IRISH MEDICINES BOARD

news LETTER

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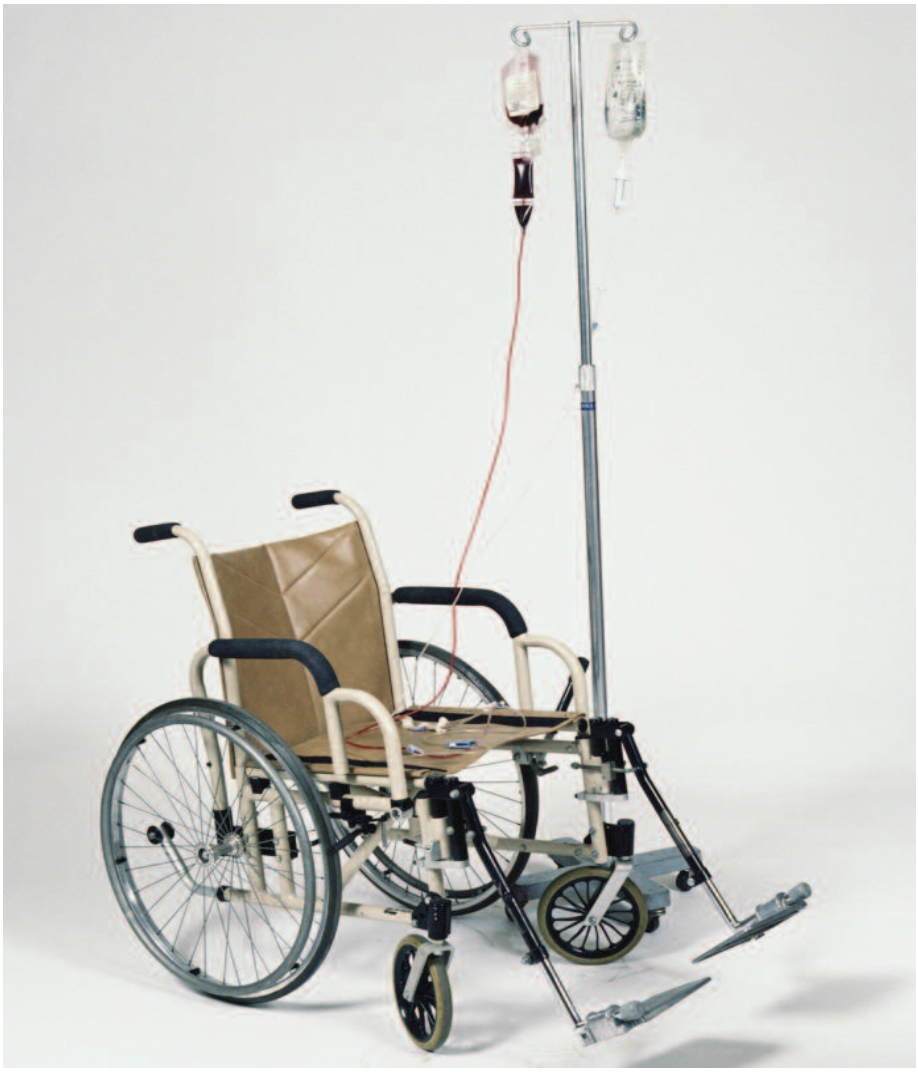
Letter from the Editor

Welcome to the last edition of the medical devices newsletter for 2007.

This has been an eventful year which has seen the publication of the amendments to the medical devices legislation and the revised MEDDEV guidance document on the vigilance system for medical devices. The interest in both these documents was evident at the recently held IMB information day where 220 delegates attended. This year has also seen the restructuring of the Medical Devices Department of the IMB. An update on the new structure is provided with a list of key contact points.

In this edition of the newsletter, we are also providing an article in relation to finite element analysis and medical devices. We are also providing an article on the EU restrictions on mercury containing medical devices in response to recent queries.

Finally, we would like to wish all our readers a very happy and peaceful Christmas.



