Medical device regulations in the european union

INTRODUCTION TO MEDICAL DEVICE REGULATIONS IN THE EUROPEAN UNION:

A Medical Device under the jurisdiction of the European Union is defined as “ an instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application, which -

a) is intended by the manufacturer to be used for human beings for the purpose of

i. diagnosis, prevention, monitoring, treatment or alleviation of disease,

ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

iii. investigation, replacement or modification of the anatomy or of a physiological process, or

iv. control of conception; and

b) does not achieve its principal intended action in or on the human

body by pharmacological, immunological or metabolic means”. [1]

The clinical investigation and the subsequent introduction of a medical device in the European market is primarily regulated and governed by the MHRA (Medicines and Healthcare products Regulatory Agency) with the assistance of competent regulatory institutions called the Notified Bodies. “ A Notified Body is a certification organization which the national authority (the

Competent Authority) of a Member State designates to carry out one or more of the conformity assessment procedures described in the annexes of the Directives.” [3]

The MHRA regulates with the help of two sets of medical device regulations viz. the Statutory Instruments 2002 No. 618 (Consolidated legislation) and 2003 No. 1697. These legislations employ the three device directives issued by the competent authority into the european law. The directives help the manufacture in better understanding of the manufacturing and the requirments for inroduction into the market of the devices. These directives are:

- Directive 90/385/EEC: Active Implantable Medical Devices directive
- Directive 93/42/EEC: Medical Devices directive
- Directive 98/79/EC: In vitro Diagnostic Medical Device directive

Directive 90/385/EEC: Active Implantable Medical Devices directive:

This directive encompasses medical devices that are active(i. e powered) and implanted(i. e left in the human body). These include pacemakers, implantable defibrillators, implantable infusion pumps, cochlear implants and implantable neuromuscular stimulators etc. Regulations realizing the Directive came entirely into force in the United Kingdom on January 01 1995.

Directive 93/42/EEC: Medical Devices directive:

This directive covers an extensive array of devices from uncomplicated bandages to orthopaedic implants and high-end radiology apparatus.

Regulations realizing the Directive came entirely into force in the United Kingdom on June 13 1998.

Directive 98/79/EC: In vitro Diagnostic Medical Device directive:

“ This Directive covers any medical device, reagent, reagent product, kit, instrument, apparatus or system which is intended to be used for the invitro examination of substances derived from the human body, such as blood grouping reagents, pregnancy testing and Hepatitis B test kits. Regulations implementing the Directive came into force in the UK on 7 th June 2000 with a transitional period until 7th December 2003. There is no clinical investigation system for in-vitro diagnostic medical devices. Performance evaluations of in vitro diagnostic devices that are performed outside the manufacturer's premises should be notified to the UK Competent Authority in accordance with the Medical Devices Regulations 2002: Section 44.” [2]

The rationale backing these directives is to permit easy movement of the medical devices throughout the European Union whilst upholding high standards of device safety and up-to-the-mark quality.

Classification of medical devices:

Devices are classified purely based on risk associated with their use. Ranging from low risk to high risk, they are Class I, IIa, IIb and III. A classic example of a *class III* medical device is a *cochlear implant* , which is both active and implantable and thus comes under the purview of *Directive 90/385/EEC: Active Implantable Medical Devices directive.* Let us discuss in detail the regulatory requirments specified as per the MHRA to bring an active

implantable cochlear implant into the market designated bt the European Union as the EFTA(European Free Trade Area). “ Examples of AIMDs include:

- implantable cardiac pacemakers
- implantable defibrillators
- leads, electrodes, adaptors for 1) and 2)
- implantable nerve stimulators
- bladder stimulators
- sphincter stimulators
- diaphragm stimulators
- cochlear implants
- implantable active drug administration device
- catheters, sensors for 9)
- implantable active monitoring devices
- programmers, software, transmitters.” [4]

Cochlear Implants:

“ Cochlear implants are electronic hearing prostheses that bypass the damaged hearing components by providing electrical stimulation directly to the auditory nerve fibres in the cochlea. The electrical stimulation is interpreted by the brain as sound. Cochlear implants consist of an external microphone, speech processor and transmitter coil, and an internal stimulator (implanted under the skin just behind the ear) attached to a

stimulation electrode which passes into the cochlea. A variation of the cochlear implant is the auditory brainstem implant where electrodes are implanted directly into the auditory area of the brainstem. This can be used in patients who do not have a functional auditory nerve.” [5]

The regulatory process of bringing a cochlear implant in the European market:

It is mandated by law that the manufacturer who intends to bring the device into the EFTA abides by the Essential Requirments stated in the Directive 90/385/EEC: Active Implantable Medical Devices directive and demonstrate the compliance of the device with the safety and efficacy standards set forth in the directive. There are essentially two ways to do it viz.

- “ either a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed, together with, if appropriate, a written report containing a critical evaluation of the compilation; or
- the results and conclusions of a specifically designed clinical investigation” [2]

Product launch on the basis of evaluation and review of scientific literature can be considered as acceptable if equivalence can be scientifically demonstrated with a device existant in the market and routinely used in clinical practice. Equivalence has to be demonstrated w. r. t technology, critical performance, design, principles of operation, biological safety, population involved, conditions of use and clinical purpose. However, unless

satisfactory evidence can be collected by means of scientific literature review, the use of a well-planned clinical trial/investigation should be considered as the best way to attest permissible levels of safety and efficacy.

