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IRISH MEDICINES BOARD, KEVIN O'MALLEY HOUSE, EARLSFORT CENTRE, EARLSFORT TERRACE, DUBLIN 2 TEL: 01 676 4971 FAX: 01 634 4033 EMAIL: MEDICALDEVICES@IMB.IE

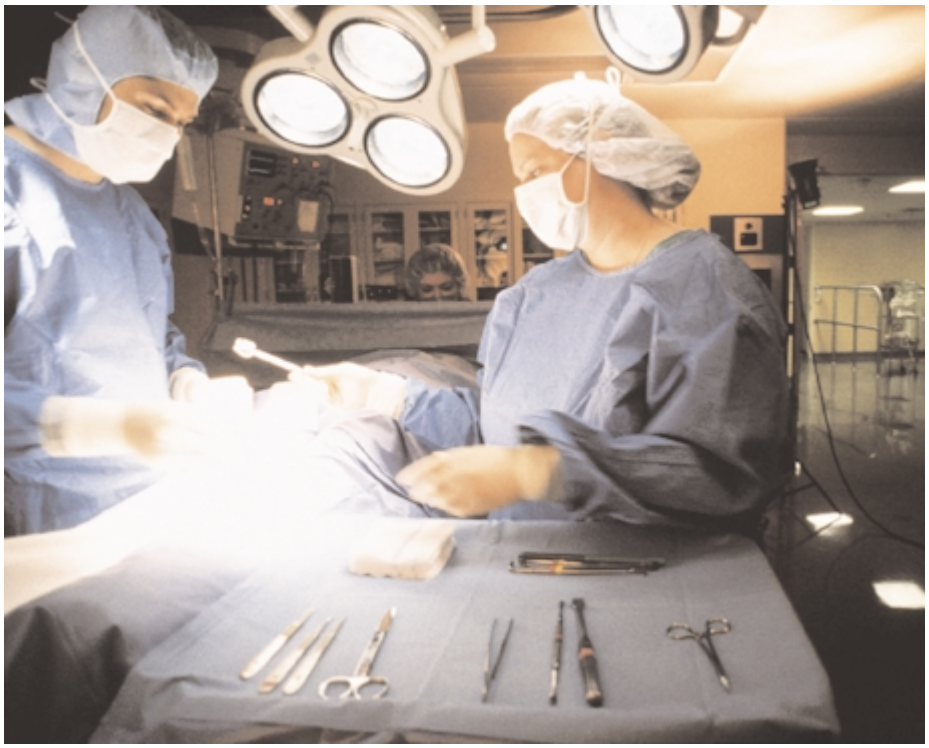
Letter from the Editor

Welcome to this edition of the newsletter.

Welcome to the second edition of the medical devices newsletter for 2005. In this months edition we have a feature article on the area of nanotechnology, which is a developing field in medical technology. Although the use of nanotechnology in medical applications is at an early stage, the potential benefits may be enormous. We also feature an article for information purposes in relation to the Clinical Indemnity Scheme run by the State Claims Agency, which is in existence since 2002. For various reasons, adverse incidents relating to medical devices are investigated on occasions by both the Irish Medicines Board and the State Claims Agency.

Over the last few months, we have had a number of queries in relation to the borderline between medical devices and medicinal products. The article on insulin pens in this edition will hopefully assist readers in understanding how the regulatory systems work in this area. We also hope to clarify regulatory points raised over the past few months for both the *in-vitro* diagnostic industry and the user in relation to the use of combination *in-vitro* diagnostic medical devices.

As always we welcome feedback or suggestions for specific topics you would like to see addressed in future newsletters.



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HOSPITAL ISSUES

The Clinical Indemnity Scheme

by DR. AILIS QUINLAN, *Head of the Clinical Indemnity Scheme*

The Clinical Indemnity Scheme (CIS) was established in July 2002, within the State Claims Agency (SCA), with a brief to:

- Provide clinical indemnity on the basis of 'enterprise liability', (i.e. the enterprise assumes liability for all its employees' alleged clinical negligence.),
- Manage claims made against enterprises in a timely and cost-effective manner,
- Reduce the numbers of clinical claims,
- Drive and support safe patient care,
- Lead and support clinical risk management in all the enterprises.

The CIS will cover all claims alleging medical malpractice or clinical negligence against an enterprise and / or its staff arising from the delivery of professional medical services by those employed by the agency.

The current position is that 87 enterprises and over 68,000 staff are covered by the scheme. The enterprises vary widely in size and service delivery, ranging from large tertiary referral hospitals, community care service, and community hospitals to small organisations providing services for clients with intellectual or physical impairment.

