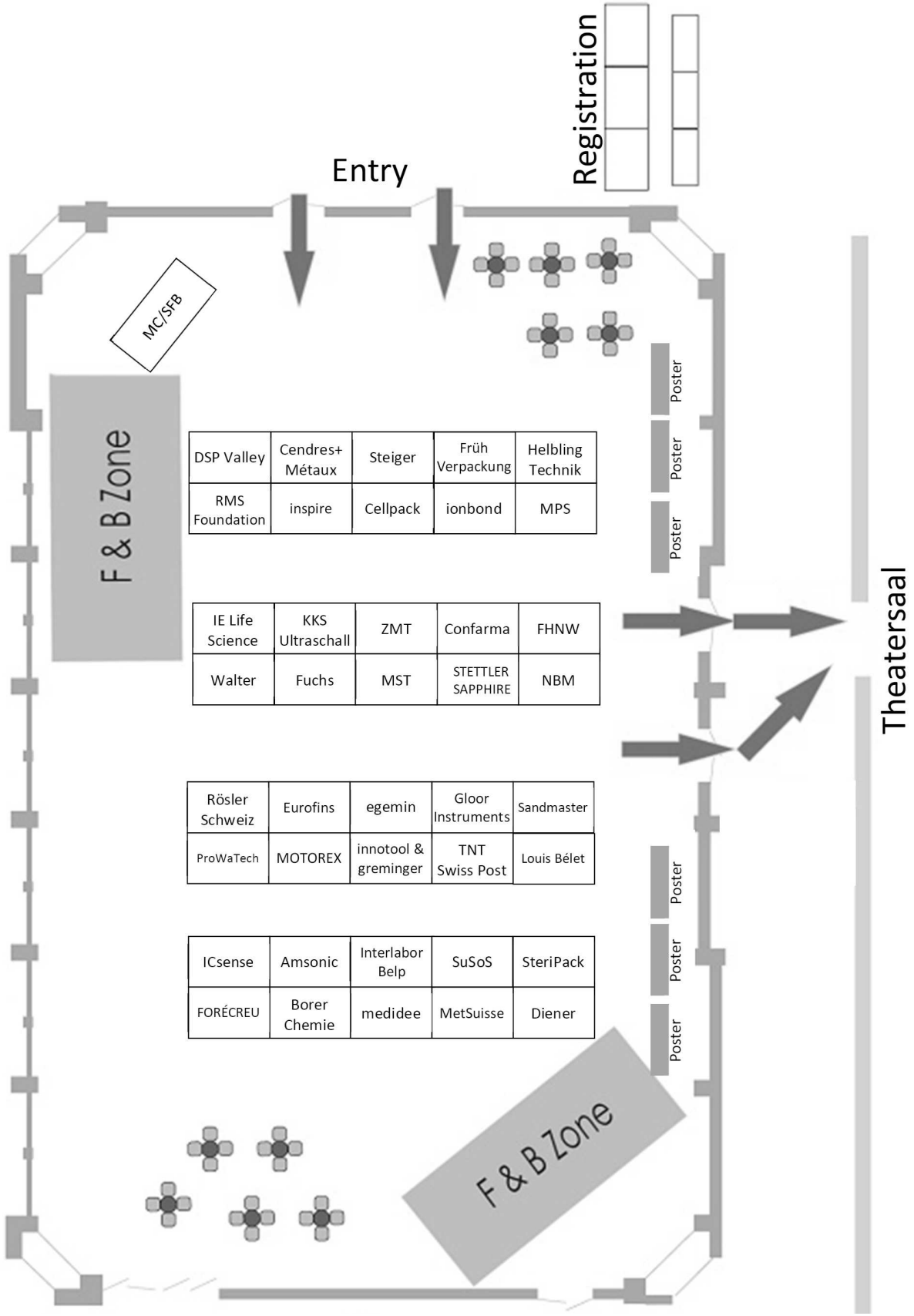
Exhibition Area



Alphabetic List of Exhibitors
Amsonic AG
Borer Chemie AG
Cellpack AG Medical
Cendres + Métaux SA
Confarma France SAS
Diener AG Precision Machining
DSP Valley VZW
egemin AG
Eurofins BioPharma Product Testing GmbH
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Sandmaster AG
Standortförderung Kanton Bern
Steiger Galvonotechnique SA
SteriPack Ltd
Stettler Sapphire AG
SuSoS AG
TNT Swiss Post
Walter (Schweiz) AG
ZMT Zurich MedTech AG

Meeting Program

Thursday, 7th May 2015

10:00 - 10:15	Welcome	
	Session 1 **Chair: Dr. Lukas Eschbach**	
10:15 - 11:00	*Presentation Industry partner: Overcoming Hearing Loss Through New Implant Technologies (EN)* Carl van Himbeeck, Cochlear AG, BE	
11:00 - 11:30	*Keynote 1: Reasons of cost pressure and possible countermeasures (DE)* Eric Perucco, MedBrainTec, CH	
11:30 - 12:15	Flash presentations exhibitors	
12:15 - 13:45	Lunch (Exhibition / Posters / 1to1-Partnering)	
	Session 2 **Chair: Dr. Lukas Eschbach**	
13:45 - 14:15	*Keynote 2: Is high-tech surgery a cost driver? Practical answers and innovative solutions from the research workshop of an oral and maxillofacial surgeon (DE)* Prof. Dr. Hans-Florian Zeilhofer, Universitätsspital Basel, CH	
14:15 - 14:45	*Keynote 3: «3D-Printing» a game changer for product development and design (DE)* Prof. Dr. Mirko Meboldt, ETH Zürich, CH	
14:45 - 15:00	Flash presentations posters	
15:00 - 15:50	Break (Exhibition / Posters / 1to1-Partnering)	
	Session 3a: Surfaces **Chair: Prof. Dr. Michael de Wild**	**Session 3b: Active Implants** **Chair: Dr. Urban Schnell**
15:50 - 16:10	*The Role of Surface Properties and Their Biological Impact on Osseointegration (DE)* Francisco Faoro, Institut Straumann AG, CH	*The development process as a central tool in cost management (EN)* Hans Bernhard, Helbling Technik Bern AG, CH
16:10 - 16:30	*Functional Thin-film coating: added value at low cost (EN)* Sina Göhl-Gusenleitner, SuSoS AG, CH	*Brain mapping for new insight in neurotherapeutic & diagnostic solutions (EN)* Dr. Arno Aarts, ATLAS Neuroengineering bvba, BE
16:30 - 16:50	*Laser assisted surface functionalization (DE)* Dr. Georg Astl, Eoswiss Engineering Sarl, CH	*Flex PCB Reliability: An objective evidence based approach for long-term cost avoidance (EN)* Dr. Hans-Peter Klein, DYCONEX AG, CH
16:50 - 17:10	*Time and Material Saving Laser Microtomy for Hard Tissue and Implants (DE)* Dr. Brigitta Stolze, LLS ROWIAK LaserLabSolutions	*Security of Wireless Implantable Medical Devices (EN)* Dr. Dave Singelée, KU Leuven, BE
17:10 - 17:30	*Roxolid® the new gold standard for implant materials in dental implantology (DE)* Dr. Florian Dalla Torre, Institut Straumann AG, CH	*World's smallest long-term implantable pressure sensor (EN)* Dr. Mark Fretz, CSEM, Alpnach, CH
17:30 - 18:30	Aperitif / Exhibition / Posters	
ab 19.00	Dinner at Hotel Metropole	

Meeting Program

Friday, 8th May 2015

	Session 4 **Chair: Sven Zybell**	
08:30 - 09:00	*Keynote 4: Trends in magnesium implants (DE)* Prof. Dr. Regine Willumeit-Römer, Helmholtz-Zentrum Geesthacht, DE	
09:00 - 09:20	*Using the Lean and Six Sigma approach to lower production cost and maintain competitiveness(DE)* Dr. Bruno Rüttimann, inspire AG, CH	
09:20 - 10:20	Break (Exhibition / Posters / 1to1-Partnering)	
	Session 5a: Regulatories **Chair: PD Dr. Christiane Jung**	**Session 5b: Simulations, Models** **Chair: Dr. Simon Berner**
10:20 - 10:40	*Efficient testing strategies for Medical Devices including new concepts in risk assessment and new in vitro test systems (DE)* Dr. Albrecht Poth, Eurofins BioPharma Product Testing, D*E*	*Skull model for craniomaxillofacial fracture and brain education* Heinz Hügli, SYNBONE AG, CH
10:40 - 11:00	*Clinical Investigations with Implants: View of the development company and of the CRO (DE)* Dr. Michel Weber, ISS AG, CH	*Reducing risk and R&D costs using medical image based population studies in orthopaedic implant development (EN)* Markus Fremmer, Materialise GmbH, DE
11:00 - 11:20	*Simulation of the use of plastics in the medical sector with respect to leachables (DE)* Bernhard Burn, INTERLABOR BELP AG, CH	*Automated workflow for patient specific robust design optimization: an example for plate osteosynthesis (EN)* Joël Grognuz, CADFEM (Suisse) AG, CH
11:20 - 11:40	*How to leverage CE data of implants used for CE marking in the US for PMA approval (EN)* Dr. Ralf Hess, PAREXEL International, DE	*Predicting Primary Stability in Novel Bone Level Tapered Implants (EN)* Francisco Faoro, Institut Straumann AG, CH
11:40 - 12:00	*Emerging & Re-emerging markets: how to navigate innovation thru global regulatory approvals (EN)* Dr. Vincent Legay, NAMSA, FR	*Modelling alterations in hemodynamics caused by aneurysm implants (EN)* Wolfgang Wiedemair, Zurich MedTech AG, CH
12:00 - 13:30	Lunch (Exhibition / Posters / 1to1-Partnering)	
	Session 6: Manufacture and process und Prozesse **Chair: Dr. Martin Stöckli**	
13:30 - 13:50	*Unchanging long tool life in titanium (DE)* Michael Zuber, Diametal AG, CH	
13:50 - 14:10	*Innovation for joint implants under cost pressure (DE)* Dr. Martin Schmidt, Jossi Orthopedics AG, CH	
14:10 - 14:30	*Balancing product safety and cost effectiveness - considerations in factory & cleanroom design (DE)* Stephan Fischer, IE Life Science Engineering, CH	
14:30 - 14:50	*Process Design for Usability EN 62366 (DE)* Raimund Erdmann, Erdmann Design AG, CH	
14:50 - 15:20	*Keynote 5: Process optimization for cost reduction: practical examples (DE)* Sven Zybell, Synthes Produktions GmbH, CH	
15:20	End of conference	

Gründe des Kostendrucks und mögliche Gegenmaßnahmen

E Perucco

MedBrainTec AG, Rapperswil Jona, CH

Steigender Kostendruck

Der Kostendruck in Europa in der Medizintechnik nimmt immer mehr zu. Besonders in Deutschland, das eine Vorreiterrolle einnimmt, aber auch in Skandinavien und Großbritannien ist dies der Fall. Gründe dafür sind u.a. wachsender internationaler Wettbewerb z.B. aus Osteuropa und Fernost, neue Anbieter mit kleinem, sehr gutem Produktportfolio, zunehmend tiefere Verkaufspreise, Einkaufsgesellschaften und Klinikverbünde, sinkende Fallpauschalen, wachsende Regulierungen und schärfere Gesetze sowie politischer Druck hin zu weniger Patientenbehandlungen.

Schweizer Hersteller stehen bei diesen Herausforderungen deutlich stärker unter Druck als Unternehmen in anderen Ländern in Europa. In der Schweiz sind das allgemeine Preisniveau sowie die Löhne im internationalen Vergleich höher, was den Produktionsstandort Schweiz im Wettbewerb mit ausländischen Standorten benachteiligt. Das ist nicht erst seit der Wechselkursfreigabe vom 15. Januar 2015 so. Planwirtschaft, tarifäre und nicht tarifäre Maßnahmen des Gesundheitswesen gepaart mit deutlich stärkerer Kostenzunahme in den letzten Jahren gegenüber Europa u.v.m. bis hin zur Gewinnmaximierung der Produktanbieter haben diesen eklatanten Unterschied verursacht. Letzterer Punkt betrifft auch Schweizer Firmen, die ihre Produkte und Dienstleistungen in Europa sehr oft deutlich günstiger verkaufen als in der Schweiz. Das trifft übrigens nicht nur die Medizintechnik zu, sondern auch für viele andere Branchen.

Gemeinsame, koordinierte Maßnahmen zur Kostensenkung produzierender schweizer Medtechfirmen sind nicht absehbar. Jedes Unternehmen muss daher für sich selber Maßnahmen treffen. Mögliche Ansätze sind Kostensenkung, Verlagerung von Arbeitsplätzen ins Ausland, Preiserhöhung, Margenverzicht, Arbeitszeitverlängerungen oder gar Lohnkürzungen. Oft ist das noch nicht ausreichend.

Mögliche Gegenmaßnahmen

Unternehmen müssen mit gezielten Gegenmaßnahmen, und das haben viele bisher unterlassen, bekannte und bewährte Lösungen anpacken und umsetzen. Im Folgenden einige Ansätze:

1. Firmen sollten für jeden Zielmarkt sowie für jeden Kunden eine Gewinn- und Verlustrechnung erstellen. Sich trennen von Ländern und Kunden, wo die Deckungsbeiträge zu klein sind. Der Fokus sollte auf Zielgruppen ausgerichtet werden wo eine Chance besteht, den Umsatz zu halten oder gar zu steigern und Gewinne realisierbar sind. Dazu gibt es bewährte Methoden welche erwiesenermaßen erfolgreich funktionieren, wie z.B. die Veränderung von Prozessen und Strukturen.
2. Unternehmen müssen neue Produktionsmodelle suchen und entwickeln und den Mut haben, ganz neue Wege zu gehen. So z.B. (Teil-) Produkte in anderen Betrieben in der Schweiz oder in Europa herstellen lassen, die günstiger produzieren können. Oder maßgeschneiderte Werkzeuge und Maschinen herstellen, die dazu beitragen, die Produktionskosten zu senken.
3. Haben die Firmen die richtigen Verkäufer? Haben diese die Expertise des „Verkaufens“ für die verantwortlichen Zielmärkte und Zielgruppen? Wenn nein, sollten umgehend personelle Korrekturen vorgenommen werden. Als weitere Alternative bietet sich an, zusammen mit anderen Betrieben ein Unternehmen zu gründen, das für alle Partner den Vertrieb, den Service, den Kundendienst und vielleicht sogar die Logistik übernimmt.
4. Die Unternehmen sollten ein „Clustering“ ihrer Kunden machen und für jede Kundengruppe eine eigenständige Strategie und einen individuellen Aktionsplan entwickeln. Die Umsetzung muss durch Experten erfolgen, die beweisen, dass sie dazu in der Lage sind.

Last but not least: Veränderungsprozesse in sich wandelnden Märkten braucht Menschen, die Persönlichkeit, Mut und die Bereitschaft mitbringen, neue Wege zu gehen.

The role of surface properties and their biological impact on osseointegration

F Faoro[1], M Dard[2], S Berner[1]

[1] Institut Straumann AG, Basel, CH. [2] New York University, College of Dentistry, Department of Periodontology and Implant Dentistry, New York, USA

INTRODUCTION: The performance of bone-related implants is strongly connected with the implant material and the properties of the implant surface. Surface topography and chemistry both influence initial wettability and peri-implant bone apposition of implants. Specific surface properties like the surface structure, with special emphasis on nanostructures and wettability were examined with respect to their biological response.

METHODS: Commercially pure titanium coin shaped samples presenting four different surface modifications were tested. All samples were sand blasted and acid etched (SLA treatment), but differed with respect to their wettability and presence of nanostructures. Samples with and without nanostructures as well as hydrophobic and hydrophilic samples were prepared [1]. The hydrophobic surfaces without nanostructures and hydrophilic with nanostructures correspond to the commercially available SLA and SLActive surfaces of Straumann, respectively [1].

