Publishable JRP Summary Report for JRP IND56 Q-AIMDS Chemical metrology tools for manufacture of advanced biomaterials in the medical device industry

Background

The global medical device industry is estimated at over €200 billion annually and European manufacturers currently hold 35% of the market. Although implantable medical devices improve quality of life for millions of people, the rates of complications and failures due to incompatibility of the devices with human tissues and device related infections are unacceptably high. A number of promising strategies are being implemented to reduce these complications and failures including thin film coatings, surface grafted biomolecules, nano-particle coatings, and drug eluting materials. Manufacture and certification of devices that employ these advanced biomaterials will require traceable, reliable metrology tools that are able to measure surface layers, surface contaminants, defects and the 3-D distribution of chemical constituents in the near-surface region. The US Food and Drug Administration (FDA) have targeted better quality management of device surface chemistry as an area of growing and concern and new regulations in this area are expected in the near future. We have identified four key needs within the European Medical Device industry:

- Reliable analytical tools capable of detecting thin coatings, grafted organic and biological molecules and contaminants on the surface of medical devices in the manufacturing environment. These analytical techniques must be traceable, reproducible, surface sensitive and chemically specific while at the same time able to operate under ambient conditions, needed in a manufacturing environment, on complex geometries.

- Analytical tools capable of detecting uniformity, thickness and defects in coatings and thin films in the on-line or in-line environment. Methods to detect defects and contaminants at the interface between the coating and the underlying material are of particular interest because they can lead to delamination, cracking and spalling of the coating/films and ultimately lead to device failure.

- Metrology tools that are capable of 3-D chemical state imaging with sub-micrometer spatial resolution for the characterization of coatings, drug eluting materials, and retrieved implants.

- Reproducible, quantitative analytical tools capable of measuring the density and distribution of nano-particles and nano-scale topographic features on device surfaces with varied sizes and geometries.

Need for the project

This project will develop chemical metrology tools for the traceable measurement and characterisation of advanced biomaterials in the medical device industry. Robust metrological tools for the rapid characterization of medical devices surfaces are needed both for patient safety and to ensure the continuing competitiveness of the European Medical Device Industries. The tools developed in JRP IND56 will improve reproducible manufacture and quality management of advanced medical device materials. JRP IND56 will develop the underpinning metrology the industry needs to improve device performance, reduce failure rates and satisfy existing and emerging regulatory requirements.

No existing chemical analytic tools are able to meet all of the industry demands. High vacuum surface analysis methods, such as XPS, Time-of-Flight Secondary-Ion Mass Spectrometry (ToF-SIMS), NEXAFS, and GIXRF, have proven valuable in the research and development of advanced biomaterials but further improvement is necessary to provide the spatial resolution and reproducibility needed to design materials and understand failure mechanisms. Furthermore, these methods are very poorly suited for in-line and on-

EMRP European Metrology Research Programme Programme of EURAMET
The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union

line analysis in the manufacturing environment. They are also generally incapable of handling the complex geometry of complete medical devices. Emerging ambient techniques that employ either optical spectroscopy or mass spectrometry are far better suited to the manufacturing environment but at this time these techniques lack the reproducibility, traceability and surface specificity needed for the characterisation of advanced biomaterials. The focus of JRP IND56 is to bridge the gap between the proven high vacuum techniques and the emerging ambient methods in order to provide a robust metrology tool set for quality management in the medical device industry.

Scientific and technical objectives

The project will have the following scientific and technical objectives organised in three work packages.

WP1 – Advancing the underpinning metrology via the use of high vacuum techniques including X-ray Photo-Electron Spectroscopy (XPS), Near Edge X-ray Adsorption Fine Structures (NEXAFS), X-Ray Fluorescence (XRF) and Grazing Incidence X-ray Fluorescence (GIXRF). Through the use of these proven complementary methods, we will develop well characterised, quantitative, traceable standards for relevant surface treatments and contaminants. Additionally, we will advance the state of the art capabilities in order to increase the practical lateral spatial resolution to under 1 µm and depth resolution to < 10 nm. Efforts will focus on improving buried interface analysis and developing the underpinning metrology for characterisation of nano-particle and nano-textured coatings. Novel advanced data analysis approaches will be developed to increase spatial resolution, improve quantitation and facilitate accurate compound identification.

WP 2 – Development of emerging ambient techniques including FTIR and Raman Spectroscopic Imaging, Scanning Probe Microscopy, IR-SNOM and Ambient Mass Spectrometry. IND56 will develop the underpinning metrology needed to enhance reproducibility, increase sensitivity and improve accurate compound identification for analysis of organic and biomolecular surface layers as well as nano-particle coatings. Novel multivariate and informatics techniques will be developed to facilitate reliable assessment of key performance parameters from the multi-technique data sets.

WP 3 – Adaptation and validation of our analytical tool set for production line medical devices and failure analysis. The techniques developed on model systems in WP1 and WP2 will be adapted and validated using production line medical devices and retrieved implants obtained from our industrial JRP-Partners. This work package will be led by Smith and Nephew, an industrial JRP-Partner.

The first two work packages will be tightly linked in order to support the complementary nature of the different analytical methods. The results will feed into the third work package to provide immediate industrial relevance.

Expected results and potential impact

JRP IND56 will provide guides, standards and protocols for the quantitative analysis of biomaterials relevant to the needs of medical device manufacturers. This initiates a new area of activity for European National Measurement Institutes (NMIs) and addresses the needs of the large and rapidly growing medical device industry. JRP IND56 will provide input to standards, protocols on the analysis and quality management of medical devices, propose VAMAS inter-laboratory studies, and contribute to meetings and relevant new work items within ISO. The JRP-Consortium will also host a stakeholder workshop and a special session on the analysis of medical device surfaces at the European Society for Biomaterials and the Surfaces and Biomaterials meetings. Peer-reviewed publications and conference presentations will also disseminate the results to academic and industrial audiences.

Progress during the first six months of the project:

The project partners have been discussing the specifications of the sample materials needed for the different kind of analysis methods. For this purpose, a table has been created where all the samples were listed with their specifications. Based on this agreed document the sample production has started.

A requirements protocol of the model systems has been delivered. In addition, the project partners are developing a procedure to have controlled amounts of silicone on the agreed substrates. Furthermore, the stability will be tested. Characterised samples will soon be available to other JRP partners. The project has established respective selection criteria for two model flat drug eluting stent systems that are suitable for the required analysis. It has been indicated that both flat model stent samples and real world device samples can be made available soon, subject to commercial clearance paperwork.

One of the project partners has prepared a set of monolayer systems. The project has started to prepare samples of polyacrylate layers deposited onto metal (i.e. steel and titanium) and silicone substrates. The production of these model sample systems is going to be finalised.

Protocols are being developed for making model systems with ethylene-bis-stearamide, sodium docecylsulphate and collogen overlays. Stability and purity of the sample systems is being evaluated and the procedures are being optimized for reproducibility, stability and purity of the films.

Although the project is in its early stages a stake holder committee has been organized for October 2013, which includes eight representatives. There has also been involvement at the Surface Analysis Working Group (SAWG) at the BIPM meeting in Paris (April 2013) and two presentations are planned for the BioInterface Conference 2013 in October 2013.

JRP start date and duration:	April 2013, 36 months
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The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union