



bringing ideas to life

Regulatory requirements for Medical Devices

May 2010

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Regulatory Framework



Legislation

3 main Directives

- Medical Devices Directive 93/42/EEC as amended by 2007/47/EC (effective 21st March 2010)
- In-vitro Diagnostics Directive 98/79/EC
- Active implantable MDD 90/385/EC

Transposed into UK law by Statutory Instruments



Definition of a Medical Device – Pg 1/2

Any instrument, apparatus, appliance, **software**, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of;



Definition of a Medical Device - Pg 2/2

- Diagnosis, prevention, monitoring, treatment or alleviation of disease,
- Diagnosis, monitoring, treatment or alleviation of or compensation for an injury or handicap,
- Investigation, replacement or modification of the anatomy or of a physiological process
- Control of conception
- And which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means.



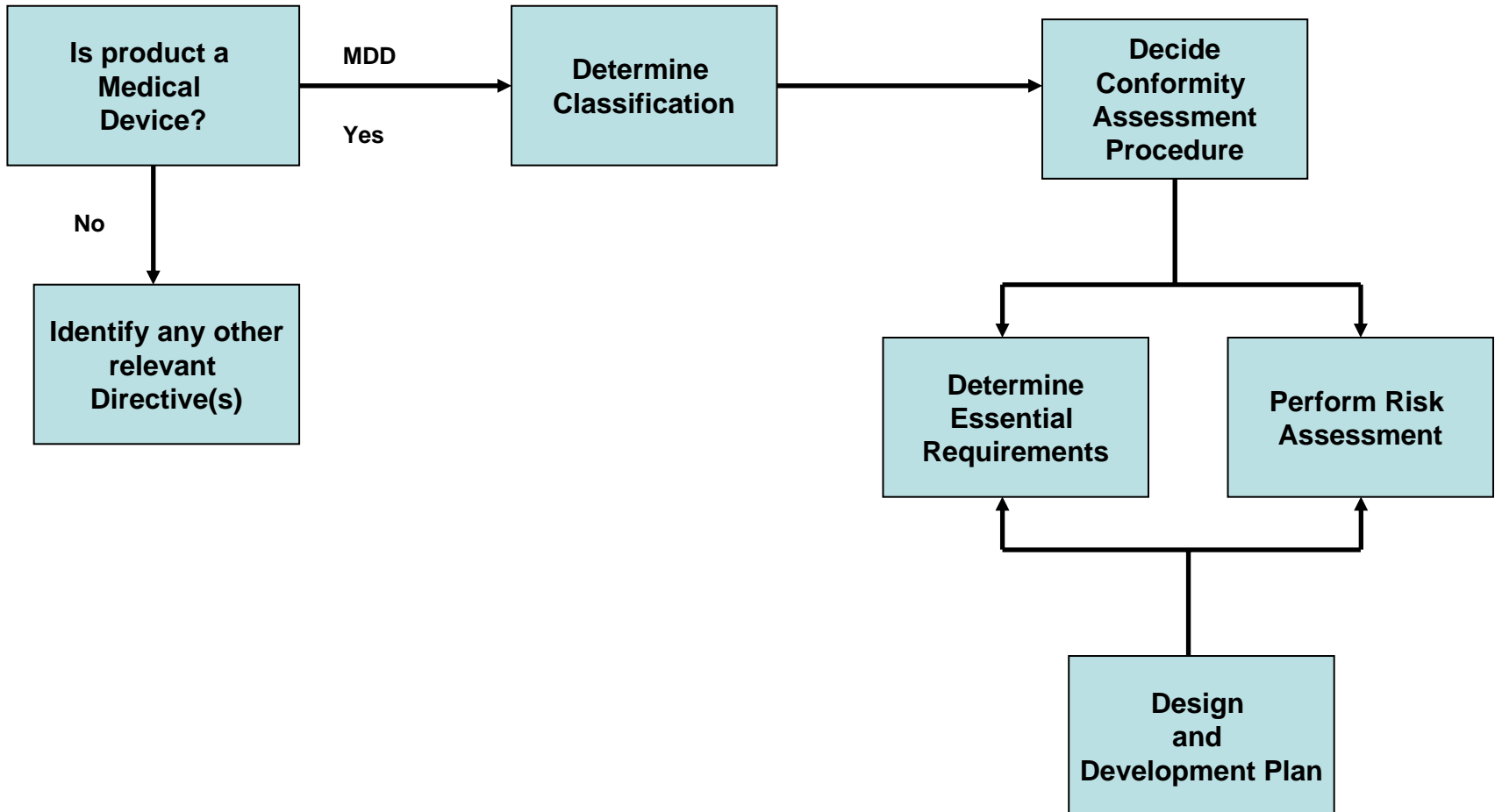
Is it a Medical Device?