The surface chemistry and topography were analysed by various techniques [1]. Protein adsorption (fibrinogen, fibronectin) and blood coagulation experiments were examined in in-vitro experiments [2]. The bone response was tested in a rabbit disc model by the measurement of pull-out forces [3].

RESULTS: The storage of SLA-type samples in NaCl solution results in the formation of TiO_2 based nanostructures [1]. Enhanced protein adsorption was observed for the samples with nanostructures, whereas hydrophilicity alone did not increase the level of protein adsorption [2]. The highest amounts of protein levels were observed for the combination of hydrophilicity and nanostructures. The blood coagulation experiments revealed a positive influence for hydrophilic as well as for nanostructured surfaces [2]. Strongest coagulation was again observed for the combination of these specific surface properties, i.e. on SLActive. Figure 1 presents results of the blood clot formation (fibrin network) on SLA and SLActive surfaces.

The bone response was influenced by nanostructures and hydrophilicity, both having a positive effect. The strongest bone response (highest pull-out values) was observed for SLActive [3].

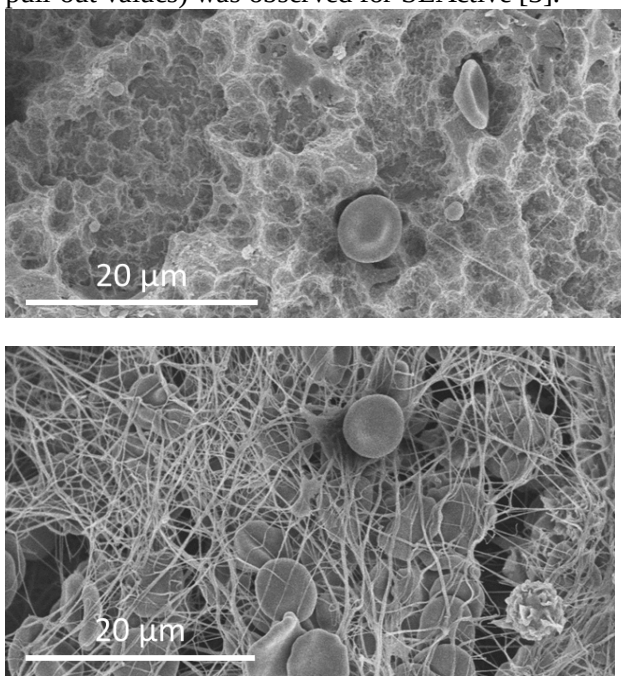

Fig. 1: SEM images of SLA (top) and SLActive (bottom) after incubation with whole human blood (partially heparinised) for 10 min at 37°C.

DISCUSSION & CONCLUSIONS: Specific surface properties, such as wettability and nanostructures, influence protein adsorption, blood coagulation and the bone response. Hydrophilicity and nanostructures both had a positive influence on the biological response.

Thus, implants with tailored surface properties for improved osseointegration might lead to more predictable outcome in challenging situations and improve the success rates.

REFERENCES: [1] A. Wennerberg et al., (2013) *Clin. Oral Impl. Res.* **24**:203-209. [2] B. Kopf et al., (2015) *J. Biomed. Mat. Res. A* DOI: 10.1002/jbm.a.35401. [3] A. Wennerberg et al., (2014) *Clin. Oral Impl. Res.* **25**:1041-1050.

ACKNOWLEDGEMENTS: The collaborations with A. Wennerberg et al. (Univ. Malmö), K. Maniura et.al. (Empa St. Gallen) and S. Stübinger (Univ. Zürich) are highly acknowledged.

Functional thin film coatings: additional value at lowest price

S Göhl-Gusenleitner, O Sterner, S Zürcher, S Tosatti

SuSoS AG, Dübendorf, CH

INTRODUCTION: Surface treatments and coatings represent a widely used strategy to provide added value to a substrate material. One of the most common examples in the application of such an approach is the use of paint and lacquers to change the colour, and thus the appearance, of a certain product. In the medical technology (MedTec) area, the functionalization of implant or instrument surfaces with specialized coatings leads to various advantages, so that, e.g. products can be protected from unwanted biological contaminations using an antibacterial polymer-coating. Or, the use of lubricious coatings can lead to minimization of pain, increase of comfort, optimized and simple handling of the coated devices, reduction of adverse events and of allergic responses.

In practical terms, when talking about approaches suitable to realize such functionality add-on, i.e. "giving color", the selection of the methods available is as large as the number of colors one can have. Thus, procedures ranging from simple painting, over spraying, printing and chemical- or electrochemical plating processes to the use of additives in the bulk materials, are today very common in several industries.

In this contribution we will present an industrial, versatile approach for application of ultrathin functional films and compare this to other strategies commonly used in the MedTec field.

METHODS: Thin functional films are obtained by a three step process involving the deposition of a monomolecular adhesion promoting layer, the subsequent deposition of a functional polymer and the final curing with UV-light in order to ensure optimal bonding between substrate and coating (Fig. 1).

In order to ensure high reproducibility of the coating process, beside the well-established dip-and rinse procedure, an automated coating device based on a 4-axis robot system carrying dosing and jetting heads was used (Fig. 2). As shown in figure 1, the coating thickness, composition and wettability has been determined by Ellipsometry, X-Ray Photoelectron Spectroscopy (XPS) and Contact Angle-measurements respectively.

Functional tests of the different coatings have also been carried out. In one case, the tribological properties have been assessed by micro-tribological and micro-traction tests. In other cases, cell cultures, biocompatibility tests, and stability tests have been performed.

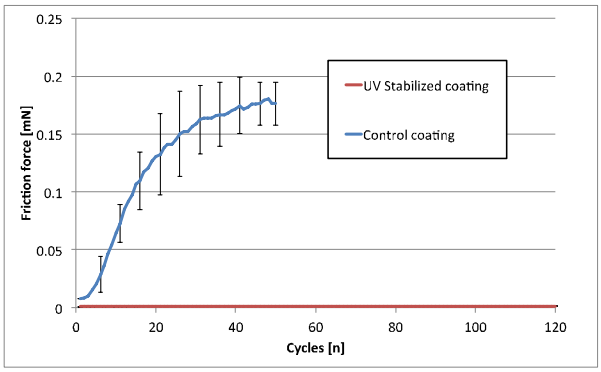

Fig. 1: Effect of UV post deposition processing on 150 nm thick lubricious coating. The UV stabilized coating was tested in water against PE-ball at a normal force of 120 mN (10 MPa pressure) showing good stability. On the control sample, tested at 50 mN (7 MPa), an increase in friction is observed after few cycles, suggesting a wear-off of the coating.

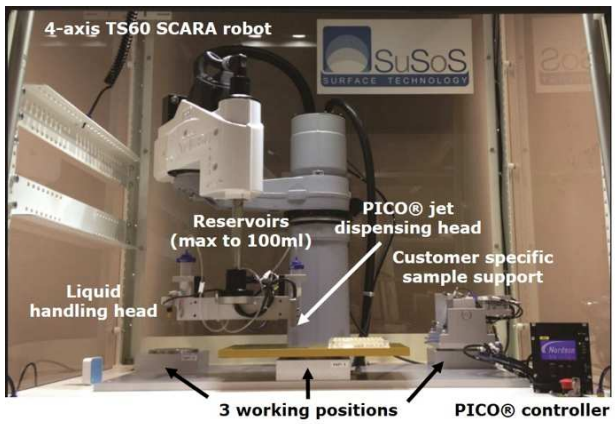

Fig. 2: Image showing the automated coating device used at SuSoS to apply thin film coating on various substrates. The device consists of a modified four axis pick and place SCARA Robot allowing fast and flexible handling with three different working platforms.

Laser assisted surface functionalization

GF de la Fuente[1], V Lennikov[1], R Lahoz[1], C Estepa[1], G Astl[2]

[1] *ICMA (University of Zaragoza – CSIC), Zaragoza , Spain.*
[2] *Eoswiss-Engineering Sàrl, Geneva, CH*

INTRODUCTION: Laser technology is used advantageously for essential cost reductions in material processing. Lasers heat the material exactly where the heat treatment is needed. The outermost surface layers can be melted without overheating the rest of the ceramic or metallic body. Consequently, furnace design and furnace power consumptions are greatly reduced, leading to much lower overall production costs. Thermal processing of larger ceramic bodies (tetragonal t-ZrO_2–Al_2O_3) with lasers is problematic because of crack formation. Defect free laser processing is reported in this paper. Also with laser technology, metallic surfaces can be structured in micrometer or nanometer range in one step. Fast laser structuring with 500 nm to 900 nm periodicity of a metallic Cr surface is reported as a second example. This technique is based on **L**aser **I**nduced **P**eriodic **S**urface Structure (LIPPS) [1].

METHODS: Eutectic Laser melting experiments of (t-ZrO_2–Al_2O_3) were performed with slip casting [2]. The aqueous suspensions of raw materials (aluminium oxide and **Y**ttria **S**tabilized **Z**irconia (YSZ) were stabilized with a polyacrylic acid based dispersion aid (Duramax, D3005, Rohm and Haas, USA). To increase optical absorption, the mixture was doped with 0.05 mol% Mn_2O_3. A Rofin-Sinar 350 W SLAB type CO_2 laser (λ = 10.6 µm) was used for directional surface melting. The experiments were conducted in a special laser furnace [3]. LIPPS generation experiments were performed on metallic, 1 µm thick Cr films deposited on a top Ni layer (20 µm) on a 1 mm thick polymer slab, with a fibre based fs laser amplifier (Tangerine, Amplitude Systems) operating at a wavelength of λ = 1030 nm, pulse duration of τ = 500 fs, a maximum pulse energy of E_{max} = 10 µJ and a maximum repetition rate of $\upsilon_{rep\text{-}max}$ = 2 MHz.

RESULTS: Wide (40 mm x 40 mm) eutectic t-ZrO_2–Al_2O_3 ceramic plates of 6 mm thickness were laser processed with preheating temperatures up to 1200 °C. A defect free 0.4 mm thick re-solidified layer was obtained. Thermal stress cracks were totally avoided as seen by flexure strength testing on an Instron 4505 testing equipment.

Figure 1 shows a LIPPS structure on a Cr film. Depending on the experimental conditions, ripple periods of either 500 nm or 900 nm, depending on the laser energy can be produced. Although the surface structure period in Figure 1 has a periodicity of only 500 nm (Peak to Peak), a highly regular surface of several square centimetres can be performed in a few minutes.

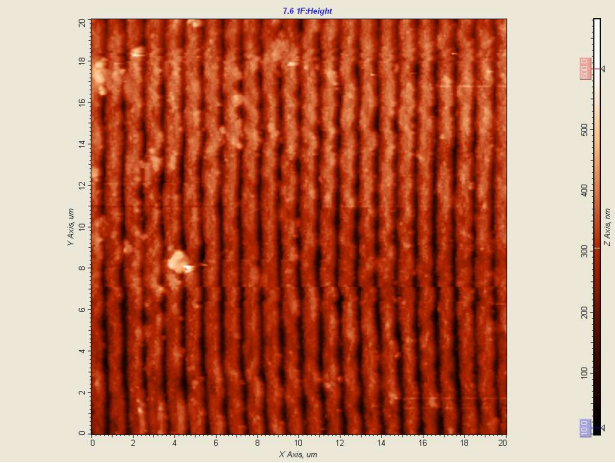

Fig. 1: AFM image of LIPPS-based diffraction grating written on Cr metal film. The image shows a 20 µm x 20 µm extract of the surface. The ripple peak to peak distance is 0.5µm (500 nm). The ripple depth is 150 nm.

DISCUSSION & CONCLUSIONS: Difficult to process ceramic objects like t-ZrO_2–Al_2O_3 plates can be produced without cracks and surface faults. This process, which is run in a special laser furnace, greatly reduces manufacturing costs and failure rate of production**.** Fast nano- structuring of metal layers with LIPPS is possible without extensive laser ablation. Nano surface structures change wetting and adsorption behaviour for cells and proteins

REFERENCES: [1] A. Ruiz de la Cruz et al. (2014) Optics Letters Vol. 39, No. 8, 2491-2494. [2] J. Gurauskis et al. (2011) J. Europ. Ceram. Soc. **31**, 1251. [3] L.C. Estepa, G.F. de la Fuente. Patent WO2007101900 (2007).

ACKNOWLEDGEMENTS: CSIC-University of Zaragoza and Spanish and EU research funds.

Time- and material saving laser microtomy for hard tissue and implants

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[2]*Ratliff Histology Consultants, 389 Nichol Mill Lane, Franklin, TN 37067, US*

INTRODUCTION: Histological analysis often is a mandatory, yet laborious part of preclinical study design. Especially the preparation of hard tissue samples or samples containing implants requires specialized and experienced technicians to perform sections with either microtomes or ground section technology. Quality of the cutting result is limited, as ground section technologies are limited in section thickness.

Laser microtomy is a novel method to prepare thin sections for histological analysis [1]. Thin sections of non-decalcified hard tissue as well as thin sections of implanted vessels and heart valves for common staining methods can be generated in adequate thickness and quality [2]. Serial sectioning is possible. Thereby laser microtomy reduces the throughput time per sample and also the effective time a technician has to work on it. This increases the efficiency of lab procedures which results in higher sample throughput. This presentation demonstrates laser microtomy by two typical samples: sheep spine from a spine fusion study and arteries containing stents.

METHODS: For this study, a sample of sheep spine (35 x 35 mm^2) and an artery containing a metal stent (14 x 14 mm^2) were chosen. Both samples were plastic embedded, the sheep spine without prior decalcification. Samples were mounted on microscope slides with cyanacrylate glue and cut planparallel to slide surface at 10 µm. Samples were routinely stained (sheep spine: Sanderson Rapid Bone Stain/van Gieson; artery: H&E) and coverslipped. For comparison to conventional ground sectioning technology, section time for each sample was measured and compared to empirical value of ground sectioning times.

RESULTS: Figure 1 shows histologic images of samples cut with the laser microtome down to 10 µm. A comparison between laser microtomy and ground sectioning is summarized in Table 1. Minimum section thickness with laser microtome is 10 µm, with ground sectioning approx. 30 µm. Both, the overall processing time and the working time a technician has to run the laser microtome are much shorter. The maximum difference between laser microtomy and ground sectioning processing one sample can be fourfold, technician working times up to ninefold.

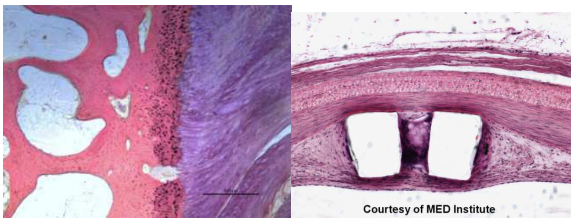

Fig. 1: Images of sections performed with laser microtome. Left: sheep spine, right: stented artery.

Table 1. Comparison of ground sectioning and laser microtomy process.

	Ground section		Laser Microtome	
	Sheep spine	Stented Artery	Sheep spine	Stented Artery
Sample size/mm^2	35x35	14x14	35x35	14x14
Section thickness/µm	30	30	10	10
Total processing time/min	122	79	33	15
Technician working time/min	74	44	8	8

DISCUSSION & CONCLUSIONS: The quality of laser microtome sections is comparable to conventional ground sections. As sections can be performed serially and thinner, down to 10 µm, the amount of information from laser sections can be higher. A further big advantage is time saving, both, the overall processing time and the technician working time. Thereby, laser microtomy works very economically and efficiently at equal quality.

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ACKNOWLEDGEMENTS: We thank Cook Med Institute for providing the artery samples.