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Regulatory Update

The guideline on a Medical Devices Vigilance System MEDDEV 2.12-1 rev 5, April 2007 was recently published and will enter into force on 1st January 2008 following a six month transitional period for implementation. The guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (Competent Authorities, Commission services, trade federations, other interested parties) during which intermediate drafts were circulated and comments incorporated into the document. There are many notable changes including a new layout for the guidance, clarification on the role of the manufacturer, Competent Authority and user. The concept of field safety corrective action was also introduced.

A request from the United Kingdom to the EU Commission to classify vCJD blood screening assays to Annex II list A under article 14 of the *In-vitro* Diagnostic Medical Devices (IVD) Directive 98/79/EC is currently under consideration. The EU Commission organised a workshop on the 26th October 2007 to consult with all stakeholders. The workshop was well attended with broad representation from a number of key organisations including Competent Authorities, government representatives, NIBSC, EMEA, manufacturers and trade federations. The main challenges highlighted at the workshop included the level of sensi-

tivity and specificity required for these tests, the lack of a confirmatory test for vCJD and the need for suitable reference materials and standards required for the validation of these assays in the absence of human vCJD blood samples. The need for the classification of vCJD assays as Annex II, List A IVDs was broadly supported by the workshop attendees. However it was agreed that this classification would require the drafting of a minimum technical specification for all vCJD assays which would need to be flexible given the evolving nature of these new assays and the availability of reference materials and samples for validation going forward. In addition, the need to develop guidance for manufacturers and Notified Bodies on the assessment of these IVDs was discussed. The Commission advised that the discussions and actions from this consultation workshop would be presented to the IVD Technical Working Group for consideration at its meeting in November and a proposal would then be presented to the Medical Devices Expert Group (MDEG) for consideration.

A meeting took place of the EUDAMED working group that handle the development of the European database of medical devices. The key topics covered were the use of general medical device nomenclature (GMDN) codes, the level of access of manufacturers to the database and the recently completed tender process GMDN codes into the different European languages.

The Clinical Evaluation Task Force (CETF) is continuing to work on the development of guidelines for drug eluting stents. They also provided collated comments from the CETF members to the EMEA on their draft guidance on drug consultations for coronary stents. The CETF is keen that a collaborative approach is used for the development of a single guideline paper for these devices. The CETF is also working on the development of the clinical section of the EUDAMED database.

At a meeting of the MDEG Classification and Borderline Working Group the process for review of classification requests was agreed. A manual of outcomes will be used to record decisions of the working group. A number of decisions were reached at the meeting.

Vigilance Guidance Note and Forms

The following guidance notes and forms have been revised to incorporate the changes outlined in the Guideline on a Medical Devices Vigilance System, MEDDEV 2.12-1 rev 5:

Vigilance Guidance Notes:

- Guidance Note 7: The Vigilance System for Medical Devices
- Guidance Note 8: Field Safety Corrective Actions for Medical Devices and *In-vitro* Diagnostic Medical Devices
- Guidance Note 13: Incident Reporting for GMDs and AIMDs
- Guidance Note 18: Guide to Adverse Incident Reporting for IVDs

Vigilance Forms:

- Manufacturer's Incident Report Form
- Field Safety Corrective Action Report Form
- Medical Device Incident User Report Form

This guideline will enter into force on the 1st January 2008. The transitional period allowing a gradual implementation of the guidelines will therefore end on the 31st December 2007. This guideline can be downloaded from the European Commission website **www.ec.europa.eu**.

The above guidance notes and forms are available on the IMB website **www.imb.ie** under the publications section.

IMB Medical Devices Information Day – Revisions to the Medical Devices Directive 93/42/EEC and Vigilance MEDDEV

The IMB held an information day on the 'Revisions to the Medical Devices Directive 93/42/EEC and Vigilance MEDDEV', at the Crowne Plaza Hotel, Dublin on Friday 16th November 2007.

This event was well attended by manufacturers and distributors of medical devices, healthcare professionals and various other interested stakeholders. The overall attendance for the day reached approximately 220 people.

Feedback from attendees indicated that aims and objectives of the day were successfully attained, where the presentations and discussions provided participants with a good understanding of the revisions to the Medical Devices Directive 93/42/EEC and Vigilance MEDDEV.

The mix of presentations from the Irish Medicines Board (IMB), the Industrial Development Agency, the European Commission and BfArM provided participants with some key practical information and advice.