Cover was extended to hospital consultants from February 1st, 2004.

Approximately 935,000 patients (in-patient and out-patient) are treated in Irish hospitals each year (HIPE Data 2003). Based on international research, unfortunately 4% are likely to experience an 'adverse event', equating to 37,000 such events each year.

Clinical Risk Management

Clinical risk management is based on three principles, i.e. risk identification, risk analysis and risk control. International research and experience suggests that this approach will be successful only in the context of a 'blame-free' systems model. This requires review of the entire process leading to the occurrence of the adverse event, rather than focusing on the individual healthcare worker involved in the event.

Each enterprise is required to develop and promote a culture that supports clinical risk management.

All enterprises covered by the CIS have a statutory duty to:

- Report all adverse incidents to the SCA.
- Preserve relevant documentation.
- Permit and facilitate SCA investigation when requested to do so by the SCA.

As a risk identification tool, the web-based Clinical Incident Reporting System, STARSweb, has been developed to facilitate enterprises to report near misses or clinical incidents in a highly secure manner. One section is dedicated to the reporting of medical equipment incidents. These may be assigned to one of three categories, namely:

1. Failure / malfunction of medical device / equipment.
2. Lack / unavailability of medical device / equipment.
3. Wrong device / equipment used.

National 'roll-out' has commenced, with the plan to have all acute sector enterprises online by the end of June 2005. Training in data entry and report generation will be provided for all enterprises, once they 'go live'. As with any new system, ongoing monitoring will be required. Thus, a Users' Group is to be established to facilitate feedback to inform the CIS of issues of ongoing concern.

In recognition of the advisability of an integrated approach to risk management, the CIS has forged links with a wide number of agencies including the Irish Health Services Accreditation Board, the Health and Safety Authority, HSE and HIQA, the Mental Health Commission, Medical Devices Safety Agency, Medical Council and professional representative bodies.

Learning from serious adverse events and models of best practice will be disseminated through seminars, workshops and the CIS website. The mapping exercise that was carried out by CIS has identified a number of patient safety initiatives. Three major themes have emerged, i.e.

1. Slips / Trips / Falls
2. Medication Safety
3. Infection Control

Topic based seminars are planned that will allow enterprises that have developed initiatives to address these topics and share their experience.

An updated website at www.stateclaims.ie will provide information regarding 'Frequently Asked Questions', quarterly newsletters and links with relevant organisations.

What is Nanotechnology?

Nanotechnology is an emerging field of science that will have a profound impact on the way we live.

Its impact on the economy will be comparable to that of semiconductor technology and molecular biology combined. With *nanotechnology*, what has been considered science fiction will become fact. So what exactly is *nanotechnology*?

Nano is the Greek prefix meaning one billionth or 0.000000001. A nanometre (nm) is one thousand millionth of a metre, or about as much as a human fingernail grows per second. *Nanotechnology* is the science and engineering of products at this nanoscale. The nanoscale is generally accepted to range from 100nm down to the atomic level or approximately 0.2nm. For comparison, a single human hair is 80,000 nm wide, a red blood cell is approximately 7,000 nm wide, and a water molecule is approximately 0.3 nm wide. The discovery of novel materials and phenomena at the nanoscale, along with the concurrent development of new experimental and theoretical research techniques, provide opportunities for the development of innovative nanostructured materials and nanotechnologies. Nanostructured materials can be made with unique nanostructures and properties. This field is expected to open new avenues in science and technology.

Nanotechnology has the potential to advance the medical devices industry due to the novel material properties that are displayed at the nanolevel. This means the possibility of much smaller and smarter implantable devices, which will conceivably be able to interact with cellular processes, essentially controlling the body's responses from a cellular level.

Nanomedicine and Nanomedical Devices

Nanomedicine is defined as the application of nanotechnology to the prevention and treatment of disease in the human body. *Nanomedicine*, an offshoot of nanotechnology, refers to highly specific medical intervention at the molecular scale for curing disease or for repairing and replacing damaged tissues and cells. The field of *nanomedicine*, due to its vast potential, will be one of the first areas of *nanotechnology* that will be commercially available. The discipline of *nanomedicine* and nanomedical devices is a discipline that is still in its infancy, but is progressing rapidly. The ability to intervene in cellular processes and to cause change at the molecular level has truly amazing implications for the future of medicine.

The 'holy grail' of *nanomedicine* research is to create nanodevices such as nanorobots that would be capable of performing therapeutic functions *in vivo*. Although this goal may now seem like science fiction, it is thought that it will quickly become a reality. The achievement of this goal is being aided by massive allocation of monies by industry and government alike e.g. the U.S. government has given a budget of nearly $1 billion dollars to *nanotechnology* research, and worldwide funding was estimated at $2.5 billion, in 2004.