Roxolid® the new gold standard for implant materials in dental implantology

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ABSTRACT: Metallic implant materials are generally either made from stainless steel, Co-Cr-Mo-alloys, or Ti-alloys. Within the dental industry, implants are mainly made of pure Titanium due to its good biocompatibility. Apart from pure Titanium it is predominantly Ti-alloys such as Ti-6Al-4V and Ti-6Al-7Nb, which are used in cases when additional strength is requested. Both these alloys are obtaining their strength by their dual phase structure, which when properly treated, results in a very fine needle-like microstructure. In return, the chemical properties of these dual-phased alloys differ within the two phases after acid etching, resulting in a surface morphology, which is unfavorable for osseointegration. To have both, higher mechanical strength and excellent osseointegration, Straumann developed a monophase alloy out of Ti-Zr. This alloy shows a mechanical strength similar to Ti-6Al-4V and Ti-6Al-7Nb and a very similar surface when sandblasted and acid etched as pure Titanium. New insights into the material properties, its surface characteristics and the performance of the material when used for dental implants will be presented and compared to currently available materials and implants on the dental market.

The development process as pivotal tool for cost management

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INTRODUCTION: Considering the life cycle of a medical device – and in particular an electro-active implant – from the first product idea to the end of life, manifold costs accumulate on manufacturer and society side. The analysis of these costs and possible ways to influence them shows that the development process plays an important role in cost management. A holistic and anticipatory development approach is required to control Life-Cycle-Costing (LCC). This represents a serious challenge for the development team and processes that need to adequately addressed.

METHODS: Figure 1 shows the basic life cycle of an active implantable device. Once the patient need and related therapy are defined, the development process lays the foundation for all the subsequent phases and has to assure the efficacy of the device.

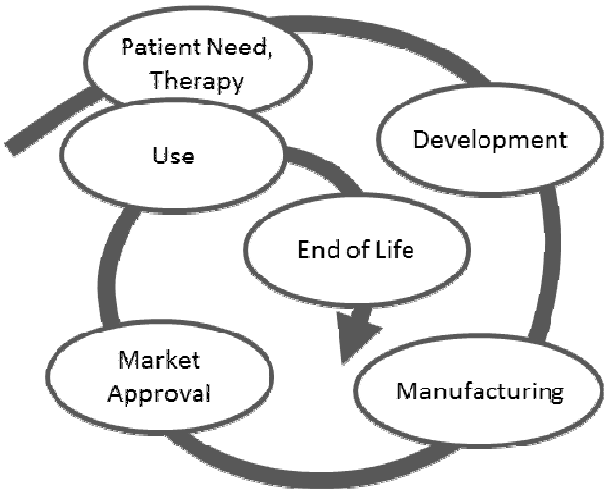

Fig. 1: Basic life cycle of an active implantable device

Considering the development phase as basis for the subsequent phases implies that subsequent costs can be directly influenced. This raises two basic questions: "Which costs can be controlled by the development process?" and "How can they be controlled?"

Some of the main cost drivers for each life cycle phase are listed and their influencing factors within the development phase (cf. Figure 2) are analysed to answer the above questions.

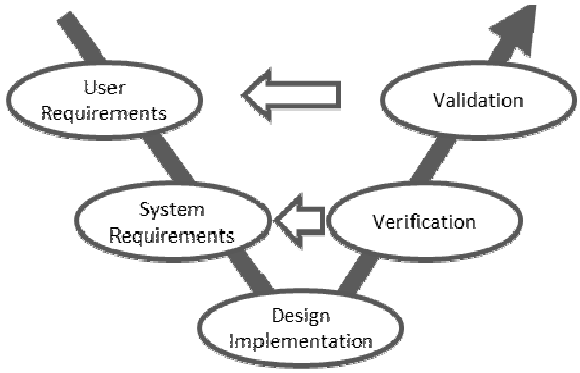

Fig. 2: Basic development process of an active implantable device

RESULTS: There are three crucial steps within the development phase:

First, it is essential that the user requirements are adequately translated into system requirements, otherwise low device efficacy and increased design efforts can be the consequences. The mitigation of these risks requires a close dialog between clinical experts and the engineering team.

Second, the design implementation defines the efficiency, safety, reliability, usability and cost of goods of the device. Especially safety and reliability issues can cause high subsequent costs.

Third, the verification has to be rigorously done. It is the last chance to discover failure modes and design issues before clinical trials start and the device is placed on the market.

The development process in general greatly influences the time to market. Late design loops or inadequate documentation can considerably delay clinical studies and approval processes.

DISCUSSION & CONCLUSIONS: The work up to design verification is essential to limit costs. This work needs to be done by considering all subsequent life cycle phases and by using appropriate development and risk management processes. Any design issue needs to be identified as early as possible – at the latest during design verification – to reduce the impact of corresponding measures on time and cost. This requires the design team to be in close collaboration with any other involved party, incl. clinics, regulatory and manufacturing.

Brain mapping for new insight in neurotherapeutic & diagnostic solutions

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INTRODUCTION: Tomorrow's neurological challenges are focused on patient specific treatment, which can read the patient's state and are not based on symptoms and signs observed from the outside. However, a new technology is required in order to differentiate between subjects and to gain better fundamental understanding. ATLAS Neuroengineering introduces a new technology to gain better understanding of the neuronal behaviour in order to differentiate between patients at the neuronal level and also to reduce the time neurosurgeons and assisting teams need to spend in high-cost surgery rooms.

METHODS: There are various diagnostic tools, such as imaging techniques (MRI, PET, etc.), electroencephalograms (EEG), biomarkers (protein detection), etc. Deep brain stimulation (DBS) is becoming a promising technology for therapeutic treatment of several neuronal brain disorders such as epilepsy, Parkinson's disease, obsessive-compulsory disorder (OCD) and many more. However, these tools cannot tell us how individual neurons communicate with each other in specific brain areas. Basically, it can be compared by an individual in front of a group of people talking at the same time generation noise without the possibility to distinguish individual voices. In order to overcome this effect, we insert micro-electrodes in the brain to have a close look at how the brain is organized at cellular level.

Today's clinically approved DBS implants only have a few electrodes (4 or 8), which are in the millimeter range (surface area of 6 mm^2) resulting in poor resolution and selectivity. The cross sectional diameter of the lead is typically 1.3 mm [1] and raises questions concerning electrode flexibility (positioning and selectivity) and safety (tissue damage). The lead of our implantable device is only 160 µm wide and 50 µm thick. The lead is covered with hundreds of electrically switchable micro-electrodes (50 µm in diameter). A CMOS integrated switching matrix enables to work with more than a thousand electrodes, while maintaining the number of output lines limited, enabling to record simultaneously from different brain areas without the need to mechanically reposition the probe. This device is called the *electronic depth control* (EDC) probe. The electrode configuration can be easily changed during the experiment by software with a few simple mouse clicks in the user interface.

RESULTS: The EDC probe contains a pointy tip that even pierces trough monkey dura. As a result, there is no reason to cut the dura, which decreases the risk of inflammation. The EDC probe functionality has been tested in an adult rat under anaesthesia, and simultaneous recordings were performed from different brain regions without mechanically repositioning the probe [2], see Figure 1. This significantly decreases the time-consuming procedure to re-position the recording electrode, which increases tissue response.

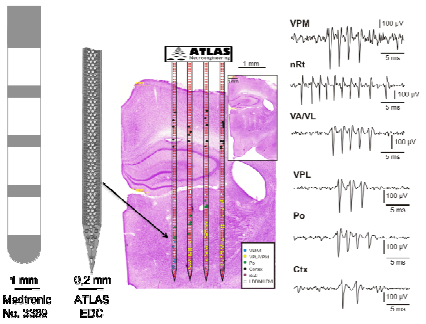

Fig. 1: Cross section of the rat brain with a sketch of a DBS probe (left) and SEM picture of the EDC shaft with individual neuronal signals recorded in different brain regions (right).

DISCUSSION & CONCLUSIONS: Combining the EDC technology with today's DBS probes will be the way towards patient specific treatment. With its high electrode resolution and selectivity, it decreases time-consuming electrode positioning in high cost surgery rooms.

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Flex PCB reliability: an objective evidence based approach for long-term cost avoidance

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[3] *Micro Systems Engineering, Inc., Lake Oswego, OR, USA*

INTRODUCTION: PCBs for active medical implants need to have a „guaranteed" reliability. However, such predictions must be based on solid acceleration models and repeatable process parameters. Finally, a meaningful product reliability monitoring has to be established to prove evidence of PCB performance in real application situations.

METHODS: The highest stress for an implantable medical device is the assembly solder process. After that, thermo mechanical cycling stress is minimal. Several common models were used to determine the acceleration factors between IST (Interconnect Stress Test) and temperature cycling exposure during the whole product build process.

Table 1 shows the results of the 4 major steps in the life cycle of an implanted medical device.

Table 1. IST cycles necessary to reflect device life.

	Number of IST-cycles reflecting the temperature stress		
Major steps	**Basquin**	**Coffin-Manson**	**Norris-Landzberg**
PCB assembly	22	10	13
Environmental stress screening	<1	<1	<1
PCB shipping / Device manufacturing	<<1	<<1	<<1
Device shipping / implanted life time	<<1	<<1	<1

The target number of cycles, which must be achieved to simulate the entire life cycle, was set to 22 IST cycles according to the largest value in Table 1 (Basquin model).

IST test runs on numerous samples were done to evaluate differences of process parameters as well as material compositions. Key focus was the reliability of microvias in flex circuits. This is influenced both by material selection and geometrical dimensions of the via itself, as well as the detailed process parameters of all processes contributing to the via generation.

RESULTS: Reliability evaluations are used to characterize new processes or new material combinations. Fig. 2 shows an example of a new process in the initial state (Process A) and the performance of this process after tuning the sub processes to an optimal setting (Process B).

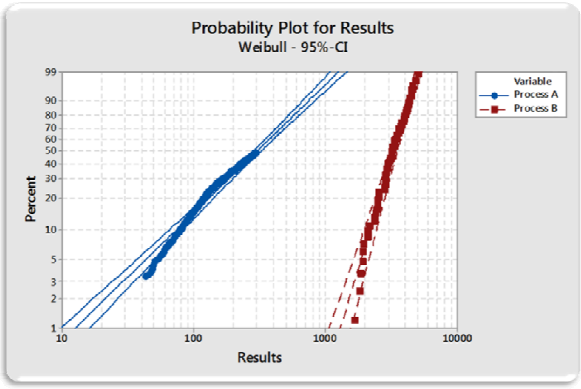

Fig. 1: Comparison of a marginal process (A) to a solid process (B).

DISCUSSION & CONCLUSIONS: It was demonstrated that via reliability could be improved by an order of magnitude through revisiting all processes and materials. IST testing and large volume hot testing was applied to show statistical evidence of improvements. In the long term this increased reliability avoids and reduces costs.

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Security of wireless implantable medical devices

D Singelée

ESAT - COSIC, KU Leuven - iMinds, Heverlee - Leuven, Belgium

INTRODUCTION: Implantable Medical Devices (IMDs), such as pacemakers or neurostimulators, are used to monitor and treat physiological conditions of a patient. Recently, most IMDs have a wireless interface to reconfigure the therapy and/or read out relevant medical data. However, besides the clear benefits of having such a wireless interface, it also allows potential adversaries to eavesdrop sensitive data and/or carry out potentially life-threatening attacks. Various security vulnerabilities have already been reported by several researchers. For example, Halperin et al. performed the first security and privacy analysis of an implantable cardioverter debrillator (ICD) [1]. They particularly focused on the short-range wireless communication channel (with a typical range of about 8 cm) between an ICD and a commercial external programmer, and implemented several software radio-based attacks that could compromise both the safety and privacy of the patient.

Based on this observation, we analysed the security and privacy properties of the wireless communication channel of several commonly used active wireless medical implants, using commercial off-the-shelf lab equipment. Furthermore, we also performed research on how strong security and privacy can be guaranteed by applying (lightweight) cryptographic algorithms. These novel techniques can be implemented both in hardware and/or software at low cost, hence reducing the cost of security-enabled implants.

METHODS: To analyse the security properties of the wireless interface of medical implants, a two-step approach is used. First of all, the communication protocol between the implant and a so-called programmer (used by medical staff to reconfigure the implant remotely or to receive telemetry from the implant) has to be reverse-engineered, since this communication protocol is often proprietary and not public. This reverse-engineering, based on a black-box approach, can be done using widely available off-the-shelf hardware: besides the medical devices, we used several wireless antennas, a Universal Serial Radio Peripheral (USRP) and an oscilloscope. In the second stage of the security analysis, the security countermeasures are studied.

Based on these security observations, we are designing lightweight cryptographic building blocks, which can be integrated in future generations of implants. This way, security can be enabled at minimal cost.

RESULTS: Given its sensitive nature, not all results of the security analysis can be disclosed. However, our research clearly shows the need for lightweight authentication and encryption algorithms. This way, an implant can assess if the wireless communication it receives was sent by a genuine device programmer, or is the result of an impersonation attack. Moreover, it also protects the privacy of medical data being exchanged.

These lightweight security solutions could rely both on hardware or software. The hardware-based solutions are based on a low-cost cryptographic co-processor. The software-based solutions are typically optimized for the microcontroller which is part of the implant.

DISCUSSION & CONCLUSIONS: Our research clearly shows that security through obscurity should be avoided by all means. Even when using off-the-shelf lab equipment such as oscilloscopes and software-defined radios, an adversary can obtain full knowledge about the proprietary communication protocol. Therefore, lightweight cryptographic algorithms need to be deployed on the implant, to offer the required level of security. There are both efficient hardware and software security solutions, which can be realized on implants, while reducing the cost compared to conventional security approaches.

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Monitoring vital signs with low-cost and long term implantable pressure sensors

M Fretz, R Jose James, G Spinola Durante

CSEM SA, Alpnach Dorf, CH

INTRODUCTION: Biocompatible miniature pressure sensors have many potential long-term applications in the human body [1]. To date, sealing processes (such as laser welding) are incompatible with ever shrinking packages. The challenge is twofold: Firstly, smaller packages place the components closer to the sealing area to be bonded. Silicon based parts might not survive temperatures above ~250 °C for a prolonged time. Secondly, medical implants increasingly rely on remote powering and data transfer, necessitating non-metallic packages.

METHODS: We present a biocompatible long-term implantable pressure sensor based on the commercial sensor P161 (Amphenol, formerly GE) and a sapphire package. The process used to hermetically seal the device is referred to as Laser Assisted Bonding (LAB). The two platinum surfaces along the peripheral on both top and bottom sapphire parts are brought to intimate contact. A focused IR laser beam is scanning along the mating metal surfaces, providing local energy to promote bonding.

The package comprises top and bottom sapphire parts with a size of 4x4x0.5 mm^3 each. Cavities (2.5x2.5 mm^2) are milled with a laser. The cavity bottom of the top part is milled to a thickness of 75 µm and has a width and breadth of 2.5 mm^2, henceforth called the outer membrane (Fig. *1*.) Thin and matching platinum layers of a few hundred nanometres are evaporated on both parts (Fig. *1*). The bonding process requires that both metal frames are brought to intimate contact. A custom made fixture was used to guarantee alignment and to apply required pressure during the LAB process.

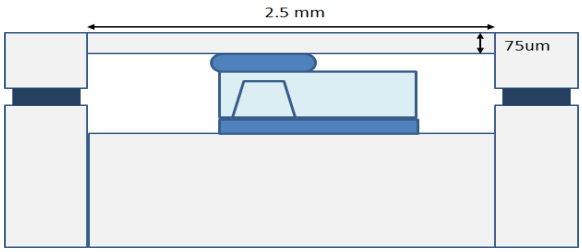

Fig. 1: Schematic of the biocompatible pressure sensor device.

