Final Publishable JRP Summary for IND56 QAIMDS
Chemical metrology tools to support the manufacture of advanced biomaterials in the medical device industry

Overview

The rate of infections and failure of implantable medical devices is relatively high and this is extremely costly, both financially and in terms of patient wellbeing. The use of novel biomaterials and surface treatments for implants can improve their interation with the body and reliable metrology tools are required to ensure they can be manufactured effectively and certifed for use. This project advanced and provided guidance in the optimal use of analytical methods for *in situ* chemical analysis and imaging of implantable medical devices such as hip liners or catheters. Specifically providing improved analytical tools to characterise thin films and buried interfaces in a reliable and traceable manner and new analytical tools with high spatial resolution and sensitivity. These enable non-analytical-experts to assess medical device advances with assured validity using state-of-art analytical tools.

Need for the project

Although implantable medical devices improve quality of life for millions of people, the rates of complication, infection and device failure are unacceptably high. For example 10 % of patients using arterial stents develop severe complications, 4 % of catheter use is associated with severe infections and 10 % of artificial joints need to be replaced within 10 years. These problems can arise for a number of reasons: incompatibility with the body; introduction of infection from the implant surface; rapid wear and tear of the surfaces; or poor interaction between the implant and the body. Medical device companies and biomaterials scientists have developed a range of novel materials that may reduce these problems by adding: surface treatments to improve compatibility; antibacterial coatings to reduce infection; thin film over-layers and drug releasing coatings to improve their interaction and efficacy in the body. These all enable advanced product development and improved quality by precise control of near-surface chemistry, essential to ensure a reproducible biological response to implanted materials. These advances require analytical tools that are able to measure and validate the near-surface chemistry, three key areas need development to enable this:

1. Precise control of near-surface chemistry is essential to ensure a reproducible biological response to implanted materials. Since established analytical methods are often operated in high vacuum, improvements in the precision, accuracy and traceability of high vacuum nanoscale chemical images of surfaces are essential to support the industry's evolving design and manufacturing goals and ensure adherence to new regulations.
2. High vacuum analytical methods require sample preparation, have a slow turn-around and are very expensive. New tools such as ambient (non-vacuum) techniques are required that can rapidly assess faults in devices directly from the production line with little or no prior sample preparation.
3. Improved image analysis of complex geometry and mixed materials. Most medical devices consist of a wide range of geometries with grooves, loops, pins and knitted, woven or felted components that can be challenging to analyse. Various analytical methods can be used to evaluate cleanliness of medical devices, but many of the more convenient methods have limitations in terms of sensitivity or surface-specificity or are indirect methods, relying on a bulk extraction step. These methods lose knowledge of the spatial distribution, that are important to identifying how or where in the manufacturing and cleaning history that the contamination occurred and also how different surface finishes may be more or less susceptible to contamination. In addition, the analysis of explanted devices (i.e. devices removed from the body) is often required to understand the reasons for failure.

EMRP
European Metrology Research Programme
Programme of EURAMET

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Scientific and technical objectives

The project's over-arching objective was develop the analytical tools required to measure and validate the near-surface chemistry of implantable medical devices and provide guidance on their selection and use to the medical device sector:

1. Underpinning metrology via the use of high vacuum techniques: Established high vacuum techniques, have proven indispensable in the development of advanced biomaterials but further improvements in spatial resolution, chemical speciation, reproducibility and traceable quantification (for selected methods) are needed to facilitate total quality management of devices, meet emerging regulatory requirements and more accurately control the biological response to implants. An objective of this project was to produce well characterised model systems, which represent key issues expressed by industry stakeholders. The model systems chosen were 3 different surface contaminants on both metal (representative of bone implants, for example) and on polymer substrates (representative of catheters and stents, for example). In addition model systems consisting of a protein coating and polymer thin films were also chosen (representative of the surface treatments device manufaturers employ to improve product performance). These model systems could be used to improve reproducibility and quantifiability of both the established techniques and emerging analytical methods on relevant materials.

2. Develop the use of ambient methods**:** Recent advances in ambient analytical methods offer great promise for meeting the medical device industry needs for on-line surface quality assessment during manufacture. In addition to providing detailed chemical information, these non-destructive chemical analysis tools are well suited to on-line analysis. For medical device surfaces these techniques lack the surface specificity desired, therefore new developments and advanced data analysis methods will be required to facilitate reproducible, accurate, quantitative analysis. An objective of this project was to develop emerging ambient techniques for *in situ* chemical analysis and imaging of medical devices.

3. Adaptation and validation of our analytical tool set for production line medical devices and explant analysis: the ambient methods need to be assessed against the existing accurate methodologies developed for high vacuum surface analytical methods to enable robust selections of appropriate techniques. The aim of this objective was to apply, adapt and validate the tools developed on model systems to real production line medical devices.