Two examples of how *nanomedicine* research is progressing toward commercial availability are given below. The examples are undergoing animal trials or are in the development stages but their large potential is evident.

Photo-thermal Nanoshells

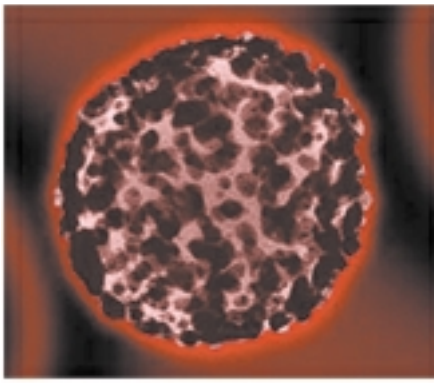


Photo-Thermal NanoShell

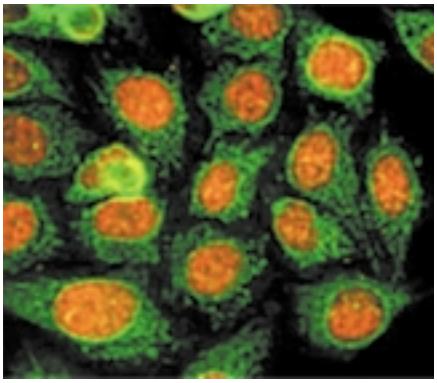
A potential cure for cancer may be closer than is commonly thought. Photothermal nanoshells are tiny gold-coated spheres, approximately 130nm in diameter, 15,000 of which could line up across a pinhead.

The interesting thing about photothermal nanoshells is that, as the name suggests, they heat up to quite high temperatures when an IR light is shone on them. Near IR light can penetrate a few centimetres into the body.

Blood vessels happen to be particularly leaky around tumours and photothermal nanoshells take advantage of this fact and deposit in and around tumours. The near IR light source can then be passed over any tumours, causing a very localised rise in temperature, burning away the tumours.

Results from animal trials show that tumours in mice were effectively removed and the mice were still healthy and cancer-free months later. If this technology is approved for use in humans, the implications are extraordinary.

Quantum Dot Diagnostics



Labelling of Mitochondria in Human Epithelial Cells

Quantum dots are tiny bits of material, just a few atoms across. The dots, when illuminated by ultraviolet light, glow very brightly with a specific colour that depends on their size: qdots with diameters of about 2 nanometres (billionths of a metre) glow bright green and 5 nanometres diameter dots glow brilliant red.

Scientists intend to use these quantum dots as research tools to help them understand how proteins, DNA and other biological molecules travel with-

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in cells and behave in intracellular processes. The scientists initially coat the dots in a material which would cause the dot to attach to desired biological molecules. They can then inject the quantum dots into cells growing in a lab and simply follow the lights.

The medical application of these quantum dots would be to use them to track proteins that are known to be early indicators of disease or illness. The current methods of detecting some of these proteins as early indicators are unsatisfactory. Using quantum dots to track them in blood samples or tissue samples could provide a powerful new diagnostic tool and if proven safe for use in the body they could be particularly useful in detecting tumours.

There are many other medical applications of *nanotechnology* such as improved burn dressings, surgical tools, and high throughput *in-vitro* diagnostic medical devices.

European medical device regulators are particularly keen to monitor progress in the field of innovative technologies. EUCOMED, the European Trade Association for Medical Devices, in close co-operation with the European Commission and the Medical Devices Expert Group (MDEG) is hosting a workshop in July 2005, in order to keep abreast of current developments in technologies such as *nanotechnology* and *nanomedicine*.

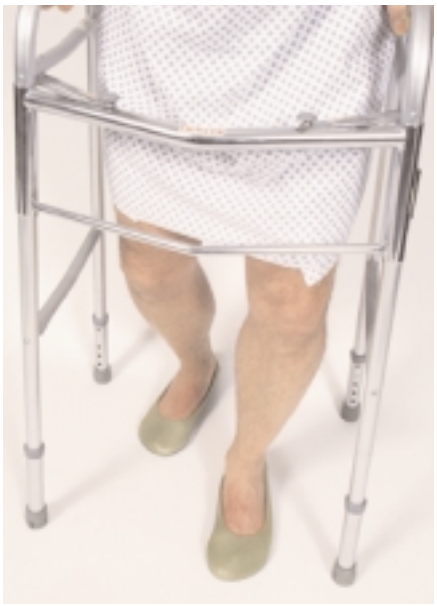
Although *nanomedicine* and the use of *nanotechnology* in medical applications is at an early stage of development the potential benefits of these fields may be enormous and the potential application widespread. Medicine by 2020 will have moved significantly forward. We will have the ability to know our genetic profile, we may be able to personalise our screening and when we do develop disease technology, we will help maintain our lifestyle providing us with more patient choice.