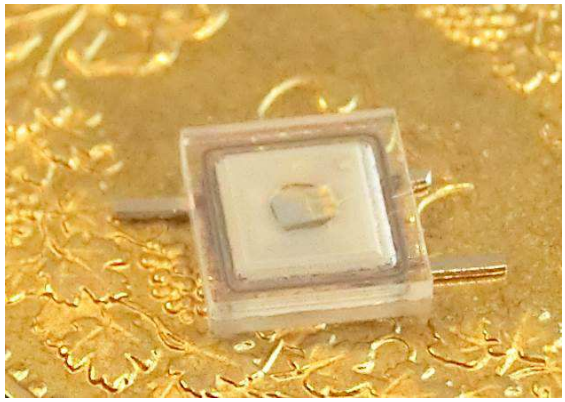

Fig. 2: Hermetically packaged commercial pressure sensor. The package is made of sapphire and is long-term biocompatible.

A soft material was used to mechanically couple the commercial pressure sensor to the outer membrane, as shown in Fig. 1.

RESULTS: In order to be useful as an implantable pressure sensor, the device has to transmit the outside pressure to the commercial pressure sensor with as little attenuation as possible and without compromising its mechanical stability. The dimensions of the outer membrane are crucial, as they define the compliance and the strength. The pressure sensitivity of the demonstrator (Fig. ***2***) is 11.3 mV/bar, which is 17 % of the specified sensitivity of the commercial pressure sensor P161.

DISCUSSION & CONCLUSIONS: The pressure sensitivity can be increased by reducing the thickness and increasing the lateral size of the outer membrane. A preliminary device with a ~3.5x3.5 mm^2 large and 50 µm thin outer sapphire membrane has a pressure sensitivity of 64.8 mV/bar, which is 95 % of the specified sensitivity of the commercial pressure sensor.

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ACKNOWLEDGEMENTS: We acknowledge the funding provided by the Swiss Confederation.

Trends for magnesium implants

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ABSTRACT: Aging populations, increasing obesity and a rise in osteoporosis-related fractures will sustain a need for orthopaedic interventions [1]. In addition, juvenile patients and active adults performing risky sporting activities also require perfect care. So far these indications are treated mainly with non-degradable metal implants or in some cases also polymers [2]. From the patient's point of view, degradable implants would clearly be preferred [3]. Here, degradable Magnesium based implants could become an alternative to permanent metallic implants which have to be removed after healing, or to replace degradable polymers which do not always show the required mechanical properties.

Mg and its alloys degrade under physiological conditions. The great challenge here is to tailor the degradation in a manner that is suitable for a biological environment. Fast or uncontrolled corrosion is associated with strong hydrogen and ion release and severe pH changes, which can lead to a fast loss of mechanical stability and undesirable biological reactions [4]. Since these processes are highly complex in a living system and sufficient data describing the degradation in vivo is missing, it is very difficult to produce knowledge based new alloys. Therefore the development of new biodegradable Mg-based implants is strongly relying on the understanding of the degradation process in the living organism and the creation of an appropriate test system in vitro.

To date, numerous papers deal with the analysis of Mg degradation under near physiological conditions. The results are manifold and partially contradictory. A comparable amount of data deduced from animal experiments is still missing [5]. Until today [6] only about 50 animal studies on Mg degradation are published so far. Most of them use techniques such as CT or histology to describe the degradation and to some extend also the physiological reaction of the surrounding tissue. The number of animals per study is rather limited and the statistical relevance of the results not always convincing. Since almost no time-resolved measurements (exceptions are e.g. studies by Medical University of Graz [7-9]) and no additional information about the corrosion environment in the bone are available, the understanding of the underlying mechanisms of degradation and bone remodelling is completely missing.

However, there is already one CE certified Mg-alloy implant available (compression screw of Syntellix AG, Germany) and several clinical studies for Mg-based drug-eluting stents are currently on the way. In China and Korea patient trials (hip surgery [10] and hand fracture [11]) are reported.

This presentation tries to outline the perspectives Mg based implants have and how a faster and tailored development might be possible.

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ACKNOWLEDGEMENTS: I greatly acknowledge the inspiration and skills of the members of the institute for Metallic Biomaterials and I wish to thank especially Dr. Bérengère Luthringer and Dr. Frank Feyerabend for their tireless support.

Reducing production costs and remaining competitive with Lean manufacturing and the Six Sigma quality approach

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INTRODUCTION: Increasing margin squeeze and unfavourable currency exchange rates force Swiss companies to rethink their business models and management approach to remain competitive in a globalizing business environment. Only ten years ago, applying Lean and SixSigma (LSS) meant to have a clear competitive advantage; today, through its dissemination and multiple benefits, these approaches have become a prerequisite for every business in order to survive. The presentation deals with the following topics: What is Lean? What is Six Sigma? Why both are important? What is the dissemination of LSS in Switzerland? What can we learn from Toyota? Has LSS to be adapted for the medical branch? How to deploy LSS?

LEAN AND SIX SIGMA: LSS, derived from Toyota's Production System (TPS), is not a flavour of the day, but represents today the most efficient and effective manufacturing theory which has evolved into a comprehensive operational excellence (OPEX) approach. Lean deals with the optimization of the whole value stream with a Kaizen team-based continuous improvement approach. The aim of the TPS is to reduce Work in Process (WIP) and thus reduce process lead time. By reducing waste, the process is getting leaner, improving the whole process key parameters, such as cycle times, change-over time, waiting time, and finally the process lead time. All this leads to a just-in-time production, where the right material in the right quantity, arrives at the right place, at the right time. Different as often divulged, Lean is not a tool-set from which to choose some tools, but it is a comprehensive tool-system (*Figure 1*). Indeed, within a single-piece-flow everything is aimed to guarantee a flawless production. Six Sigma on the other hand, deals with the reduction of variation in the process in order to improve quality, i.e. to have capable processes. Six Sigma is often combined with the DMAIC problem solving method to achieve six sigma quality level (3.4 ppm). Since 2000, the Six Sigma DMAIC method has evolved incorporating also the Lean tools becoming universally applicable to solve manufacturing issues in a sustainable manner.

LSS IN SWITZERLAND: A recently conducted field survey [1] regarding LSS dissemination in Switzerland revealed an increasing dynamic in applying LSS. Nevertheless, Swiss industry rests behind other European countries. The topics examined were: approach applied, reasons for deployment, satisfaction, improvement achieved, collateral effects. Interesting was the statistical significance of correlation between employee attitude and leadership behaviour. This shows the crucial importance of change management.

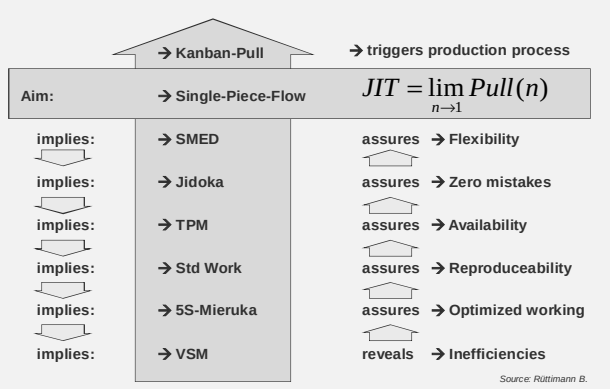

Fig. 1: Lean is not a tool-set as often reported, Lean is a tool-system to be applied as a whole.

THE IDEAL APPROACH: Lean has been developed in the automotive industry where, in the meantime, it has been universally adopted and is conquering also other industries and service companies. Nevertheless, in certain sectors, LSS is misunderstood and reduced to the application of some tools aimed only at waste reduction, not exploiting the full potential it offers. The medical sector too, shows increasing interest in this OPEX management approach with positive results. However, personal experience shows that often companies don't choose the optimal way to start and loose opportunities; this is mainly due to limited knowledge about LSS and the advantages of the different approaches they offer.

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Efficient testing strategies for medical devices by using new concepts for risk assessment and new *in vitro* testing methods

AH Poth

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INTRODUCTION: An assessment of toxicological risk is necessary for the assurance of biological safety, which is evident from Annex VIII of the EU Medical Device Directive (93/42/EWG and 2007/47/EG, respectively). Several of the Essential Requirements in the Medical Device Directive refer to, or also apply to, the biological and toxicological safety of the medical device. The main safety aim is that the device will not compromise the clinical condition or safety of the patient or user or other persons.

METHODS: The biological and toxicological risk assessment should include considerations for all toxicological endpoints relevant for the medical devices. Biological/toxicological safety cannot be demonstrated adequately using a "check-list" approach. A systematic analysis of biological risk is required. This based on the general principles applying to the biological evaluation of materials and devices set out in ISO 10993-1 [1]. The important standards for biological evaluation and risk analysis are explained in three parts. ISO 10993-1 provides the frame-work and describes the general principles of the biological evaluation; ISO 10993-18 [2] provides information on the qualitative and quantitative characteristics and finally ISO 10993-17 [3] gives guidance on the derivation of the allowable limits for the leachable components of the medical devices. New concepts are planned to be included in ISO 10993-17, which will contain the Threshold of Toxicological Concern (TTC concept) and concepts addressing potential synergistic effects. The TTC-concept refers to the establishment of the level of exposure which there would be no appreciable risk to humans, including also cases in which there is no toxicity data available for any leachable compound. This concept may be a useful tool for evaluating and waiving subacute and subchronic toxicity studies. ISO 10993-17 Annex B describes the hazard approach for the risk assessment of mixtures for additive effects. Potential synergistic effects are not covered at present. For synergistic effects it is proposed to include the TTC concept, assuming that interactions are unlikely to occur at low concentrations and including some *in vitro* assays (e.g. cytotoxicity, genotoxicity and hemolysis).

For all medical devices the two toxicological endpoints, irritation and sensitisation have to be considered to evaluate the biocompatibility of certain devices. For these endpoints still animal experiments are carried out according to ISO 10993-10 [4]. However, promising new *in vitro* assays are going to be validated for their use in medical device safety assessment including the use of 3D human skin equivalents.

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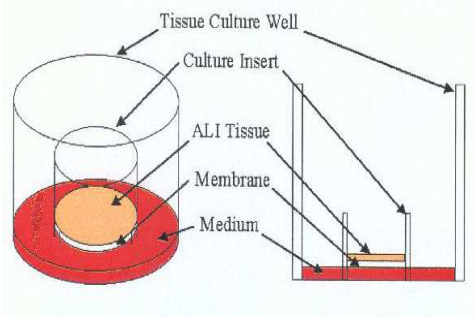

Fig. 1: Experimental set-up for performance of the irritation assay using human skin equivalents.

DISCUSSION & CONCLUSIONS: New concepts in risk assessment and the inclusion of new *in vitro* assays for certain toxicological endpoints may lead to a significant reduction of animal experiments in the near future for the safety assessment of medical devices. With these approaches also the medical device industry is following the principles of the 3R´s: Replacement, Refinement and Reduction.

REFERENCES: [1] ISO 10993-1: *Evaluation and testing within a risk management process* (2009) [2] ISO 10993-18: *Chemical characterisation of materials* (2005). [3] ISO 10993-17: *Establishment of allowable limits for leachable substances* (2002). [4] ISO 10993-10: *Tests for irritation and skin sensitisation* (2010).

Clinical investigations with implants: View of the development company and of the CRO

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INTRODUCTION: Increasing demands on the performance evaluation of medical devices lead to a growing importance of clinical trials. The new MDR and IVDR place greater emphasis on clinical data and to a Clinical Evaluation Report (CER) and request clinical testing of high-risk products. Smaller companies often do not have the specific knowledge and/or the resources required in the planning, implementation and evaluation of clinical trials and need to outsource these increasing and demanding tasks to specialized Contract Research Organizations (CRO).

RESULTS & DISCUSSION: SpineWelding AG is a small Swiss company focused on the research and development of medical devices based on an innovative, proprietary technology. The company is currently conducting two clinical studies with Class III bioresorbable implants: a prospective case series with a newly CE approved micro-suture anchor for hand surgery in Austria, and a feasibility investigation with a very innovative spinal implant in Switzerland. For the company these were the first clinical studies it has ever conducted. Support of an experienced and competent CRO has therefore been fundamental from the very first day. The key challenge for the CRO in the preparatory phase was to help the company to navigate through the regulatory requirements of the respective countries, to mediate first discussions with the regulatory bodies and to help in the generation of the extensive documentation required.

Changes in the law during this preparatory phase required major adaptations of the clinical documents and additional trainings of the involved parties. All this caused a significant delay in the start of the investigation and inevitably additional costs.

During the conduct of the clinical investigation, it is fundamental that all parties involved understand the importance of a complete and regulation compliant documentation. In addition to a flexible and experienced CRO, here it is advantageous to have a dedicated and competent investigation coordinator at the investigation site itself. Thereby it is advisable to have a well GCP-experienced clinical research group at hand.

A challenge in the view of the CRO is to make the sponsor company and the investigator site aware about the obstacles of a clinical investigation. According to MEEDEV2.7/4 a properly conducted clinical investigation, including compliance to the clinical investigation plan and local laws and regulations, ensures the protection of subjects, the integrity of the data and that the data obtained are acceptable for the purpose of demonstrating conformity to the Essential Requirements. The standard ISO 14155 outlines good clinical practice for clinical investigations of medical devices. To reach a common vision on the requirements with all involved parties is important for success. Critical points to consider are a proper study design including statistics, regulatory and ethical requirements, selection of investigators, patients' availability, resources, transparency, proper study conduct and monitoring.

CONCLUSION: From the perspective of a developing company working with Class III implants and being exposed to the need to conduct clinical trials, the key challenges are in the planning and submission process as well as in the implementation of a clinical investigation (Start, FPFV, and recruitment). It is highly recommended to seek experienced support not only to manage the above operative processes but also to adapt the company quality management structures and processes to the specific requirements of a clinical investigation. Furthermore, it is advisable to accord the design of an investigation well in advance with the regulatory bodies. Both, CE Notified Bodies as well as the FDA provide suitable platforms therefore. Last but not least, especially for small companies as ours, the importance of the good and professional relationship with the principle investigator is not to be underestimated. The preparative phase as well as the investigation depend greatly on the quality of the communication and the personal commitment of all involved parties. Specific support from an experienced CRO is the key in conducting a successful clinical investigation.

Simulation of the use of plastics in the medical sector with respect to leachables

B Burn

Interlabor Belp AG, Belp, CH

INTRODUCTION: Plastics have become indispensable in our modern times and are also widely used for medical devices and implants. Examples are dental implants, stents, coatings, screws, and adhesives. The use of plastics has a number of advantages, but there are also some challenges. One problem may be the so-called leachables. Leachables are ingredients of the material such as residual monomers, additives or side products of the polymerisation, which are washed out slowly, if the device is coming into contact with body fluids or tissue. To prevent any risk for the patient, these substances have to be identified and assessed for potential toxicological effects. One possibility to get the required data are extraction studies. Such studies performed in an early state of product development may be helpful to select appropriate materials and to recognize potential problems with incompatibilities.

METHODS: In a first step the sample is extracted using a suitable solvent under conditions depending on the type of study. One possibility is to perform an exhaustive extraction. With this type of extraction the total amount of potential leachables in a sample is released. This method is used for worst case scenarios. An alternative is to perform a simulated-use extraction. This type of study is suitable to determine leachable exposure to the patient simulating the intended use of the tested product. The experimental conditions for such a study are selected based upon real conditions. For details see [1]. The obtained extracts are subsequently screened for leachables using chromatographic method coupled with mass spectrometers or other appropriate techniques. The screening methods are selected in such a way to cover the largest possible range of substance classes. Unknown leachables are identified as good as possible by means of for example mass spectrometric methods. This database allows in many cases a profound toxicological assessment [2].