Presentations were made on the following topics:

- Welcome Introduction – *presented by Mr. Richard Hendron*
- Irish Position on Current Medical Device Issues – *presented by Ms. Ann O'Connor*
- Overview of Changes to the Medical Devices Legislation – *presented by Dr. Sharon Frank*
- Impact of Changes to the Medical Device Directive for Stakeholders – *presented by Ms. Mairead Finucane*
- Clinical Investigations and Changes to Annex X (Medical Devices Directive) – *presented Dr. Niall MacAleenan*
- Introduction / The Impact of Changes on the Manufacturer (Vigilance MEDDEV) – *presented Dr. Ekkehard Stösslein*
- Impact of the Changes on Other Key Stakeholders (Vigilance MEDDEV) – *presented Ms. Andrea Hanson*

The IMB would like to thank the speakers, Mr. Richard Hendron (Industrial Development Agency), Dr. Sharon Frank (European Commission), Dr. Ekkehard Stösslein (BfArM) and the various IMB speakers for giving up their time to prepare and present such informative presentations. We would also like to thank all those that attended this event to help make the day such a success.

If anyone would like to suggest ideas for future information days, please do so by emailing **medical devices@imb.ie**.

From left to right: Dr. Ekkehard Stösslein (BfArM), Prof. Tim McGloughlin (University of Limerick) and Ms. Andrea Hanson (IMB)

From left to right: Mr. Wilf Higgins (HSE), Ms. Ann O'Connor (IMB), Dr. Sharon Frank (European Commission) and Mr. Richard Hendron (IDA)

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Extension of Date of Withdrawal for EN ISO 14971: 2007 Application of Risk Management to Medical Devices

There is a short timescale prescribed in the new standard of only six months for transition from the EN ISO 14971: 2001 to the EN ISO 14971: 2007 version. Feedback from Notified Bodies and manufacturers considered this six month timeframe as being extremely challenging, if not impossible, for medical device manufacturers to make the necessary changes in order to demonstrate compliance with the revised version of the standard.

The Management Centre of CEN the European Committee for Standardization following review of the feedback has agreed an extension of the date of withdrawal for EN ISO 14971:2007 - Application of risk management to medical devices from 9th September 2007 to 9th March 2010.

Update on the Medical Devices Department

In 2001, the Irish Medicines Board (IMB) became the Competent Authority for *in-vitro* diagnostic medical devices (IVDs), general medical devices and active implantable medical devices. Prior to this date, activities relating to the regulation of medical devices were carried out by the Department of Health and Children. Over the last number of years, the complexity of medical devices and device technologies has increased, new legislation and guidance has been published, a significant increase in vigilance and compliance cases has been noted and in addition there are increasing demands from stakeholders.

Resulting from this the IMB undertook a development study to review the current organisational arrangements within the Medical Devices Department in order to identify any changes that may be required to meet these challenges. The development study recommended a new organisational structure which more closely reflected the needs of the Medical Devices Department in meeting the challenges that they are currently facing. A key element of the changes sees the introduction of a management team with responsibility for three core process areas. The new organisational model addresses the need to develop an effective knowledge network to support the core skills within the department; provides ownership and responsibility for key activities; and enables the Director to adopt a more strategic management role. The key features of the new organisational model which is shown below are as follows:

- Increased operational management focus
- Supports increasing workload
- Improved alignment of technical skills and resources
- Integrated focus on market compliance activities
- Facilitates the incorporation of new products and technologies
- Supports a more comprehensive knowledge management model

This new structure is outlined in table 1

The structure has been divided into pre-market and post market activities with a support function being provided from the audit section. The core activities of the pre-market evaluation section relate to the evaluation of medical devices in advance of being placed on the market. In particular it entails the:

- Classification of medical devices
- Management of the devices register for low risk medical devices
- Assessment of clinical investigation submissions
- Management of the Notified Body

Post-market activities are the remit of the post-market evaluation section. This comprises all of the activities associated with:

- Reviewing compliance and vigilance issues arising in the market
- Carrying out proactive and reactive technical file reviews
- Determining any actions to be taken by manufacturers and / or users
- Determining if there is a requirement for any audits and coordinating these with the audit group and monitoring the implementation of any required actions.