Regulatory Update

In relation to the proposed reclassification of total knee, shoulder and hip orthopaedic implants, the Article 7 regulatory procedure was completed in February 2005. The outcome of the procedure was that Member States voted in favour of a reclassification of the above products from a medium risk class IIb to a high-risk class III classification. The revised text is now with the EU Commission for final legal review and translation.

The study on competitiveness commissioned by the EU Commission following the review of Directive 93/42/EEC is at the final stage of preparation. The University of Sienna, Italy is finalising the document following comments from stakeholders. The Steering Committee of the EU Commission for this study will meet in April 2005 to agree the final text. This study should provide up-to-date data in relation to the medical devices sector in Europe. The data is currently not available.

At the recent meeting of the Commission's TSE / BSE Working Group, the 'end date' for completing the assessment process of the complementary certificates in the framework of the TSE Directive 2003/32/EC was agreed as the 30th April 2004. The Market Surveillance Operations Group (MSOG) of the Medical Devices Expert Group (MDEG) is working on a common European enforcement project to subject products remaining on the market after that date to uniform European regulatory action. This programme is



expected to be initiated in May 2005.

Following the success of the previous four workshops for new Member Countries, the EU Commission has obtained funding to host a fifth workshop in Prague, Czech Republic in June 2005. This workshop is aimed at assisting the new Member Countries with specific aspects of the implementation of medical device legislation. Ireland will be providing a workshop in relation to proposed changes to the medical devices legislation.

The first meeting of the Electronic Labelling Task Force took place in March 2005. The terms of reference have been agreed and the principal work of this task force will be to develop a MED.DEV in relation to labelling of *in-vitro* diagnostic medical devices. This guidance will address the issue of electronic labelling for IVDs specifically for use by professional users. Ireland is leading the drafting group in relation to this guidance and it is envisaged that the first draft paper will be presented to the MDEG at its July 2005 meeting.

Emerging technologies and the need to keep abreast of current and future developments continues on the agenda of both industry and regulators. It was agreed at the MDEG that Eucomed, in close co-operation with the MDEG, would host a workshop in July 2005 that would specifically look at this subject.

With regard to medical devices containing DEHP plasticised PVC, the first meeting of the dedicated working group of MDEG to look at this subject took place. The group has decided to prepare a recommendation in relation to high-risk groups, especially neonates. It was also agreed that in the absence of new scientific information, the position of the MDEG on this issue remains in line with the opinion taken by the European Scientific Committee on Medicinal Products and Medical Devices of the 26th September 2002. This position can be downloaded from the European Commission website http://europa.eu.int/comm/enterprise/medical_devices/index_en.htm.

The Use of Combination In-vitro *Diagnostic Medical Devices for Diagnostic Purposes*

The Irish Medicines Board (IMB) advises manufacturers that if they intend *in-vitro* diagnostic medical devices to be specifically used in combination for diagnostic purposes they need to CE mark the combination system in order to be compliant with the *In-vitro* Diagnostic Medical Devices (IVD) Directive 98/79/EC as per Article 1.2 (b).

'In-vitro *diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used* in-vitro *for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information'.*

When manufacturers produce IVDs that are designed and intended to work in combination with other devices for diagnostic purposes, validation data must be provided to demonstrate that when a test kit is used in combination with another device, e.g. an automated ELISA processing system that the original device maintains its specific performance characteristics. This is outlined in the EC Declaration of Conformity procedure, Annex III section 3, 9th indent.

'if the device is to be combined with other device(s) in order to operate as intended,

proof must be provided that it conforms to the essential requirements when combined with any such device(s) having the characteristics specified by the manufacturer'

If a manufacturer is promoting an IVD test kit for use in combination with an automated ELISA processing system for diagnostic purposes without having the appropriate validation data in place to support this claim for at least one system, they are not fulfilling the essential requirements of the Directive as outlined in Annex I, 8.7 (m).

'if the device must be used in combination with or installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe and proper combination'

This is of particular concern for high risk reagents and reagent products that are included in Annex II, List A and B of the IVD legislation 98/79/EC as the conformity assessment process for validation and CE marking of these devices is more complex and would require assessment by a Notified Body, as outlined in Article 9.3 of the Directive.