These objectives are of high relevance and value to the medical devices industry and will help both new product research and development and licensing, and existing product manufacture and quality control.

Results

1. Advance the underpinning metrology via the use of high vacuum techniques

In order to advance the underpinning metrology via the use of high vacuum techniques, the project developed well characterised quantitative, traceable model systems to enable quantification and quality assurance of medical device surface chemistry. These model systems were used to improve reproducibility and quantitative performance of both the established techniques and emerging analytical methods, and advanced data analysis methods were used to increase precision and accuracy and improve lateral and depth resolution, key results are outlined below.

The project improved analytical tools to characterise thin films and buried interfaces in a reliable and traceable manner. Thin film coatings are being used in medical devices to improve lubrication, prevent corrosion, reduce fouling, prevent bacterial infection and promote healthy tissue integration. Defects in the films, such as pinholes or contaminants at the buried interface between coating and substrate, can result in corrosion of the substrate or delamination, cracking and spalling of the coating. The ability to detect these defects will enable an important advance in the quality management of such devices. We developed methodologies to characterise thin films and buried interfaces (the surface between films) in a reliable and traceable manner. Using these methodologies, a multi-technique approach and advanced data analysis enabled us to elucidate the picture at the buried interface.

Using Ar (Argon) cluster 3D-SIMS, a form of high precision spectrometry, we were able to look at the sputter depth profiling of polymer thin films. An analytical protocol was developed to improve depth resolution on samples with non-uniform thickness. Using X-ray based spectroscopies, elemental depth profiling and interfacial compositional analysis of polymer thin films with defects was also achieved. This analysis enabled,

for example, a catheter model system to be studied to demonstrate how the enhanced adhesion between the polymer coating and the O_2 plasma treated catheter are facilitated by hydrogen bonding and dipole interactions.

The 2-D and 3-D distribution of chemical moieties (parts of molecules) in the near-surface regions is critical to the performance of many types of medical devices such as drug delivery devices, tissue engineering scaffolds and bio-resorbable bone implants. XPS (X-ray photo electron spectroscopy) and SIMS methodologies were employed for characterisation of flat drug-releasing stent model systems. This enabled the characterisation of drug distributions in bioabsorbable matrices with better reliability. Through the use of post-acquisition data analysis and data fusion from multiple techniques, the project was able to achieve an enhancement in the veracity and reduction in the effect of noise in results. Through the development and validation of the use of mono capillary optics, the project also achieved high resolution 2D X-ray imaging.

2. Develop the use of ambient methods

The surface sensitivity of ambient analytical methods is poorly understood and detection limits are not known for most systems. Model systems were used to advance the techniques, to develop the metrology, to ensure measurements are valid and accurate and to qualify the technology for use in the sensitive and highly regulated medical device industries.

The project successfully illustrated the power of a combined ambient multimodal surface analysis to reveal homogeneity and physicochemical properties of surface contaminants. The project also delivered well-qualified model reference materials for use in the construction of calibration curves for quantitative analysis. We were able to qualitatively image across complex surfaces to identify contaminants and determine causes of product failure.

We developed post analysis procedures and methods for the use of multivariate and informatics tools for the interpretation of the complex data sets generated by the analytical methods. This improved the accuracy of results and sped up interpretation and ensures reproducibility of analysis through best practice and automated interpretation of complex and multimodal data sets.

Through the use of model reference materials the project was able to increase our understanding of different analytical techniques, supply users with training and test samples and understand and improve tool limitations, reproducibility, repeatability and sensitivity.

New analytical tools developed in this project include an ambient imaging mass spectrometer with high spatial resolution and sensitivity and a Raman based methodology to confirm identity of complex biolabels.

3. Adaptation and validation of our analytical tool set for production line medical devices and explant analysis

The project was able to successfully integrate and test the metrological tools developed in the project for analysis of production line medical devices and establish a suite of tools for failure analysis of production line and explanted medical devices. We carried out comparative work using surface mass spectrometry in vacuum and ambient conditions for the analysis of production line medical devices, such as wound dressings, hip liners, contact lenses, stents and catheters. Recommendations for industrial use of these techniques for surface mass spectrometry of medical devices to detect surface defects is presently being written up for a peer reviewed paper. Methodologies for the use of ambient analytical tools for the detection of common contaminants direct from medical devices have been developed. Comparisons and recommendations of the appropriate use and application of the five different ambient and high vacuum techniques are available. These enable rapid assessment of device failure due to contaminations in the fabrication process, allowing product lines to rapidly be repaired and restarted. Protocols for the use of vacuum techniques for the detailed 3D analysis of drug releasing stents have been tested. Guidance on optimal analytical parameters and technique selection will enable more robust experiments and interpretation and hence aid in the development of new products.