Due to the wide scope of this area, it has been further divided into product groups, class I/IIa, class IIb/III and IVD's, with overall responsibility for the market compliance activities associated with their respective products. Certificates of free sale are also issued by the post-market evaluation section.

The core activities of the audit section relates to the planning, implementation and reporting of medical device audits, as well as following up on any actions to be taken and debriefing the department on any relevant issues that arise. Market surveillance is also conducted by the auditing section. The key objective of this process is to analyse market data to provide an overview of

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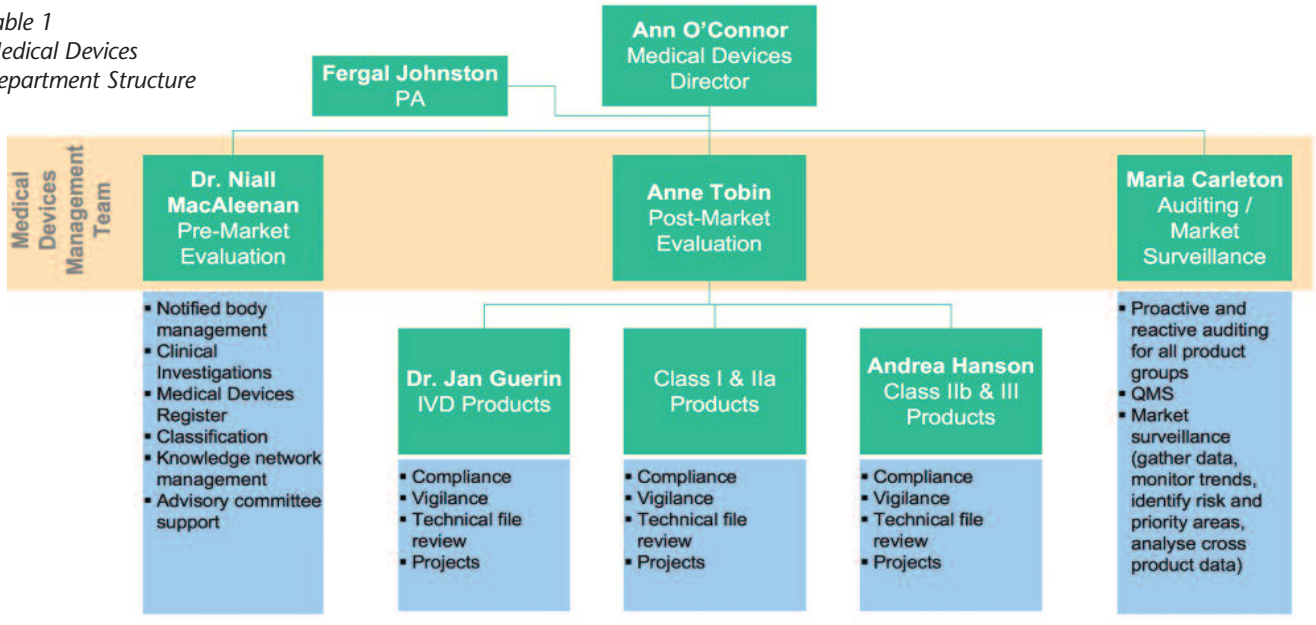
Table 1
Medical Devices Department Structure



the medical device market place, highlighting issues, trends and identifying priority areas for action.

The medical devices management team was appointed in May 2007. Over the past few months, Ann O'Connor as Director and the management team has been instrumental in the transition to the new organisational structure which went 'live' on the 8th October 2007. Existing staff have been positioned or promoted with in the new structure in their areas of expertise. Recruitment of new staff for the structure has been ongoing for the past few months and new appointments have been made. Further recruitment is underway to fill the position of Class I/IIa Product Manager and Medical Officer for the post-market evaluation section.

The new management team and their sections will be responsible for developing and implementing the detailed programme of work required.