Consider;

- The **intended purpose** taking in to account the way the product is presented
- The method by which the principal intended action is achieved.

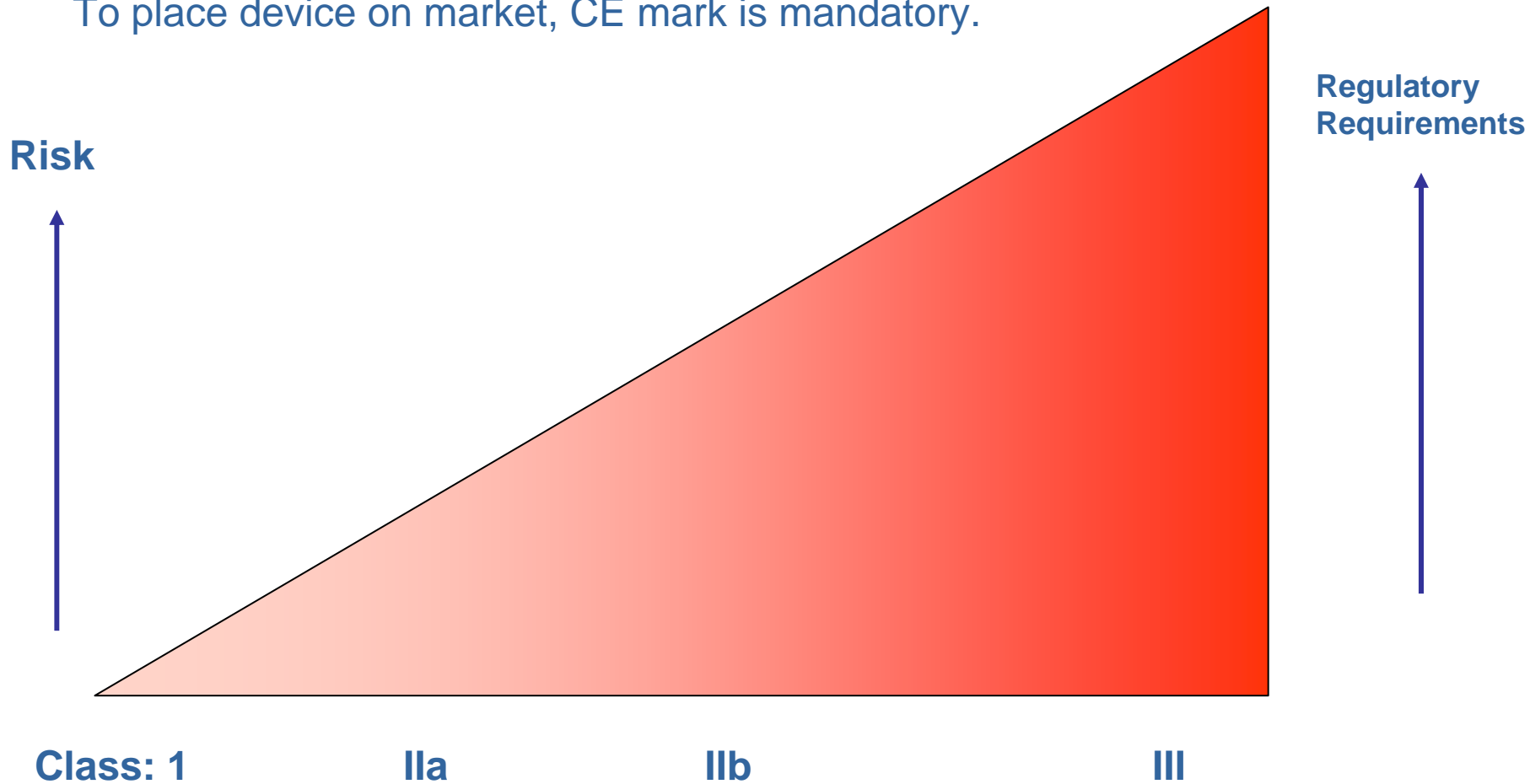
- Action typically fulfilled by physical means (incl. mechanical action, physical barrier, replacement of, or support to, organs and body functions)

Process



MD Classifications

18 rules used to classify Medical Devices.
To place device on market, CE mark is mandatory.