The power of a range of different analytical techniques for the analysis and subsequent development of implanted medical devices has been shown through a multimodal experiment on a device, post-implantation, to assess the integration of the implant into living bone regions.

Methods for multiple analyses of single samples and subsequent data fusion of different techniques allow all available data to be easily accessed and more rapidly interpreted by non-experts.

In summary, the project has developed the surface analysis of real medical device products and new practical approaches to optimising and utilising existing and developing methods. Importantly, this includes provision of greater confidence in the use of recently available and more practicable ambient analytical methods in an industrially relevant setting, with validated improvements to reproducibility achieved by the project partners.

Actual and potential impact

The project aimed to advance methodologies and provide guidance in the optimal use of chemical analytical methods for *in situ* chemical analysis and imaging of implantable medical devices. As such the impact from this project needed to address a wide range of communities, from biological physicists, chemical and polymer physicists, researchers and engineers that work in the field of thin films, materials and surface physics, analytical scientists and biomedical device producers. In order to ensure this, a wide range of dissemination activities, addressing different audiences were carried out, with 11 submitted papers, 8 papers in draft, 49 presentations, 17 training events and 5 funded follow up collaborations. The 49 presentations were a mixture of oral and poster, to enable the widest audience and interactivity, and took place in over 15 countries given to an estimated audience of > 5000 participants. The 17 training events involved over 200 people including students, industrial end users, analytical specialists and research scientists.

A suite of new tools are now available at European NMIs to support medical device characterisation as well as tools and techniques suitable for research and idustrial use. These will enable improved use of chemical metrology tools for the support of biomaterial manufacture: improving reliability of analysis; application to medical devices; development of novel analytical tools; solving industrial problems. The project's outputs have been disseminated widely to: the metrology community; high-level users of precision instrumentation in research environments; regulators and medical device manufacturers.

Early Impacts:

The improvement in analytical techniques developed in the project and the guidance on appropriate selection of technique has already lead to a number of examples of improved industry capability:

- Analysis developed in this project by NPL and University of Meunster has enabled a clearer understanding of the adhesion and failure mechanisms of coated catheters which resist bacterial attachment. This has enabled the University of Nottingham, another project participant to develop a coating of novel urinary catheters with Camstent Ltd who are working towards medical device approval.
- A global medical device company recently made use of ambient methods when determining the source of contamination along a production line. This resulted in a rapid turnaround which enabled production to be resumed quickly with minimal loss of earnings.
- A global prosthesis manufacturer is working with NPL in a feasibility study to improve performance by plasma immersion ion implantation to reduce sliding frictional losses internal to the device and providing more efficient actuation by surface treatment. The study will address processing challenges relating to surface characterisation, process design & scale-up and demonstrates techniques developed as a part of this project being used in a product development lifecycle that, if successful will lead improved patient wellbeing.
- This project enabled the use of different techniques for analysis of implants removed from the body to assess bone growth adjacent to the implant and corrosion of the implant into the surrounding tissue. The advantages gained from using a multi-technique approach is essential to obtain the relevant information, and a number of medical device companies have shown interest on these approaches. Ultimately, this understanding has the potential to aid both product development and the meeting of regulations.

These early examples of improved industry capability illustrate that the surface characterisation techniques and guidance developed as part of this project have the ability to contribute to the quality assurance, product development and regulatory requirements of the medical device industry. This will ultimately have a direct impact on the health and wellbeing of patients requiring medical implants (an estimated 100 million people in the EU have a permanent implanted medical device) and will contribute to the continued growth of the EU medical device industry.

List of publications

A. Hornemann, D. Eichert, S. Flemig, G. Ulma and B. Beckhoff, Qualifying label components for effective biosensing by advanced high-throughput SEIRA methodology, *Phys. Chem. Chem. Phys.*, **2015**, 17, pp 9471-9479. doi: 10.1039/c4cp05944a

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JRP start date and duration:	01 April 2013, 36 months
JRP-Coordinator: Fiona Moriarty, NPL, Tel: +44 20 8943 6782 E-mail: Fiona.Moriarty@npl.co.uk JRP website address: http://projects.npl.co.uk/IND56-Q-AIMDS	
JRP-Partners: JRP-Partner 1: NPL, UK JRP-Partner 2: BAM, Germany JRP-Partner 3: INRIM, Italy	JRP-Partner 4: PTB, Germany JRP-Partner 5: DFM, Denmark JRP-Partner 6: Medtronic, Netherlands JRP-Partner 7: SMN, UK
REG1-Researcher: (associated Home Organisation):	Carla Vogt LUH, Germany
REG2-Researcher: (associated Home Organisation):	Morgan Alexander UNOTT, UK
REG3-Researcher: (associated Home Organisation):	Heinrich Arlinghaus WWU, Germany
REG4-Researcher: (associated Home Organisation):	Antje Hermelink RKI, Germany

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