The key points of contacts are:
Ann O'Connor – Medical Devices Director
Fergal Johnston – PA to the Director

Management Team
Maria Carleton - Audit Manager
Dr. Niall MacAleenan - Pre-Market Evaluation Manager
Anne Tobin - Post-Market Evaluation Manager

Other key contact points:
Andrea Hanson – Product Manager (Class IIb & III)
Dr. Jan Guerin - Product Manager (IVDs)
Mairead Finucane – Medical Devices Auditor

Please continue to forward all medical device queries to **medicaldevices@imb.ie**

Medical Devices in the Community Setting

A safety notice entitled 'Medical Devices Recommended by Healthcare Institutions for Use in a Community Setting' was published recently by the IMB Medical Devices Department. This document highlights some of the important issues associated with the use of medical devices in a community setting especially relating to device training, management and maintenance issues. The document makes specific recommendations for healthcare professionals making devices available for use or recommending devices for use in a community setting.

The use of medical devices in a community setting is becoming increasingly common and the devices used increasingly complex e.g. blood glucose meters, wheelchairs, infusion pumps, automated external defibrillators, ventilatory support devices, etc. While this phenomenon allows for a greater array of medical conditions to be treated in a community setting it does raise important safety considerations.

Key recommendations include:

- Any device to be used in the community must firstly be suitable for use in that setting.
- Users and carers must fully understand how to use the device to ensure that it operates effectively and safely
- Users and carers should receive any appropriate training in device use
- Systems should be maintained to ensure that devices provided for community use can be traced effectively if a safety issue or device recall arises
- Devices used in the community should be appropriately serviced and maintained to allow optimal and safe device performance on an ongoing basis
- Servicing and maintenance should be undertaken according to the manufacturer's recommended schedule by appropriately qualified personnel
- Any consumable components / ancillary equipment necessary for use of the device must be readily available
- Records of training, servicing and maintenance should be kept updated
- To enhance traceability, device users should be encouraged to complete all device warranty cards / registration forms and return these to the manufacturer
- Devices should be stored safely and used in appropriate environmental conditions e.g. temperature, humidity, etc
- Devices used by multiple consecutive patients should be appropriately cleaned, decontaminated, sterilised and serviced prior to each distribution
- When a device has reached the end of its service live it should be disposed of safely and responsibly
- Members of the public considering medical device purchase on the advice of a healthcare professional should purchase only CE marked medical devices from established suppliers
- Adverse events resulting from device use should be reported both to the device manufacturer and to the IMB Medical Devices Department at **vigilance@imb.ie**

This document (reference SN2007(06)) is available on the IMB website www.imb.ie under the publications section. The IMB intend to publish a series of documents in the near future to provide specific advice to members of the public considering purchase of a medical device for their personal use.

Monthly Circulation of Medical Device Safety Notices

To date, the IMB have been circulating medical device safety notices on a monthly basis by post and email to the Irish health services. It is proposed from 1st January 2008 that all safety notices will be circulated by email only. Each safety notice will be sent by email as soon as the impact on the Irish market has been established. At the end of each month, we will circulate an email containing a listing of all the safety notices issued in the previous month.

If you would like to continue receiving copies of the safety notices by email, please send your contact details along with your email address to medicaldevices@imb.ie.

Finite Element Analysis (FEA) and Medical Devices

Aside from the traditional methods of pre-clinical evaluation of medical devices, such as laboratory bench testing and animal experiments, the use of Finite Element Analysis (FEA) is becoming more common and complex.

What is finite element analysis and how can it be used as a method of pre-clinical evaluation?

FEA at a Glance

The first step in performing a finite element analysis is the generation of a finite element (FE) model during a stage known as pre-processing. A finite element model is a numerical mathematical model which describes the physical behavior of a structure. To create a finite element model the structure under investigation is divided into multiple discrete regions called elements. Each element is bordered by a set of nodes to which material and structural properties are assigned by means of a stiffness matrix [Ke]. It is this stiffness matrix which defines nodal displacements {δ} under an applied force {F}; {F} = [Ke]{δ}. To recreate the entire structure adjacent elements are joined at the nodes. In doing so, a global stiffness matrix [K] for the entire structure can be formulated and the next stage of the analysis of the model, known as computational analysis, can begin. Using the applied forces and global stiffness matrix it is possible to calculate all nodal displacements for the model. Knowing these displacements, the stress and strain for each node in the model can be determined. The last stage of the analysis is known as post-processing during which the results can be analysed both numerically and visually.