RESULTS: Extracts of a simulated use study of a medical device showed numerous unknown leachables using UPLC-HRMS. The origin of these leachable could by identify as an adhesive on acrylate base.

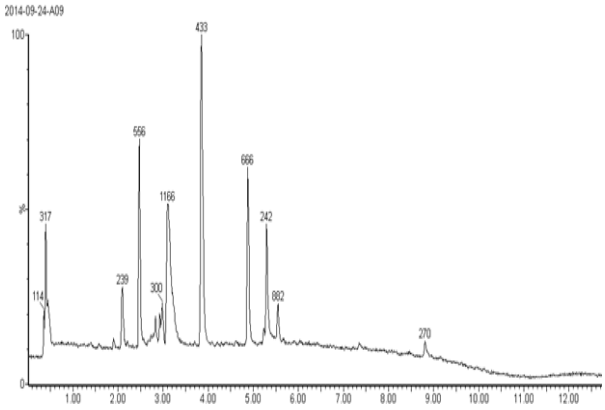

Fig. 1: UPLC-HRMS chromatogram of adhesive leachables in an extraction medium (total ion count).

The main leachables could be identified as cyclic esters from adipic acid and diethylene glycol which are probably side products of adhesive curing.

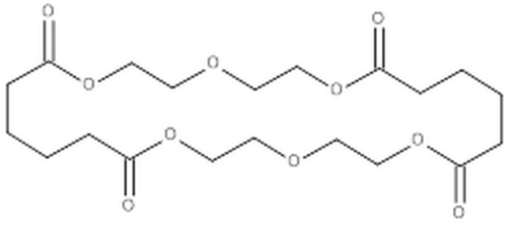

Fig. 2: Chemical structure of one of the main leachables elucidated based on the mass spectrum.

DISCUSSION & CONCLUSIONS: The example described above shows that leachables may origin even from unexpected sources like adhesive bonds. Extraction studies of plastic material coming into contact with body fluids or tissue are therefore a helpful tool to recognize potential risks due to leached compounds.

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How to leverage CE data of implants used for CE marking in the U.S. for PMA approval

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INTRODUCTION: Medical devices are regulated quite differently in the US and in Europe. This creates challenges for both US and European device manufacturers seeking subsequent approval for their devices in the EU and in the US (or vice versa) based on largely non-harmonized regulatory requirements in these two jurisdictions. This manuscript aims at providing an outline of the regulatory requirements for class III implantable medical devices either seeking FDA (Food and Drug Administration) approval through a PMA or the CE-marking process with a the Notified Body in Europe, respectively and discusses how to leverage non-clinical, GMP- and clinical documentation and data, likely to be acceptable to both regions.

METHODS: U.S. and EU device regulations were reviewed with respect to high risk class III devices. European legislation as given in Directive 93/42/EC for medical devices classifies long-term implantable devices such as hip and knee joint replacements into class III devices. Directive 93/42/EC allows for various conformity assessment procedures (CAP) and to meet Essential Requirements (Annex I). European "device GMP" (Good Manufacturing Practice) is stipulated in ISO 13485:2012 and compliance to this standard is required for the manufacturer for CE-marking of the device. In the USA, class III devices are subject to the Pre-Market Approval (PMA, 21CFR 814) process for FDA approval. During the development process, the sponsor must comply with design controls according to 21 CFR (Code of Federal Regulation) part 820.30 (Quality System Regulation, Design Controls) conduct pre-clinical evaluations, functional testing (*in vitro*, *in vivo*), shipping, package integrity and shelf life testing and, if necessary obtain approval for an IDE (Investigational Device Exemption).

RESULTS: Fundamentally, pivotal non-clinical data in the development of the devices performed under Good Laboratory Practice (GLP) conditions addressing the ISO 10993 series of standards are likely to be accepted in both regions, based on the concept that in principle FDA recognizes some of the ISO 10993 standard series and that the US and the EU are signatories to the MAD (Mutual Acceptance of Data) [1]. Device manufacturing data obtained under EU GMP conditions are less stringent as compared to US GMP requirements, especially concerning design control (21CFR 820.30). Thus, design control adopted to meet 21 CFR 820.30 under ISO 13485 would facilitate design control data acceptance. In the EU, clinical studies must comply with the ISO 14155 standard, which is recognized by FDA. Nevertheless, clinical trial studies must primarily follow US device GCP regulations (21 CFR 56, 54, 50, 812).

DISCUSSION & CONCLUSIONS: For non-clinical data acceptance one must evaluate exceptions and exclusions for standard acceptance. CDRH (Center for Devices and Radiological Health) recommends the "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing - Draft Guidance for Industry and Food and Drug Administration Staff" [2]. 21CFR part 820 requirements go beyond ISO 13485 and thus US-based GMP data are deemed largely acceptable in the EU region, provided EU-specifics are considered such as the regulatory and statutory requirements in the documentation. The regulatory focus in the US is based on safety and effectiveness for devices. The EU focusses on safety and performance. Thus clinical trial data are likely not interchangeable, the very least HFE (Human Factor Engineering) data must be obtained in the country of approval. In conclusion, a thorough gap analysis is necessary to understand the commonalities between the two regulatory systems. Once these are identified, selected common data might be acceptable in both regions. Thus, sponsors need to carefully evaluate the standards that are part of the Essential Requirements as well as relevant FDA guidances.

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[1] http://www.oecd.org/env/ehs/mutualacceptanceofdatamad.htm

[2] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/Search.cfm

Emerging and re-emerging markets: how to navigate innovation thru global regulatory approvals

V Legay

NAMSA, Selby, UK

INTRODUCTION: Innovation in the medical device area can be disruptive or incremental. The optimum regulatory strategy will require specific approaches for each case and in each market you intend to enter. In addition, global regulatory bodies are increasing their scrutiny to ensure patient safety and the days of US or EU approval alone opening access to all other countries no longer exists. With longer times to market in the US and EU, it is increasingly challenging to get the return on investment in established markets alone. With growing demand in established markets as more people expect better treatments, this still forces to look at these markets and secure the devices availability. In parallel, companies should be looking at emerging markets from Day 1 to improve revenue globally. This can allow for accelerated product development and a growing portfolio of registered devices to add value to your company and increase your bottom line. However, time changes as well in emerging markets and if regulatory pressures were lower, these markets tend to strengthen their Regulations as well to make sure safe devices are marketed. This talk will review some of the key learnings over the past few years around synergetic efforts to optimize global regulatory path and compliance, as well as to understand the global regulatory and testing requirements to rapidly decrease the time to market; saving time & money to obtain global regulatory approvals.

METHODS: Global requirements need to be reviewed and discussed to highlight key areas of concern and identify similarities to be leveraged, as well as differences to be anticipated to avoid last minute gaps.

Pre-clinical and Clinical evaluations for medical devices tend to be harmonized now worldwide but still some local specificities should be anticipated. Last, cultural and historical characteristics still influence the regulatory agencies in their reviews. Since 2014, acceleration of harmonization worldwide is visible and will continue until reaching a steady state so manufacturers may integrate those increasing demands in their timing and resources.

RESULTS: Standards and guidelines typically used and known applicable in USA and in EU are reviewed and updated to take into account recent health scandals and protect patients better. Risk management (ISO / EN ISO 14971) is becoming the cornerstone of every medical device development and authorities now include this concept in their review, even in China (New Regulation n°650 dated March 2014) and Malaysia (new regulation to come in 2015) where this Risk Based approach is now part of the registration process. Testing needs are growing to demonstrate safety and performance for higher risk devices under their new/actual classifications, unless an adequate risk management approach can help demonstrate safety with omission of testing (ISO 10993-1, ISO/TR 15499). Clinical evidence requirements tend to increase as the “equivalency assessment” is more challenged nowadays to make it different than a list of competitors (MEDDEV 2.7.1, SG5.N2). Last clinical claims are expected to be identified and demonstrated to clearly show benefit for patients as compared to risks all along device life cycle, which calls for Post Market Clinical Follow Up (SG5.N4; MEDDEV 2.12.2; ISO/EN ISO 13485).

DISCUSSION & CONCLUSIONS: Despite some local specificity still exists, harmonization in regulatory requirements is in progress. Hence, manufacturers clearly need to make sure all requirements are known and anticipated to avoid last minute delays, and also better forecast resources needed for global marketing, and refine the return-on-investment the regulatory submissions generate.

ACKNOWLEDGEMENTS: This presentation is a summary of information captured from all NAMSA experts worldwide, working together as a team to ensure regulatory intelligence for the medical device industry.

Skull model for craniomaxillofacial fracture and brain education

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[1] *Inspire AG, irpd, St. Gallen, CH.* [2] *SYNBONE AG, Malans, CH*

INTRODUCTION: Innovative education models for orthopedic and surgical training purposes need to improve to advance the outcome of the practical training exercises.

SYNBONE is one of the world's leading high-tech companies developing a wide variety of artificial realistic anatomical workshop models for hands-on training, especially for craniomaxillofacial fracture CMF), trauma and neuro surgery education. The challenge was to add more functionality to the product and to reduce the price by 40 %.

In co-operation with INSPIRE irpd, SYNBONE developed an entire new skull product portfolio including the brain and dura.

METHODS: To meet such challenging targets (cost reduction of 40 % with 20 % more features) it was important to consult the best experts and partners.

Based on the analysis, we quickly decided to define an entirely new design and production concept. Methods used were brainstorming with several experts; reviewing the existing production process, remaining open for new production processes and new production technologies, but continually focusing on the cost factor right from the start. With these simple but consistent methods, the project could be realized within the defined time frame.

PROJECT CHALLENGES: The new skull model must contain all relevant additional anatomical details. This meant a modular product concept with brain and dura for the neurosurgery education.

First we had to select the optimal skull containing all required details. Then we digitalized the model by CT. INSPIRE irpd, created the first prototype using 3D printing technology (Additive Manufacturing, AM). The model was produced using the laser sintering process and was later used for a cast made of polyurethane (PUR).

In order to optimize the production process and be able to add all details inside the Skull, the decision was made to split it into two parts. With 3D-software SYNBONE adapted the existing design to allow production with Polyurethane. Parallel to this task, the brain and the dura were designed with the same 3D software. After the model had been released by the education experts and surgeons, the final 10-part production molds were produced.

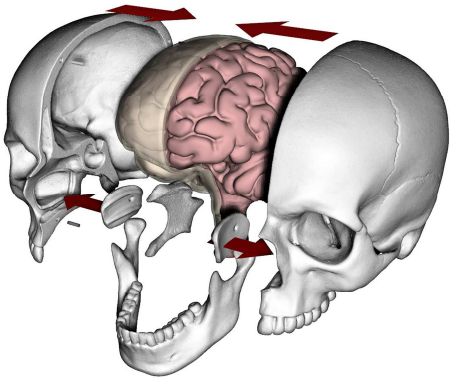

Fig. 1: Images of a Skull – divided into six parts – with brain and dura – additive maufacturing – Polyamid 12

RESULTS: Due to a strict focus on the set targets at the beginning of the project, the team could even outreach their goals. The production costs could be reduced by 42 %. And the products could be integrated into the standard production processes. All product details could be added and all expectations of the medical professionals were met. Today a much broader spectrum of applications can be performed with this smart modular concept skull model.

This very detailed skull model is new on the market and is unique in the neuro education field.

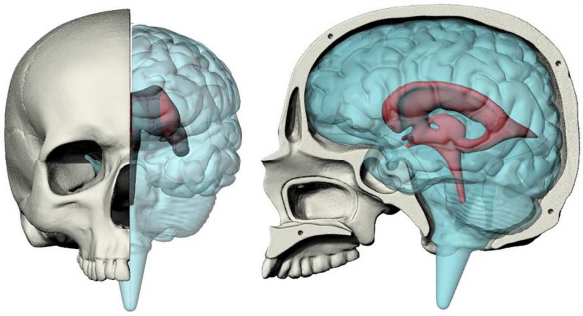

Fig. 2: Images of a skull – brain model inserted

DISCUSSION & CONCLUSIONS: Such results can be achieved only when the best experts work together with the motivation, spirit and focus on the best technology available for the implementation. This approach allows SYNBONE to stay competitive on the global market and to keep a leading position in this niche market.

Reducing risk and R&D costs using medical image based population studies in orthopaedic implant development

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Materialise NV, Gilching, Germany

ABSTRACT: People come in all shapes and sizes and the anatomical variation is not just a matter of a person's size, but also varies across gender, age, ethnicity and other demographics. In order to design an implant system that fits well on this variety of patients, product development engineers need the right design input. Medical image data, like CT and MRI scans are a valuable source of 3D geometrical information, but extracting the relevant size and shape variations and correlations from hundreds of scans can be a challenging task. This presentation will explain how statistical shape modelling can create a bridge between large databases of medical images and the design space of a standard implant. Using examples from the orthopaedic industry, we can show how this technology can significantly reduce R&D costs and minimize the risk for delayed product launches and implant failure.

Predicting Primary Stability in Novel Bone Level Tapered Implants

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ABSTRACT: Intrinsic to the successful placement of a dental implant is a good primary stability, typically measured by insertion torque and resonance frequency analysis. Because there are many factors effecting primary stability (i.e. bone quantity, implant geometry and the surgical technique), measurements can vary drastically from bone defect to bone defect, often in a subjective manner. An alternative to these aforementioned retrospective measurements is to prospectively determine primary stability based on defined parameters, thus enabling one to define a surgical workflow that would optimize primary stability for the specific defect site and implant used. Recently, it has been shown that Finite Element Analysis (FEA) can be used to predict primary stability of implants based on given implant size parameters and the specific bone class at the defect site. In this study, we created an FEA algorithm to predict primary stability of a novel bone level tapered implant based on an experimental model using poly urethane plates. We then tested the robustness of the FEA model in both ex- and in-vivo animal models. This validated FEA model can predict the primary stability resulting from a defined surgical workflow, thus maximizing the clinical outcome and reducing costs associated with implant complications.

Automated workflow for patient specific robust design optimization: an example for plate osteosynthesis

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INTRODUCTION: Since the same procedure on two patients may lead to both implant failure and success, predictive numerical models controlled by robust design optimization (RDO) algorithms could become strong allies to the surgeon. The aim of this interdisciplinary project was to optimize the patient specific screw arrangements and position on locking compression plates in diaphyseal fractures of the femur using numerical finite element analyses integrated in an automated procedure [1].

METHODS: Computed tomography data of a 22-year old non-osteoporotic female were used for patient specific modeling of the inhomogeneous material properties of the bone. Hounsfield Units (HU) were exported and assigned to the elements of a finite element mesh. HU of the bone were correlated with mechanical properties, such as the Young's modulus. Linear finite element analyses were performed with the ANSYS software. An ideal interfragmentary movement between 0.5 mm and 1 mm [2] together with the maximum stress values in the plate, screws and bone were selected as constraints for the optimization [3]. The objective of the optimization was to find the ideal number of screws and the best position of the plate to support the healing process. This was achieved by the use of an evolutionary algorithm. Further stochastic analyses, accounting for uncertainties in the procedure, allowed to quantify implant failure probabilities.

RESULTS: The optimal screw arrangement for the selected patient included only four bicortical screws and a medium bridging length. A positive correlation between bridging length and interfragmentary movement was observed (Fig. 1). Optimal healing conditions were found to be in designs with medium bridging lengths. A larger gap between the plate and bone resulted in an increase in movement at the fracture site. The usage of monocortical screws instead of bicortical ones had negligible influence on the evaluated parameters when modeling the non-osteoporotic bone. Stainless steel implants are stiffer than titanium alloy implants and, therefore, the former were found to reduce the interfragmentary movement and stress in the bone. The automated workflow and the optimization were controlled by the optiSLang RDO toolbox.