In case of scientific review or pre-clinical assessment, the following fees apply: Class I, IIa, or IIb other than implantable or long-term invasive: £3, 000 (Re-notification incase of objection by MHRA £2, 100). Class IIb implantable or long-term invasive, *Class III, and active implantable: £4, 100 (Re-notification incase of objection by MHRA £2, 700).*

Applications for a proposed clinical investigation of the medical device should be made by filling the forms PCA1 and PCA2 along with the necessary information required by the clauses in the forms. Applications should be labeled clearly as " documentation only". The use of English language is mandatory. Documentation should be clear and legible and remain so after reproduction. Electronic applications should be discussed with the MHRA. The manufacturer, for scrutiny by the MHRA should make a total of eight full submission copies available. The charges for the scrutiny of applications are laid out in the Medical Devices Regulations 2002: section 56. They are as follows: " Fees for Group A (low risk) devices are £2, 700 (initial application) or £1, 800 (resubmission). Increasing to £3, 000 and £2, 100 on 1st April 2008. Fees for Group B (high-risk) devices are £3, 800 (initial application) or £2, 400 (resubmission). Increasing to £4, 100 and £2, 700 on 1 st April 2008."

[2] Applications should be forwarded to:

Mrs Daniella Smolenska, Medicines & Healthcare products Regulatory Agency (MHRA), European and Regulatory Affairs, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ, Tel: 020 7084 3363, Email Daniella. Smolenska@mhra. gsi. gov. uk .

Approval from the MREC (Multi-centre Research Ethics Committee)/LREC (Local Research Ethics Committee) can be obtained along with the notification to the Competent Authority. However, a clinical investigation can begin only after approval has been obtained from the MREC/LREC and the Competent Authority has not raised an objection to the investigation within the 60 days time constraint period; or approval has been obtained from both the authoritative bodies.

General Requirements:

A well-defined clinical plan whose methodology and ethical considerations conforms to the standards set forth in the Medical Devices Regulations 2002: section 16 and section 29, the Active Implantable Medical Devices Directive, Annexes 6 and 7, and the Medical Devices Directive, Annexes VIII and X.

Supplementary standards are set forth in Standard BS EN ISO 14155-1; 2002, “ Clinical Investigation of Medical Devices for Human Subjects-part 1: General Requirements”, and BS EN ISO 14155-2: 2002, “ Clinical Investigation of Medical Devices for Human Subjects-part 2: Clinical Plan”.

The CA should be notified incase of differences in the EU and non-EU protocols and the reasons for the same.

“ All applications must contain a statement (Active Implantable Medical Devices Directive: Annex 6, 2. 2; Medical Devices Directive: Annex VIII, 2. 2): *that the device in question conforms to the Essential Requirements except with regard to those aspects of the device that are to be investigated and that in respect of those aspects, every precaution has been taken to protect the health and safety of the patient.* By signing this statement, the manufacturer is declaring that the device meets all of the relevant Essential Requirements, other than those subject to the investigation. Manufacturers must therefore ensure that at the time a notification is made to the Competent Authority, they have all documentation required to demonstrate conformity with the relevant Essential Requirements available for submission to the Competent Authority when requested.” [2]

Device information like name, model, materials used and sterilization standards etc must be provided as set forth in the directive.

Pertinent information about the clinical investigation plan, investigation parameters and design, data collection and analysis methods etc. should be made available to the CA.

It is strongly advised that Class III devices follow a well-designed post-marketing plan under the Medical Devices Vigilance.

Extra care should be taken when labeling devices meant for clinical investigations. “ All devices intended for clinical investigation must bear the wording " exclusively for clinical investigation" (Medical Devices Directive:

annex 1, para 13. 3(H) and the Active Implantable Medical Devices Directive: annex 1, 14. 1).” [2]

Reporting of adverse incidents: “ A serious adverse incident is one which:

- led to a death
- led to a serious deterioration in the health of the patient, user or others and includes:
- a life threatening illness or injury
- a permanent impairment to a body structure or function
- a condition requiring hospitalisation or increased length of existing hospitalisation
- a condition requiring otherwise unnecessary medical or surgical intervention and which might have led to death or serious deterioration in health had suitable action or intervention not taken place. This includes a malfunction of the device such that it has to be monitored more closely or temporarily or permanently taken out of service
- led to foetal distress, foetal death or a congenital abnormality or birth
- defect
- might have led to any of the above” [2]

All such incidents should be recorded and reported to the CA as set forth in the Regulation 16(10)(a) of the Medical Devices Regulations 2002 (SI 618) and Annex X of the Medical Devices Directive 93/42.

Final written report: A report in conjunction with the Medical Devices Directive (Medical Devices Regulations 2002: Section 16(10) and Section 29(9)) should be submitted to the CA for devices undergoing investigation for a *CE marking.*

However, Class III devices need to be highly regulated, before, after and during the clinical investigation. Owing to the high risks associated with their use, some say the risk can be quantified only as social and not scientific. " Risks, rather than being inherent within these implant devices, may be seen as socially derived, in processes of negotiation and conflict such as those in the case of hip and breast implants.... most recently, in the wake of the controversies surrounding breast implants and the 3M Capital hip, attention has been drawn to the uneven performance of notified bodies in the EU, which approve new products. This has led to the setting up of a new European Notified Bodies Operations Group (NEBOG) and calls by the MDA for all implants to be reclassified as high risk, Class III. A review of the operation of EU EMDD is also about to begin (MDA, 2001b). It thus appears that increased political scrutiny is being focused on this sector." [6]

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