Application of FEA to Medical Device Design

In comparison to both animal and bench testing, finite element analysis is relatively inexpensive and quick to perform. Hence, this method is an attractive option for medical device manufacturers during the design stage of a device. It allows the manufacturer to perform numerous design parametric studies, such as variations in device geometry and material properties, to help determine which design will provide optimal functionality. Furthermore, advances in computational power and an increased sophistication in predictive algorithms now allows for better modeling of material behavior, including biological tissues such as bone.

Two of the most widely studied medical devices, in both industry and in university research labs, are the femoral component in the total hip arthroplasty (THA) and the cardiovascular stent.

Case Study 1: Total Hip Arthroplasty:

Historically speaking the first application of finite element analysis in the field of orthopaedics was over 30 years ago. Since then, the femoral hip joint prosthesis has become one of the most commonly studied medical devices with an ever increasing complexity of the finite element models used. Early models of the hip prosthesis comprised of simplified two-dimensional axi-asymmetric representations. Today, anatomically correct three-dimensional models comprising of many thousands of elements are commonplace, see Figure 1. These models allow for the prediction of the stresses and strains which are likely to occur in each component of the THA during use. And it is these stresses and strains which ultimately determine the long-term success of the prosthesis.

Hip replacements can be classified as either 'cemented' which use PMMA to interlock the prosthesis to the bone, or 'cementless' which rely on bone in-growth into the prosthesis surface. Failures of the both cemented and cementless do occur, and is generally observed as aseptic loosening and thigh pain for the patient. Loosening of cemented prostheses commonly occurs by fatigue

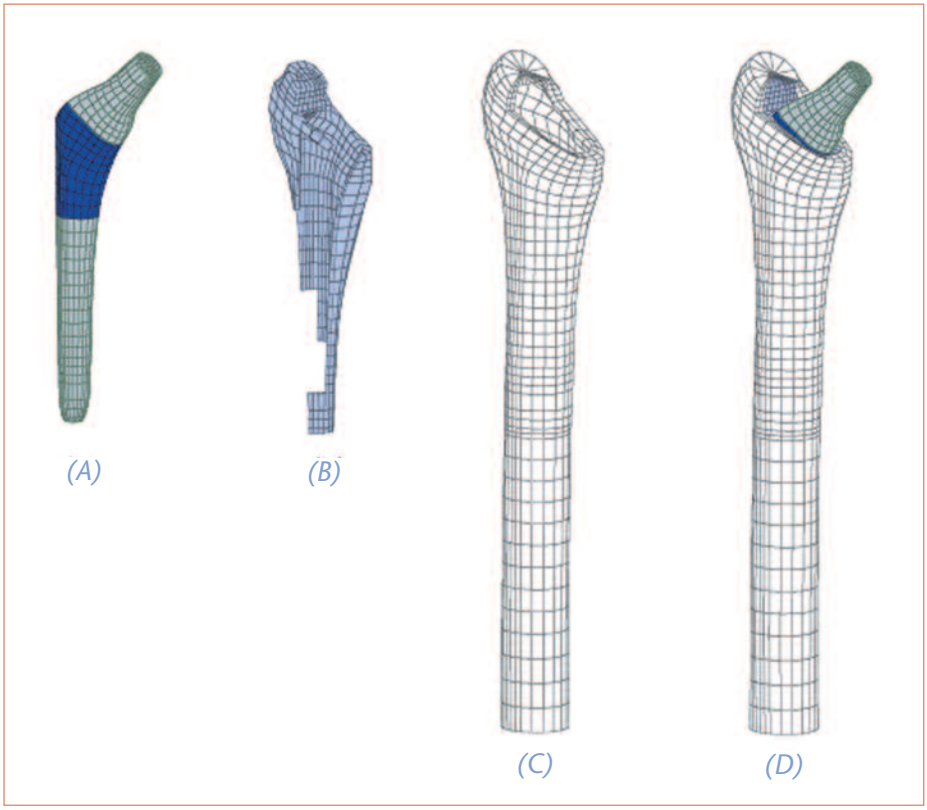


Figure 1: Finite Element Model of a cementless hip arthroplasty showing (a) hip prosthesis (b) cancellous bone (c) cortical bone and (d) completed model.