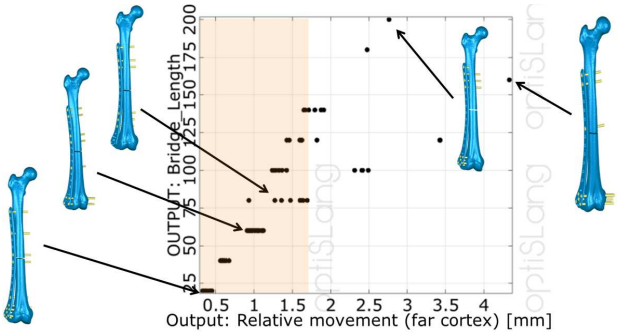

Fig. 1: A correlation between the bridging length and the relative movement of the far cortex was obtained.

DISCUSSION & CONCLUSIONS: An automated workflow for optimization of fracture treatment was successfully developed and implemented. It allowed to select the best layout out of hundreds of designs (including 21 free parameters each) with reasonable effort and offered a basis for a decision on how to handle the fracture treatments. This method is now being implemented as a standard tool by surgeons.

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ACKNOWLEDGEMENTS: C. Wittkowske, S. Raith (TU München), J. Bauer, E. Grande Gracia (Institut für diagnostische und interventionelle Radiologie der TU München), A. Nolte (CADFEM GmbH), B. König, S. Döbele (Berufsgenossenschaftliche Unfallklinik Tübingen).

Modelling alterations in hemodynamics caused by aneurysm implants

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INTRODUCTION: Minimizing the risk of rupture and growth of a detected aneurysm is of major clinical concern. Aside from clipping the aneurysm, altering the blood flow condition using flow diverters, blocking and embolizing the aneurysm are less invasive treatments. The best suited method is determined based on the aneurysm shape, size and location. However, pressure and shear stress caused by the actual flow pattern in the aneurysm and adjacent vessels are not taken into account, since this data is usually not available. Knowledge about these forces acting on the aneurysm [1] and their change due to implantation [2] could help to assess the patient-specific benefits of the available types of surgery more accurately.

METHODS: Aneurysm geometries are segmented from medical imaging data and virtually placed implants, e.g. flow diverters, endovascular coils or aneurysm clips are added. The hemodynamics in such setups is simulated using a finite element based fluid dynamics solver with Schur complement preconditioning in the computational life sciences platform Sim4Life. The Navier-Stokes equation system is solved on an unstructured, tetrahedral mesh resolving this complex vascular structure.

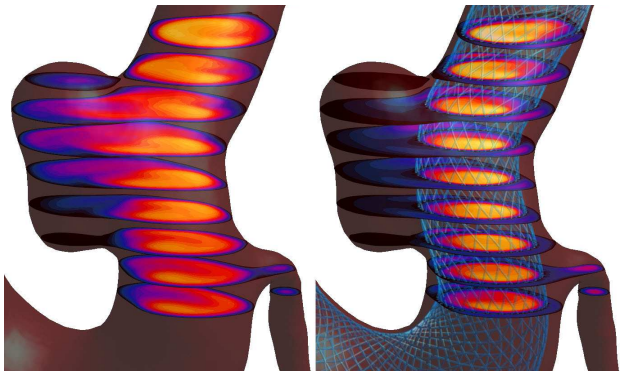

Fig. 1: Velocity profiles in the aneurysm region without (left) and with implanted flow diverter (right).

RESULTS: The changes in flow patterns resulting from placement of aneurysm implants are assessed (Fig. 1). Important parameters like pressure distribution and wall shear stress patterns (Fig. 2) offer information about the straining of the vessel in general and the aneurysm in particular. These are extracted, visualized and quantified to allow a comparative evaluation of the impact of the implant placement.

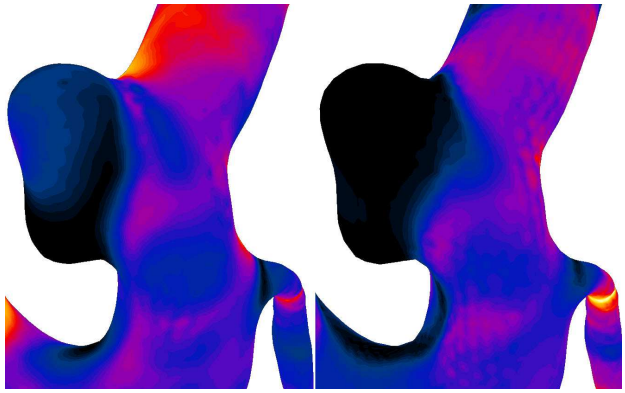

Fig. 2: Comparison of wall shear stress patterns in the pristine aneurysm (left) and after implantation of a flow diverter (right).

DISCUSSION & CONCLUSIONS: Simulations of the alteration of hemodynamics due to surgically placed aneurysm implants offer additional insight into the impact of such treatments and can help to optimize the treatment prospects. Thoroughly validated flow simulations could reliably aid the decision of the surgeon by predicting the post-treatment blood flow conditions prior to the actual surgery. Especially the resulting alterations in pressure and shear stress distribution can provide valuable insight into the expected mechanical forces acting on the aneurysm. Offering these additional, numerically determined decision parameters is expected to benefit the surgery outcome and reduce costs attributed to postoperative complications. We present such simulations of hemodynamics in complex vascular structures before and after aneurysm treatment using the computational life science platform Sim4Life.

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Constant long tool life in titanium

M Zuber

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INTRODUCTION: There are numerous tools on the market nowadays for titanium machining. Indeed, all players in the tool sector seem to agree on the fact that every blade for this kind of material needs an exact cutting edge. Diametal, as a producer of grinding wheels and carbide tools, is able to take advantage of its expertise in these two fields. A perfectly sharp cutting edge is the result of this synergy.

METHODS: All the carbide tools are basically produced using the sintering process. At this juncture, the two main elements tungsten carbide and cobalt are compressed under high pressure and temperature. After an additional coating, the tools are then ready for common applications. The rounding of the edge is thereby not the main focus.

Titanium and also stainless steel, among others, possess high tensile strength, but they also have a ductile property. In order to obtain a proper cut and chip forming process, it is very important to have a sharp cutting edge without any micro chipping. This becomes even more important the smaller the part diameter is. That is why Diametal grinds the rake and clearance face of the DCET inserts, as shown in *Fig. 1.*

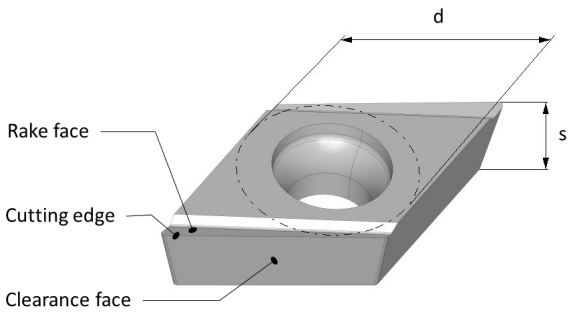

Fig. 1: ISO DCET insert. Through grinding of the rake and clearance face, a well-defined cutting edge results. In addition, the centre height s is kept within ± 0.01mm, and the standardisation even allows ± 0.025mm.

The indexable inserts for cutting tools are standardised in DIN ISO 1832. With 4 letters followed by 6 or more numbers, the insert is then geometrically defined. An example of a frequently used kind of term is the following expression:

VCGT 110304

Supplier-specified indications such as right- or left-hand orientation, coating details etc. can be added after the numbers. The manufacturing process with which the different surfaces or edges have been produced is not stipulated. The only specification is the tolerance of the in-circle diameter d and the thickness s. Tight tolerances i.e. ± 0.025 need definitely a grinding process. *Table 1* shows some usual insert designations as well as possible manufacturing processes.

Table 1. Comparative summary of manufacturing processes and tolerance classes in the 3 letters (underlined) of the DIN ISO standardisation

DIN ISO code:	In-circle **d** tol.:	Thickness **s** tol.:	Chip face:	Clearance face:
DC<u>M</u>T…	± 0.05	± 0.13	Sintered	Sintered
DC<u>G</u>T…	± 0.025	± 0.13	Sintered	Grinded
DC<u>E</u>T…	± 0.025	± 0.025	Grinded	Grinded

It is also important that the coating is appropriately adapted for titanium manufacturing. Thickness, hardness, the coefficient of friction and the temperature resistance are the main criteria for a cutting tool coating.

Usually implants have relatively short turning contours of a few millimetres. The temperature and the hardness are therefore secondary. The thickness and the friction are the main concern. That is why Diametal uses one of the thinnest coatings with a very low coefficient of friction for implant turning.

RESULTS: The advantages of grinded inserts are numerous. Thanks to the narrow tolerance of the thickness s, it is not necessary to re-adjust the centre height when changing the insert in the machine. This saves non-productive time. The long tool life through a smooth cut, however, is clearly the main benefit. It is therefore all the more important that this tool life be as constant as possible. This is achieved with the aid of a selected grinding process for the entire insert geometry. As no area in which the cutting process is involved remains sintered, a reliable level of high quality can be provided.

Innovation for joint implants under cost pressure

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INTRODUCTION: Being a solution-oriented contract manufacturer of joint implants, Jossi Orthopedics is part of a complex network of suppliers, subcontractors, clients (orthopaedic companies), their clients (hospitals and surgeons), as well as end-users (patients, usually represented by insurances). During the product life cycle phase of growth, innovation could be easily justified by an overall benefit, e.g. faster recovery of the patient. Since 2005, when the phase of maturity was entered [1], innovative efforts increasingly fail if one of the parties needs to pay more. Successful innovation has to be accompanied by cost reduction, otherwise mostly being rejected.

CHALLENGE: Occurrence of hospital-acquired infections is up to 5% [2], of deep infections of implants about 1% [3]. Thus, hygiene is a predominant issue and leaves space for innovative approaches. In the following, 2 possible solutions are outlined.

EXAMPLE 1: For many applications, it is necessary to tighten screws with a certain torque. Mechanical torque wrenches have complex mechanics that cannot be dismantled for cleaning and sterilisation, in some cases leaving little crevices where contamination can accumulate. An accurate, completely encapsulated system would be desirable. One possibility is an electronic system in the handpiece detecting forces, transform it to torque and give tangible, visible or audible signals when the limit is reached. However, which are the optimum choices to make for such a system?

- How to program the necessary torque for a certain application?
- Can electronic devices, such as displays and batteries, be autoclaved?
- Should the electronics be disposable and be delivered with each implant?
- Could everything be integrated in a power tool?
- Can the device be competitively priced?
- Would it be accepted?

It is evident that these questions go far beyond the competence of a contract manufacturer being only familiar with metallic implants and instruments.

EXAMPLE 2: Rasps and reamers are used to prepare the implant bed for hip endoprostheses. The surgeon starts with the smallest instrument, increasing successively the size until the final size is reached. Rasps and reamers may be used a few dozen to a few hundred times until they are replaced by new, sharp ones. Due to the complex shape with edges and corners, there are doubts whether these instruments can be cleaned properly before being autoclaved. Therefore, for a long time, disposable instruments made from polymers have been discussed. Again a number of questions appear.

- Does a polymer exist with the necessary mechanical properties?
- Would particles be generated?
- Is the material biocompatible or even resorbable?
- How can it be sterilised?
- Can it be competitively priced?
- Is it compatible to existent instrument sets?
- Would it be accepted?

Pricing is decisive since a full set of instruments needs to be delivered with each implant, e.g. for a stem size 8 a set of 8 rasps size 1-8. The additional costs must be lower than those for handling of cleaning and sterilisation to offer a benefit. Again, it is evident that a supplier manufacturing metallic instruments is unable to handle these challenges on his own.

CONCLUSIONS: Innovation not only needs to offer an economic benefit but also, in many cases, goes far beyond the competences and resources of a small or mid-sized company. A functioning, active network like the *Medical Cluster* with companies of similar culture and spirit, governed by mutual confidence, is beneficial for the efforts to stay ahead of competition.

In the described cases, a network approach was crucial to realistically evaluate risks, efforts and potential benefits of the projects.

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[3] http://orthoinfo.aaos.org.

Wirtschaftlichkeit und Produktsicherheit im Einklang – Aspekte aus der Fabrik- und Reinraumplanung

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EINFÜHRUNG: Die Weiterentwicklung und Kombination von Technologien ermöglicht neue Medizinprodukte und Prozesse. Dies bietet die Chance, sich auf anspruchsvollen Märkten zu behaupten und den steigenden regulatorischen Anforderungen gerecht zu werden.

Viele Medizinaltechnik-Unternehmen haben in den letzten Jahren kontinuierlich an den Produkten und Prozessen gearbeitet und sich mehrheitlich erfolgreich im Markt behauptet. Durch die prozessbedingt steigenden Raumanforderungen – Mikrobiologie und physikalische Parameter – müssen diese zunehmend als Teil des Prozesses betrachtet werden.

Bedingt durch den ständigen Wandel der Produktionsprozesse sind viele Fabriklayouts historisch gewachsen. Kontrollierte Zonen sind dann meist Insellösungen und entsprechen weder einem optimalen Materialfluss, noch sind sie auf die Produktsicherheit ausgelegt.

GANZHEITLICHER ANSATZ: Ein ganzheitlicher Ansatz berücksichtigt sowohl die Wirtschaftlichkeit als auch die Produktsicherheit schon bei Planungsbeginn. Das spart am Ende Zeit, Geld und Nerven. Es ist daher von Bedeutung, dass sämtliche Einflussgrössen entsprechend ihrer Relevanz berücksichtigt werden. Um diese risikobasierten Beurteilungen durchzuführen und alle firmenspezifischen Parameter zu berücksichtigen, wird eine optimale Teamzusammensetzung benötigt.

Auf der Seite des Planerteams müssen die Prozesse des Bauherrn verstanden und entsprechend in einem Gebäude- und (Rein-)Raumkonzept abgebildet werden. Je nach Grösse und Ausrichtung des Projektes sind dabei Planungsdisziplinen von Reinraumtechnik, Logistik über die Statik bis zur Architektur, Haustechnik und Brandschutz gefragt.

Auf der Seite des Auftraggebers wiederum muss ein Team die Anforderungen klar definieren können. Die Trennung von Anforderungen und Lösungen ist dabei von zentraler Bedeutung. Strategische Entwicklungen müssen dabei ebenso berücksichtigt werden, wie Prozessdetailfragen oder Anforderungen an die Qualifizierung oder Reinigung.

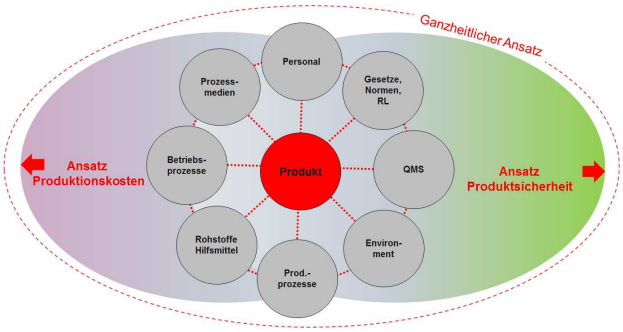

Fig. 1: Ganzheitliche Betrachtung von Produktionssystemen als Chance.

Nur wer es schafft, die Anforderungen der einzelnen Anspruchsgruppen und der relevanten Disziplinen aufzunehmen, in Gebäuden abzubilden und schlussendlich auch zu realisieren, kann durch Wirtschaftlichkeit und Produktsicherheit einen echten Wettbewerbsvorteil schaffen.

Planungsmodelle: Grundsätzlich unterscheiden sich die Planungsmodelle [1] (z.B. SIA / HAOI) nicht wesentlich von den klassischen Qualifizierungsansätzen.