In the case where a hospital laboratory chooses to buy an IVD from a manufacturer for use with an automated ELISA processing system which is different to that validated by the manufacturer, it would be the responsibility of the user to validate the combination when used together for diagnostic purposes. In this case it would be prudent for the user to work with the manufacturer of the IVD test kit to ensure that the test procedure is correctly programmed for the automated ELISA processing system to provide a diagnostic result. At present there are no guidelines for hospital laboratories for the validation of combination IVDs. The IMB recommends hospital laboratories to review the principles of CE marking and adopt this approach, wherever possible, for the validation of IVDs for use in combination.

It is clear that the future for hospital laboratories is moving towards the use of automated systems for diagnostic purposes in order to reduce operator interaction with potentially pathological specimens and also to facilitate the throughput of large volume of samples. We expect that manufacturers are aware of this trend and are considering the requirements of the evolving diagnostic environment in the CE marking process for IVDs, which are being used in combination.

Staff Update

The Medical Devices Department is delighted to announce that **Mr. Daniel Smyth** *has joined the medical device team. Daniel has a background in mechanical engineering and is currently undertaking an MSc in bioengineering. He will be working primarily in the area of compliance and auditing.*

In May, **Dr. Barbara Tucker**, *Medical Assessor will be leaving the medical devices team. In her absence, any issues should be addressed to Ms. Ann O'Connor or the medical devices general e-mail address medicaldevices@imb.ie.*

Guidelines on the Label Claims of Medical Devices

An issue in relation to the label claims of medical devices continues to be highlighted through correspondence with manufacturers. If a manufacturer claims that the products have a medical purpose, the claims should be substantiated with the appropriate supportive clinical information in order for CE marking to be obtained. We recommend that readers refer to the guidance note MEDDEV 2.1/1 of April 1994 - Definitions of "medical devices", "accessory" and "manufacturer" where it states in Section 1.1 b:

"Medical devices are defined as articles which are intended to be used for a medical purpose. The medical purpose is assigned to a product by the manufacturer. The manufacturer determines through the label, the instruction for use and the promotional material related to a given device its specific medical purpose. As the Directive aims essentially at the protection of patients and users, the medical purpose relates in general to finished products regardless of whether they are intended to be used alone or in combination. This means that the protection ensured by the Directive becomes valid for products having a stage of manufacture, where they are supplied to the final user."

MANUFACTURING ISSUES

Insulin Pens

The Medical Devices Directive encompasses a wide range of products ranging from low risk products like bandages to higher risk products like cardiac stents. There are a small number of products which are in the borderline area between medical devices and medicinal products, and their classification depends on their principal intended purpose and the label claims. In general, medical devices achieve their principal intended action by the following means:

- Mechanical action
- Physical barrier
- Replacement of, or support to, organs or body functions

A medicinal product typically achieves its intended action by the following means:

- Pharmacological
- Immunological
- Metabolic

Medical devices may be assisted in their function by pharmacological, immunological or metabolic means but as soon as these means are no longer ancillary with respect to the principal purpose of a product, the product becomes a medicinal product.

There are three types of medical device that incorporate, or are used to administer, a product:

(a) Devices used to administer medicinal products e.g. a syringe marketed empty. These devices are covered by the relevant medical devices regulations.

(b) Devices used to administer medicinal products where the device and the medicinal product are marketed as a *single integral product* designed to be used exclusively in the given combination and which are not re-usable e.g. a pre-filled syringe. These integrated products are covered by medicinal products legislation.

(c) Devices incorporating a medicinal substance as an integral part of the device where the medicinal substance is liable to act on the body with action *ancillary* to that of the device e.g. drug-coated stent. These devices are covered by the medical devices legislation.

In the last few months, manufacturers / users of some borderline medical devices such as insulin pens have been confused by which legislation applies to them. The following is a summary to help clarify the correct regulatory regime that applies.

- A reusable insulin pen sold without an insulin cartridge is regulated as a **medical device** (this is an example of category (a) above).
- An insulin-containing cartridge (or vial) supplied on its own is a **medicinal product**.
- A disposable insulin pen sold with an integral insulin cartridge is regulated as a **medicinal product** (this is an example of (b) above).
- A reusable insulin pen sold with a replaceable insulin cartridge. In this case the insulin pen is regarded as a **medical device** and the insulin cartridge as a **medicinal product**.
- A disposable insulin pen sold without an insulin cartridge intended for single use with an appropriate cartridge. In this case the insulin pen is regarded as a **medical device** and the insulin cartridge as a **medicinal product**.

It is also worth noting that where a drug preparation is packaged, sold and intended for use together with an administration device, then the medicinal products legislation takes precedence and the combination is generally regulated as a medicinal product.