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failure of the bone cement, which may be caused by: crack growth from pores within the cement or stress concentrations at the implant / cement interface, or bone resorption causing an increase in stress in the cement. For cementless prostheses, excessive relative micro-motions and interfacial stresses between the bone and implant inhibits bone ingrowth leading to failed ingrowth, bone resorption, soft tissue interposition and eventual loosening.

It is widely believed that these changes in bone around a prosthesis are related to the changes in bone stress/strain patterns that inevitably result from the introduction of the prosthesis. It is the aim of finite element models incorporating sophisticated mechanobiological algorithms to predict these changes so as to gain a better understanding of the intimate relationship between prosthesis design factors, such as material choice and geometry, and the host bone response. An ultimate objective would be to use such algorithms for pre-clinical testing.

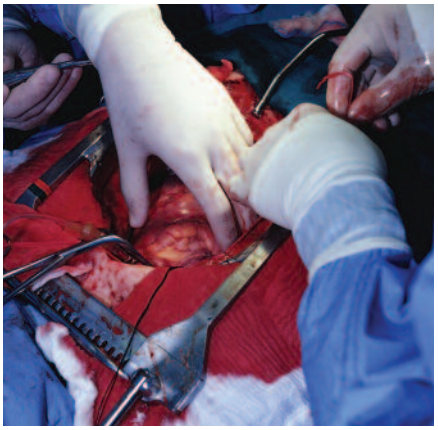
Case Study 2: Cardiovascular Stents

A cardiovascular stent is a tubular wire mesh used to expand and restore blood flow to arteries which have been blocked due to atherosclerosis. There are numerous stent designs ranging from balloon-expanding to self-expanding nitinol stents, and drug eluting stents (DES). One of the main post-intervention complications of this procedure is in-stent restenosis, and clinically it has been shown that in-stent restenosis rates vary depending on the design of the stent. One hypothesis on the cause of in-stent restenosis is that vascular damage, caused by the implantation of a stent, may influence the extent of restenosis. After the stent has been expanded it is the localised contact stresses at the stent strut / vessel wall interface which are most likely to stimulate in-stent restenosis. This is a further example of where finite element analysis may be used, pre-clinically, to optimise stent design to reduce stent / vessel interface stresses, thus reducing vascular damage and potential in-stent restenosis.

Future Applications of FEA

Whilst advances in pre-clinical evaluation methods of medical devices has vastly improved both their performance and survival rates a key step which may ultimately determine their clinical success or failure is the pre-operative planning. One technique which could possibly improve this aspect may be the inclusion of predictive computer simulations in the pre-operative planning stage. Current THA pre-operative planning techniques involve the use of radiographic templates of the implant components which are placed over patient x-rays. These templates come in a variety of sizes, and calling on the implanting surgeon's skills and experience the optimum combination of component sizes are chosen. However, this process may only provide an idealised situation, i.e. a perfect fit and position for that patient's anatomy, and having both a perfect fit and position does not always occur in practice.

Currently work is being carried out by Professor Patrick Prendergast and Dr. Alex Lennon of the Trinity Centre for Bioengineering to develop a finite element analysis tool, incorporating predictive algorithms, for patient specific pre-operative planning of total hip arthroplasties which not only caters for the surgeons intuitive choice of the appropriate size and position of the prosthesis, but also provides the surgeon with feed back on the expected long term performance of their chosen implant components. Based on this feedback the surgeon may choose to resize or reposition the prosthesis such that a balance is struck between geometrical and biomechanical optimisation to enhance the clinical outcome. This work was considered a breakthrough when published in the prestigious Journal of Orthopaedic Research.