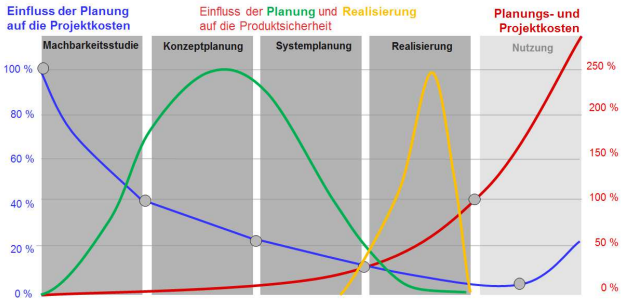

Fig. 2: Einfluss der Planung auf die Produktsicherheit

In der konzeptionellen Planungsphase ist die Beeinflussbarkeit der Produktsicherheit am grössten, da die folgenden Phasen darauf aufbauen und konzeptionelle Fehler meist nur mit hohem baulichen Aufwand eliminiert werden können. Diese Phase wird jedoch von unerfahrenen Planern regelmässig unterschätzt.

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Process Design for Usability EN 62366

R Erdmann

Erdmann Design AG, CH

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 raises the question: Can the concept of human centered design be developed 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 collecting new 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 integration and improve the decision-making and iteration processes.

Taking blame gladly

An essential question that defines design driven product development is the characterisation 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 workflow 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 solutions to meet with the user needs of 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 indicate that larger, cheaper components can be used for the final version.

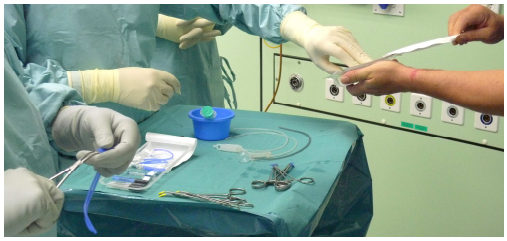
The shaping of things to come

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. Solutions-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. During this iterative process 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. Human centered design studies in an early stage with external help reduce overall development cost and significantly increases acceptance by the end-users.

Laser osteotomy, design prototype usability study



Implantation of a new incontinence device

Navigated implanting prototype for early testing

Poster Session

1 *Predictive in-vitro models for the study of tissue-implant interaction*
Dr. Samantha Chan, Empa St. Gallen, CH

2 *Investigation of Stiffness-isotropy of Different Lattice Geometries*
Simon Zimmermann, FH Nordwestschweiz, CH

3 *Thin Film Flexible Circuits for Medical Applications: Technology and Characteristics*
Maximilian Bee, Cicor AMS Reinhardt Microtech GmbH, CH

4 *Cell viability on titanium implant surfaces modified with antibacterial copper*
PD Dr. habil. Christiane Jung, KKS Ultraschall AG, CH

5 *Cost-reduction via in silico trials: MR-safe implant design and evaluation*
Earl Zastrow, IT'IS Foundation, CH

6 *Evaluation of implant surface coating bioactivity obtained by atomic layer deposition technique*
Evgeny Zolotukhin, CONMET, LLC, RU

7 *Smart electronics: the eye opener for the future*
Stefan Gogaert, AnSem, Heverlee, BE

8 *Outline of European and US requirements for device approval - intersections and differences*
Alexander Kappes, PAREXEL International, DE

9 Pitfalls in the evaluation of local tolerance in medical device studies
Dr. Klaus Weber, AnaPath GmbH, CH

Predictive in-vitro models for the study of tissue-implant interaction

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Empa, Swiss Federal Laboratories for Materials Science and Technology, St Gallen, CH

ABSTRACT: The biological seal of peri-implant soft tissue is crucial for successful long-term prognosis of implants. While in-vitro investigations of the implant-soft tissue interface are usually carried out using monolayer cell-culture models, they fail to replicate the complexity of the three-dimensional native tissue. With the aim to better predict tissue-implant integration, we have therefore established different advanced in-vitro models that represent different stages of the host response to implant materials. In our models, we develop analogues of the 1) coagulation (blood-implant interface); 2) early inflammation (macrophage-laden 3D fibrin hydrogel); and 3) remodelling (bi-layered keratinocyte/fibroblast collagen gel) phase.

Implementation of the coagulation model using human blood showed that distinct dental implant materials promote different adsorption of blood and plasma proteins onto the implants. This resulted in altered cell attachment and matrix production, correlating well to observations from clinical applications. These complex 3-D models are valuable tools to study tissue-implant integration and hold a promise to reduce the need for animal experimentation.

Stiffness-anisotropy of porous implant geometries

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INTRODUCTION: Cellular lattice structures can be used to adjust mechanical properties of bone implant materials, preventing *stress shielding*. Additionally, open-porous structures allow bone cells to migrate into the openings and form a strong connection between the surrounding bone material and the load bearing implants. Under anatomical conditions, such implants are usually exposed to biomechanical forces acting in various directions. This study evaluates the stiffness anisotropy of different lattice geometries, calculated by Finite Element Analysis (FEA).

METHODS: The angular stiffness anisotropy is simulated by COMSOL Multiphysics (Stockholm Sweden, version 5.0). The validity of the FE-Model was proved in a preliminary FEA-study [1]; furthermore, the stiffness anisotropy was investigated by simulating the rhombic-dodecahedral (RDH) lattice geometry rotated around one single axis [2].
In this study, we compare the stiffness anisotropies of four different lattice structures: Type A consists of orthogonal struts with thickness 0.2 mm. Unit cell type B is built by subtracting cylinders (Ø = 0.6 mm) along the room-diagonals of a cube. Type C is based on a cube resected by a sphere (Ø = 1.36 mm), and the unit cell type D represents an extended RDH beam model with strut size 0.4 mm. The porosities of the corresponding lattice structures are given in Tab. 1. The stiffness anisotropy is investigated by rotating the geometries around two axes γ and δ.

RESULTS: For all four types of lattice geometries, the elastic gradient (EG) is calculated for all rotation angles γ and δ in the range of 0°-45° (Fig. 1). The ratios between minimum and maximum EG, as a measure of mechanical anisotropy, differ significantly among the varying lattice types A - D (Tab. 1).

Table 1. Porosity and anisotropy of elastic gradients (EG) referring to structures A - D.

Lattice Type	A	B	C	D
Porosity	0.83	0.76	0.71	0.73
EG Ratio	700 %	450 %	200 %	120 %

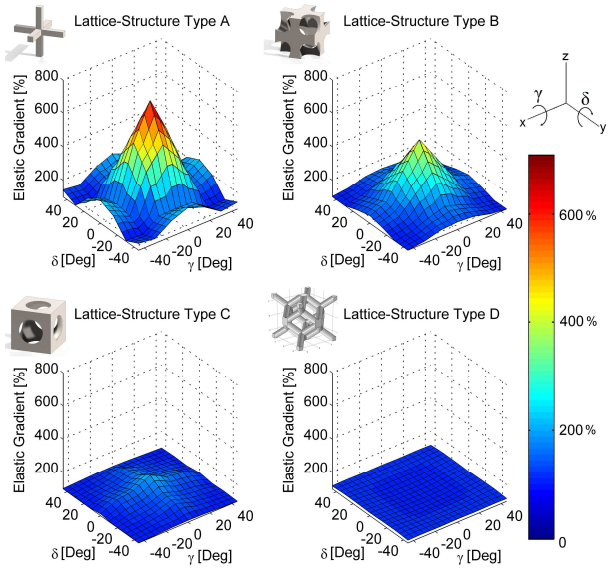

Fig. 1: Elasticity map of all four lattice types in relation to the rotation around the angles γ and δ.

DISCUSSION & CONCLUSIONS: The numerical results show distinctive elasticity maps among the four individual lattice types. Depending on the direction, the stiffness varies between 120 % and 700 %. The high stiffness anisotropy of lattice types A and B can be explained by the pronounced orthogonal struts included in the geometries of these unit cells. The RDH lattice structure type D shows the highest mechanical isotropy and represents a promising candidate for the design of isotropic implants. This leads to an isotropic displacement of the lattice structure under varying compressional directions which might be important for continuing stimulation of the surrounding bone.

REFERENCES: [1] S. Zimmermann (2014) *Structure -Mechanical FEM Analysis and Physical Validation of Porous Titanium Bone Scaffolds*, Master Thesis, FHNW, p 78. [2] S. Zimmermann, M. de Wild (2014) *Density- and Angle-Dependent Stiffness of Titanium 3D Lattice Structures*, *BioNanoMat* **15 S1**:35.

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Thin Film flexible circuits: Chances for overall cost reduction in medical applications

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INTRODUCTION: Interconnecting structures are a fundamental element within an efficient electronic system. Thin Film type substrates are able to provide features with very high resolution and tight tolerances, combined with a wide variety of possible substrate materials and metal systems. Flexible substrates are of particular interest in the field of medical applications, when used on the surface or inside the body. Special challenges arise by the additional demand for biocompatibility and biostability.

In addition, Thin Film technology allows the direct fabrication of, e.g., electrodes or sensor elements together with the interconnecting structures in one fabrication flow, reducing the number of required processes and/or suppliers, and therefore reducing cost and control effort.

TECHNOLOGY: Thin Film technology allows the use of thin and flexible substrates/insulator layers (down to 7 µm and thinner), and the use of noble metals for the fabrication of electrical connections with minimum feature size of 10 µm and smaller. The addition of functional surfaces like, e.g., platinum electrodes is also possible.

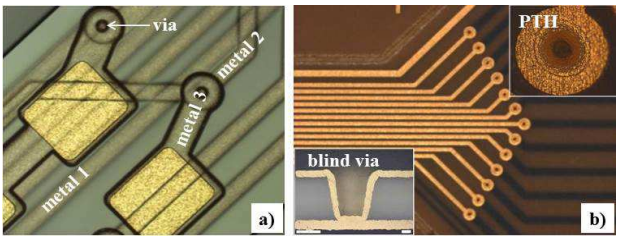

Fig. 1: Example detail view of flexible circuits: (a) build-up method based on liquid polyimide; (b) circuit on flexible foil material.

Two different methods of manufacturing Thin Film flexible circuits are used: (a) the application of a sequential build-up technology [1], based on liquid spin-on polyimide as insulator material, and (b) the method of using flexible foil material, which is adopted from standard PCB technology [2].

Figure 1a shows a detail view of a circuit produced with the liquid polyimide method. A major benefit of this technology is the free choice of insulator thickness and the compatibility with conventional semiconductor processing equipment. The fact that the manufacturing flow is always based on a temporary rigid carrier substrate allows the achievement of very small metallization features, and tight registration and feature tolerances, as the flat rigid configuration represents ideal processing prerequisites. Another important aspect is that the temporary carrier can be kept during subsequent assembly operations and thus allows handling like every standard rigid board.

The second method of using flexible foil material is based on a modified PCB-type manufacturing flow (Fig. 1b). Typically, the generation of metal lines and features after the via hole drilling can be done parallel on the front and the back side, which allows more efficient fabrication. Different substrate materials such as polyimide or LCP (Liquid Crystalline Polymer) can be utilized, which provides an additional degree of freedom in the design of the circuits.

CHARACTERISTICS: Low resistivity lines can be produced by using, e.g., gold (Au) electroplating for layer thicknesses up to 30 µm or more, which is especially important for wireless power supply and data transmission applications in medical implants. Reliability of circuit examples has been measured in cyclic bending tests without failure above 80k cycles under current load, and proven also in various product examples.

CONCLUSION: Thin Film technology on flexible substrates with the possibility of using only biocompatible materials provides an excellent platform for the realization of new applications in health and life science. Miniaturization and high possible packaging density are only two points which can lead to cost efficient realization of implantable devices.

REFERENCES: [1] A. Kaiser et al (2008) *Technology for Medical Human Implants: Vision Chip on Thin Film Multilayer*, Proceedings of the 2008 IMAPS Conference, USA, November 2008. [2] A. Kaiser et al (2013) *Thin Film Flexible Circuits: Technology, Characteristics and Applications*. Proceedings EMPC 2013, France, September 2013.

Cell viability on titanium implant surfaces modified with antibacterial copper

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INTRODUCTION: Implant associated infection is a burden for patients and a cost problem for the health care system. Infection preventing measures would significantly contribute to cost reduction. We have recently developed an electrochemical method to deposit antibacterial copper on titanium implants. In the present *in vitro* study, the biocompatibility of copper (Cu) functionalized surfaces on 3 different human cell types was tested. The viability of human primary gingival fibroblasts (HFIB-G), of immortalized gingival keratinocytes (IHGK) and of an osteosarcoma cell line (SaOs-2), seeded onto Cu-doped titanium discs was investigated.

METHODS: Discs of cpTi grade 4 (∅12 mm, 2 mm) were anodized and Cu-deposited using the spark-assisted anodizing method run in a combined deposition-anodisation process using proprietary electrolyte and proprietary process parameters (KKS TioCel^{TM}) [1]. The amount of deposited Cu was determined by dissolving the Cu in 65% HNO_3 at 50 °C over night and analyzing by atom absorption spectroscopy (Perkin Elmer, AAnalyst 800). Cu amounts between 1-50 µg/disc (5-164 ng/mm^2) were obtained. HFIB-G cells were cultured in monolayer using DMEM/F12 supplemented with 10% fetal bovine serum (FBS). SaOs-2 cells were cultured in DMEM/F12 supplemented with 10% FBS and 2 mM L-glutamine, while IHGK were expanded in EpiLife medium complete of growth supplements. Dried, ethanol and UV sterilized, discs at 6 different Cu concentrations were transferred into pre-coated poly-(2-hydroxyethyl methacrylate) 12-well plates and seeded at the following cell concentrations: 5'000 cells/cm^2 (HFIB-G) and 10'000 cells/cm^2 (SaOs-2 and IHGK). Samples (n=4) were cultured for 3 days. Cell viability was determined using the WST-1 assay. IC_{20} and IC_{50} were calculated with a four-parameter fit using the software GraphPad Prism® (confidence interval 95%).

RESULTS: Cu deposits are homogeneously distributed over the disc surface (Fig. 1). Inhibition curves and IC_{20} and IC_{50} values resulting from the viability tests are shown in Fig. 2 and Tab. 1, respectively. Fibroblasts are more sensible to Cu, showing an IC_{20} of 7.4 µg/disc, while the keratinocytes are the more resistant cells (IC_{20}: 8.6 µg/disc).

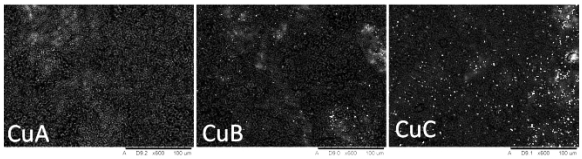

Fig. 1: Scanning electron microscope images of titanium discs with Cu deposits (white spots); CuA: 1.6 ± 0.5 µg/disc; CuB: 18.7 ± 3.1 µg/disc, CuC: 49.7 ± 5.5 µg/disc (x600; TM3000 Hitachi; 15 kV; backscattered electrons).

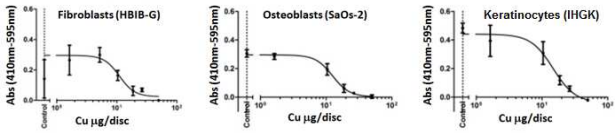

Fig. 2: Inhibition curves for determination of IC_{20} and IC_{50} for the three cell types (n=4).

Table 1. Inhibition values IC_{20} and IC_{50} for the different cell types given in µg/disc and ng/mm^2.