Recently the Trinity Centre for Bioengineering hosted the Summer Workshop of the European Society of Biomechanics. Science Foundation Ireland was the primary sponsor. The focus of this workshop was the role of Finite Element Modelling in Biomechanics and Mechanobiology. The workshop began with tutorial lectures showing the fundamentals as well as the latest advances in the method. There were two themes regarding advanced methods: patient-specific finite element modeling, and high-resolution finite element modeling, and three application areas: 'Orthopaedic Devices', 'Cardiovascular Devices', and 'Tissue Engineered Implants and Cell Engineering'. A pdf of the proceedings can be downloaded free of charge or a hardcopy can be had from Ms. Sheena Brown at brownsh@tcd.ie. What became clear is the emerging technology of using medical images from patients to create models to simulate how the medical device function for the patient – and this is possible for orthopaedic and cardiovascular implants. Furthermore FEA – which is traditionally a mechanical engineering tool – is becoming integrated with biological information to create simulations of tissue reactions to the presence of medical devices. In fact, one of the ambitions is to create a 'Virtual Physiological Human (VPH)' which is a validated computational model in which medical treatments, including surgical interventions, can be trialed. The VPH is one of the targeted areas in the new Framework 7 Programme of the European Commission. Therefore we can envisage computer simulation as becoming more integrated into the preclinical testing environment for medical devices in the future.

The Irish Medicines Board would like to thank Professor Patrick Prendergast of the Trinity Centre for Bioengineering for contributing his review of the Summer Workshop of the European Society of Biomechanics to this article.

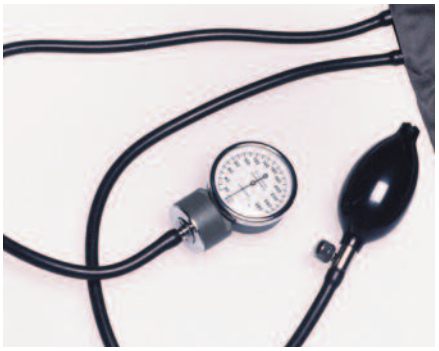
http://www.tcd.ie/bioengineering/documents/ProceedingsoftheEuropeanSocietyofBiomechanicsWorkshop_000.pdf

EU Restrictions on Mercury Containing Measuring Devices

Directive 2007/51/EC, published in the European Union Official Journal on 3rd October 2007, provides details on the European ban on the marketing of certain mercury containing measuring devices intended for sale to the general public. This Directive amends Directive 76/769/EEC, relating to restrictions on the marketing and use of certain dangerous substances and preparations

The Directive restricts placing on the market of **new** measuring devices containing mercury intended for sale to the general public, in particular all fever thermometers. Medical devices containing mercury such as medical thermometers, manometers and sphygmanometers intended for sale to the general public, are among those non-electrical measuring devices affected by the ban.

The introduction of the ban forms part of a wider European strategy in relation to mercury. This strategy aims to reduce the quantity and circulation of toxic mercury within the EU. Mercury is highly toxic to humans, ecosystems and wildlife. 33 tonnes of mercury is used for measuring and control devices every year in the EU. Most of this mercury is used in medical (fever) thermometers and other thermometers for general household use. The Directive states that fever thermometers and other measuring devices intended for sale to the general public e.g. manometers, barometers, sphygmomanometers, thermometers other than fever thermometers may not be placed on the market after 3 April 2009. The main benefit of the restriction on mercury containing devices will be a reduction of mercury in municipal and healthcare waste streams and reduction in mercury emissions from landfill and incineration. The long term benefits are less mercury in the environment resulting in lower levels of human exposure to mercury.



The restrictions **do not apply** to measuring devices that are more than 50 years old on 3rd October 2007. Measuring devices containing mercury that are already in use and on the second hand market are not affected by this ban and may still be sold, repaired and maintained. In addition, barometers are subject to an additional phase-out period until the 3rd October 2009. This is to allow specialist manufacturers to adapt their production appropriately.

The Commission is to carry out a review of the availability of reliable safer alternatives that are technically and economically feasible for mercury containing sphygmomanometers and other measuring devices in healthcare and in other professional and industrial uses. This will be completed by 3rd October 2009. On the basis of this review, or as soon as new information is available, the Commission shall, if it is appropriate, present a legislative proposal to extend the restriction to these products so that mercury in measuring devices is phased out whenever technically and economically feasible.

The Directive must be transposed into the national law of Member States by 3rd October 2008. Its measures will apply from 3rd April 2009.