Cell type	µg Cu/disc		ng Cu/mm^2	
	IC_{20}	IC_{50}	IC_{20}	IC_{50}
Fibroblasts	7.4	11.1	24.4	36.7
Osteoblasts	8.3	12.5	27.5	41.5
Keratinocytes	8.6	14.8	28.5	48.8

DISCUSSION & CONCLUSIONS: The cells presented slightly different resistance against Cu (fibroblasts < osteoblasts < keratinocytes). A mean Cu amount of 8 µg/disc (27 ng/mm^2) for 80% cell viability (IC_{20}) and 13 µg/disc (43 ng/mm^2) for 50% cell viability (IC_{50}) could be used as future benchmark for implant functionalization. All Cu was released in the medium during the culture period as seen from the absence of Cu on the disc surface after the viability analysis. A tolerated Cu concentration of 2.7 µg/ml = 42.5 µM for 80% and of 4.3 µg/ml = 67.8 µM for 50% cell viability is calculated. The 50% value is in the range of the lethal Cu concentration for *Staph. aureus* (~5 µg/ml [2]) indicating a good antibacterial effect with an acceptable cell viability of 50%.

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Usage of *in silico* trials in MR-safe implant design and evaluation

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INTRODUCTION: Clinical trials can be costly and time-consuming. More importantly, patients are subjected to additional health risk during the trial. With the growing computing power and advancement in the modeling techniques to capture the interactions of implants with external inputs inside the human body, it has become conceivable that clinical trials can be replaced or reduced by the use of *in silico* tools and methods to eliminate or reduce the risk imposed on patients during clinical assessment. The use of *in silico* evaluation to facilitate the assessment of implant-related risk associated with MRI exposure is demonstrated.

METHODS: Safety assessment of elongated implants (e.g. pacemakers, spinal cord stimulators, and deep-brain stimulators) during MRI exposure is a complex task. To that effect, a joint-working group of experts from the fields of MRI and active implantable medical devices (AIMDs) has composed the technical specification ISO/TS 10974 [1] that outlines the assessment methods of implant interactions with static, gradient and RF fields of the MRI. We shall focus our attention to the assessment of RF-induced heating of AIMD.

The piece-wise excitation (πX) method is proposed by [1] to be one of the methods suitable for characterizing RF-induced heating of elongated AIMD. Based on the concept described in [2], a πX model, *h(l)*, is the electric field transfer function that can be derived numerically or experimentally [3] and *h(l)* presented in [3] is considered for the demonstration in this study. 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 **r** is evaluated. Fig. 1 shows a schematic of the method.

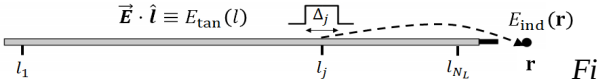
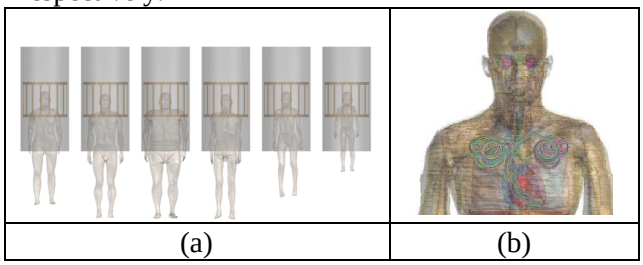


Fig. 1 Schematic of the πX method.

The total induced electric field at point **r**, attributed to E_{tan} coupling along the AIMD of length *L*, can be approximated similar to that demonstrated in [3]. For brevity, readers are referred to [3] for the discussion on the πX model and method.

E_{tan} along the clinical AIMD routings can be evaluated *in silico*, and the induced field due to the RF-implant interactions may be estimated over a large number of exposure conditions. Figs. 2(a) and 2(b) demonstrate a subset of possible MR imaging scenarios and clinical routings for cardiac implants, respectively.



(a) (b)

Fig. 2 in silico trial of a patient population (6 – 82 years old) receiving head MRI scans, utilizing the Virtual Population anatomical (ViP) models [4].

RESULTS: Fig. 3 illustrates the local deposited power in tissue due to the RF-implant interaction, estimated by *h(l)* and E_{tan} obtained for 'Ella' model under MR exposure during a chest imaging. The deposited power is calculated for 24 routing groups. Each routing group is defined by the locations of the distal and proximal terminations, e.g., right pectoral and left ventricle terminations.

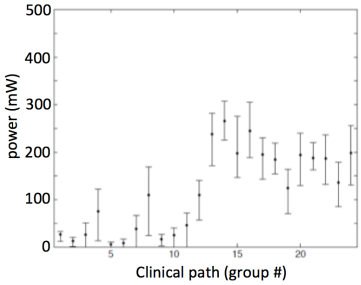


Fig. 3 Estimated RF-induced power deposited by implant in tissue obtained for a subset of the trial.

DISCUSSION & CONCLUSIONS: *In silico* trial enables the assessment of local heating due to the RF-implant interactions over a large number of exposure conditions without imposing any risk to the patients.

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Evaluation of implant surface coating bioactivity obtained by atomic layer deposition technique

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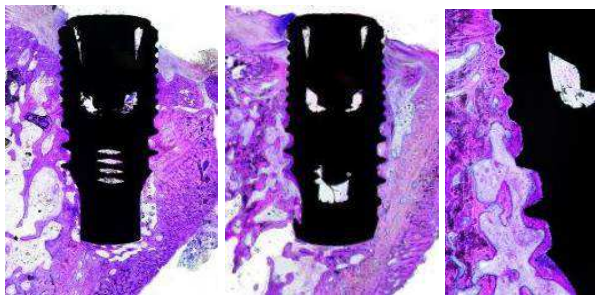
INTRODUCTION: After 6 years of research and development, the company CONMET designed the dental implant coating method based on the atomic layer deposition (ALD) technique of titanium dioxide (TiO_2) with anatase crystal lattice [1]. The objective of the research was to study the bioactive properties of the coated surface and compare it with the same surface without coating.

METHODS: *In Vivo* experiment of dental implantation biomodeling was performed on 10 mini-pigs. Animals were divided into 5 groups, two animals in each. A total of more than 60 dental implants with and without bioactive surface coating were installed in the maxillae of mini-pigs from the 1st, 2nd, 3rd, and 4th groups. The implants of the test group (bioactive surface coating) were sandblasted and ALD TiO_2 coated, whereas the implants of the control group were only sandblasted. The condition of dental implants and surrounding tissues was evaluated after the osseointegration periods of 2, 6, 8, and 16 weeks. Histological, morphometric studies and X-ray Computed Tomography (CT) with the analysis based on Hounsfield scale were conducted. For the 5th group of mini-pigs 16 cylindrical implants without thread were prepared and installed in their maxillae. The Pull-out test and X-ray CT analysis were conducted after an osseointegration period of 6 weeks. The data obtained from all studies were statistically processed using the single-factor dispersion analysis.

RESULTS: The Pull-out test as well as the histomorphometric analysis and CT data of all specimens show significant differences in the qualitative and quantitative characteristics of osseointegration between dental implants with the bioactive surface and uncoated specimens. After 8 weeks of osseointegration period the implants with bioactive surface demonstrated results exceeding the histomorphometric data of specimens without coating after 16 weeks. Parameters indicating the osseointegrative properties of designed ALD TiO_2 coating are presented in *Table 1*.

Table 1. Major quantitative parameters of histomorphometric analysis: BIC – bone-to-implant-contact; FIC – fibrous-tissue-to-implant-contact

	Period of osseointegration	Parameters	
		BIC, [%]	FIC, [%]
Implants **with ALD TiO_2 coating**	2 weeks	77	12
	6 weeks	58	7
	8 weeks	**85**	0,5
	16 weeks	86	0
Implants **without coating**	2 weeks	58	6
	6 weeks	56	29
	8 weeks	**47**	30
	16 weeks	78	0



a) *b)* *c)*

Fig. 1: Images of histotopograms after 8 weeks of osseointegration period: a) uncoated specimen; b) ALD TiO_2-coated specimen; c) enlarged area of image "b" - the newly formed bone tissue tightly adjoined to the implant surface.

DISCUSSION & CONCLUSIONS: The results of the present study demonstrate that ALD TiO_2 coating allows to accelerate the process of dental implant osseointegration by a factor of two. Future research directions should examine clinical implications for the successful benefits.

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Smart electronics: the eye opener for the future

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ABSTRACT: Glaucoma is an eye disease affecting about 4 % of the population over 40 years of age which can lead to blindness unless treated early. One of the symptoms of glaucoma is an increased intraocular pressure. It has long been recognized that, since intraocular pressure varies during the day, continuous monitoring of glaucoma patients is needed. Sensimed AG, a Swiss company, developed a soft hydrophilic single use contact lens. The passive and active strain gauges embedded in the silicone of the lens monitor fluctuations in intraocular pressure through variations in diameter of the eye.

Since there is no possibility to place a battery within the structure of the lens the system must power itself from a localized magnetic field emitted by an Antenna worn around the eye. AnSem developed an ASIC for Sensimed to mount directly within the contact lens. The ASIC digitizes the MEMS sensor reading and transmits the measurements back to the recorder via the same RF link used to power the device using load modulation techniques.

AnSem was able to incorporate power capture and conditioning, RF signalling, high linearity ADC and digital control functionality on a single die within the meager power budget and at low cost.

Outline of European and US requirements for device approval – intersections and differences

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INTRODUCTION: While the US regulations for the development of medical devices put a focus on safety and effectiveness, the European legislation emphasizes the medical device safety and performance. Both regulatory frameworks differ significantly nevertheless one can find commonalities or intersections. This presentation outlines a strategy to follow for the simultaneous development and approval of a medical device in both jurisdictions.

METHODS: Review and gap analysis of the applicable legislation and standards in both jurisdictions were evaluated. European medical device legislation is stipulated in three Directives, with the Directive 93/42/EC (MDD) being the applicable one for the CE-marking of *non-active implantable devices*, that allows marketing and putting into service in the European Economic Area (EEA) and the European Free Trade Association (EFTA) countries prior to notification with the respective national Competent Authorities. The Directives have to be transposed into national legislation, leaving a leeway for Competent Authorities in the respective European Member States. Both jurisdictions (EU and U.S.) fundamentally leverage the availability of various type C ISO standards, while even US specific standards (e.g. ASTM) may also be applied to European device development, but not necessarily vice versa.

RESULTS: ISO standards may be available as CEN, EN ISO or additionally covering national requirements, such as e.g. DIN EN ISO and may also differ in details from FDA (Food and Drug Administration) recognized standards [1]. The European legislation mandates application of harmonized standards under the respective Directive. Non-active long-term implantable devices are classified as class III according to MDD. US regulations include primarily reference to 21 CFR part 820 (Quality System Regulation) for the manufacture and design control of medical devices. High risk class usually require a Pre Market Approval (PMA) process (21CFR 814) for FDA approval. Interestingly, many non-active long-term implantable devices are classified as class II and are cleared under the 510(k) Premarket Notification process.

DISCUSSION & CONCLUSIONS: There are some elements that are in common between the U.S. and EU systems. Non-clinical studies needed for implantable devices include the ISO 10993 series. cGMP (current Good Manufacturing Practice) requirements are similar but not identical (21 CFR 820 vs. ISO 13485). Clinical requirements - even though ISO 14155 is an FDA accepted standard - also differ substantially, while HFE (Human Factor Engineering) studies should be performed in the jurisdiction of approval. Provided the device developer initiates design controls with the intention concomitantly rather than subsequently seeking approval in both jurisdictions, a dual strategy might facilitate data acceptance in the U.S. and in Europe. Pivotal non-clinical data obtained in compliance with GLP (Good Laboratory Practice) is frequently acceptable; however, device developers must be aware of regional differences in the application of various sections of the ISO 10993 standard. A development plan should evaluate differences in regional expectations and describe a common testing strategy. As an example, FDA currently discusses the "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing - Draft Guidance for Industry and Food and Drug Administration Staff" [2]. This Draft guidance requires additional testing e.g. for sensitivity according to ASTM F2148-07e1 "Standard Practice for Evaluation of Delayed Contact Hypersensitivity Using the Murine Local Lymph Node Assay (LLNA)." A series of applicable ISO 10993 standards will be gap-analyzed and intersections will be defined.

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Pitfalls in the evaluation of local tolerance in medical device studies

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INTRODUCTION: Local and systemic tolerance studies for medical devices are usually routine studies according to ISO guidelines [l-2]. As simple as it sounds as complicate may be the interpretation of the recorded effects.

METHODS: Local effects after implantation are evaluated histologically according a scoring system defined by the ISO guideline [2].

RESULTS: This system is misguiding under certain conditions, especially when different parts of medical device materials are implanted together, or when the devices have sharp edges.

Studies for mucosal irritation bear a further problem when e.g., cyclic changes in the vaginal mucosa are not respected by the pathologist or in case of pre-existing lymphoid follicles in the penile or rectal mucosa are not excluded from the scoring results.

Furthermore, special designed protocols are often under discussion before the study starts. The studies may become even more complex whilst studies are running, i.e. testing strategies may change during the evaluation of interim sacrifices. Different classes of test items (i.e. stents, bone replacement, dental materials or replacement, engineered tissues etc.) need different approaches for histological evaluation.

DISCUSSION & CONCLUSIONS: The existing ISO scoring system needs to be reviewed in order to account for some physiological changes and the multiple classes of devices. The armamentarium is not necessarily restricted to the use of different histological techniques (i.e. staining methods, immunohistochemistry, hard material embedding, image analysis, electron microscopy, etc.) but also needs a change in thinking on a most adequate evaluation. New technologies translated from other sciences may provide solutions for problems and mechanistical understanding. Such technologies may adapted from material sciences (e.g., laser scanning microscopy), computer chip quality control (e.g. digital microscopy) and even from astrophysics (hyperspectral nanoscale analysis).

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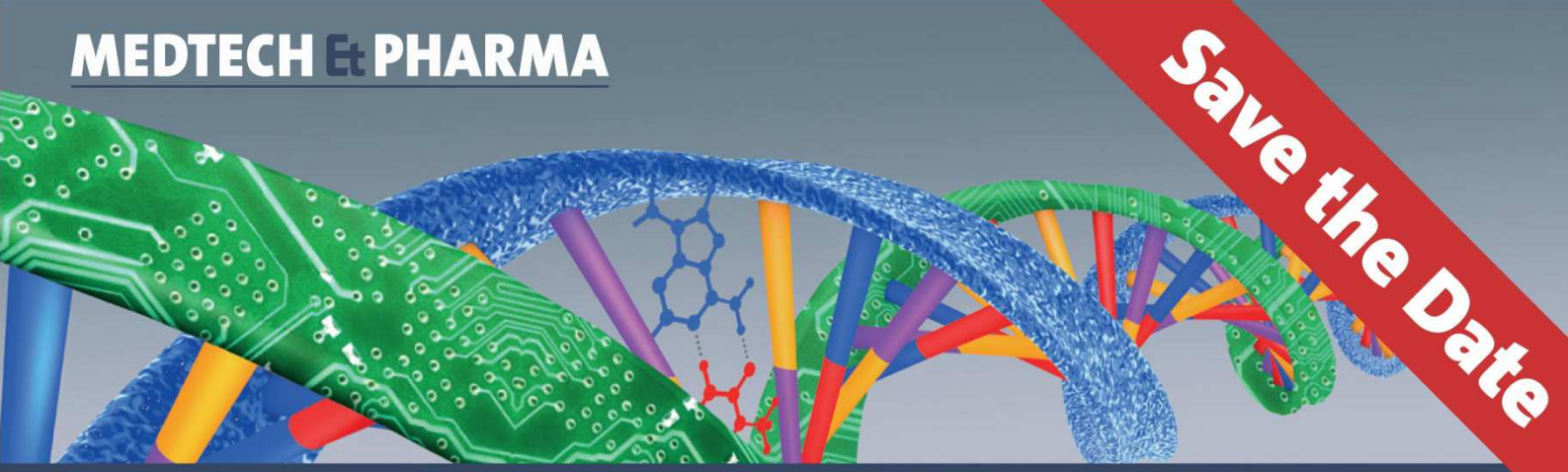

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