Practical

- Determine the classification for;
- CPR assistant (pg 11): support and aid to resuscitation
- Multi-focal Imager (pg 7): stimulates the retina and maps the response
- Can you change the classification by changing intended use?



CE marking routes: Class 1

- Self certification
Annex VII: Prepare Technical File to support DOC
- If sterile and/or includes a measuring function, a Notified Body (NB) must review these controls (Annex IV, V or VI)
- Sign Declaration of Conformity (DOC)
- Register with Competent Authority (MHRA/RG2 form)
- Affix CE mark



CE marking routes: Class 11a

- Annex II: **NB** audits full QS system – ISO 13485
or
- Annex VII: Prepare Technical File to support DOC
and
- Annex IV: every batch verified by NB *or*
- Annex V: NB audits production QA *or*
- Annex VI: NB audits inspection QA

- Sign DOC
- Affix CE mark



CE marking routes: Class 11b

- Annex II: **NB** audits full QS system – ISO 13485
or
- Annex III: Type examination by NB
and
- Annex IV: every batch verified by NB *or*
- Annex V: NB audits production QA *or*
- Annex VI: NB audits inspection QA

- Sign DOC
- Affix CE mark



CE marking routes: Class 111

- Annex II: **NB** audits full QS system – ISO 13485
- Design Dossier examination by NB
or
- Annex III: Type examination by NB
and
- Annex IV: every batch verified by NB *or*
- Annex V: NB audits production QA *or*

- Sign DOC
- Affix CE mark



Essential Requirements (ER)

- All devices must meet ER – Annex 1
- Provide evidence that solns have been adopted to meet the applicable ER
- Justify any “not-applicable”
- Manufactured & designed so they will not compromise clinical condition & safety of patients
- Document how risk has been minimised
(keep updated)

Multi-focal Imager

1. For information to support clinicians management of an eye pathology
2. For diagnosis

How would this change the risk assessment?



Essential Requirements (ER)

- Radiation/Electrical safety
- Chemical, physical & biological properties
 - Biocompatibility
- Infection & microbial contamination
- Construction & environmental properties
- Control of measuring functions
- Packaging & Labelling
- Clinical Evaluation (ongoing/PMS)



Clinical Investigation



EU Regulations

2007/47/EC (amends 93/42/EEC)

Annex 1, Essential requirements (ER)

6a. Demonstration of conformity must include a clinical evaluation in accordance with Annex X

Annex X, clinical evaluation

Confirmation of ER must be based on clinical data. Evaluation of this data linked to harmonised standards and follow a defined and methodical procedure.



What is clinical data?

Article 1, definitions/scope

Clinical data (safety/performance information relevant to intended use)

Either

- *Critical* evaluation of **relevant scientific literature** of an essentially similar device or;
- *Critical* evaluation of **all clinical investigations** made; or
- *Critical* evaluation of the combined data from literature and clinical investigations



Intended use

- Clinical condition being treated
- Severity and stage of disease
- Site of application
- Patient population
- Technical characteristics
- Principles of operation
- Conditions of use
- Biological characteristics/biocompatibility



Clinical investigation – when?

- The device is an implantable or Class III medical device.
- When a completely new device is proposed for the market, whose **components, features and/or method of action are previously unknown**,
- Where an existing device is modified and the **modification might significantly affect the clinical safety and performance**
- Where a previously established device is proposed for a **new indication**
- Where a device incorporates new materials, previously unknown, coming into contact with the human body or existing materials applied in a location not previously exposed so that material, and for which there is no convincing clinical experience, or that the device will be used for a significantly longer time.
- Where *in vitro* and/or animal testing cannot mimic the clinical situation



Clinical Investigation Plan

- To verify that under normal conditions of use the performance characteristics of the device are those intended by the manufacturer; and
- To determine any undesirable side effects under normal conditions of use and to allow an informed clinical opinion to assess whether these are acceptable when weighed against the intended performance of the device.

It is worthwhile to scope out a full clinical development plan from early “proof of concept” to pivotal studies for efficient evaluation of safety & performance.



Clinical Development Plan

Consider;

- The marketing strategy with regard to claims, indications, territories and therefore competitor(s) that may be used as comparators/controls.
- Determine how each trial contributes to determining statistical significance of safety and performance claims.
- Ensure intended conditions of use are covered.
- Examine appropriate features involving safety and performance and their effects on patients so that the risk/benefit balance can be satisfactorily addressed
- Are staged to take account of the development and validation of manufacturing/testing processes, which may alter the characteristics of the device.



Notification to Regulators



Clinical investigation & MHRA

- The manufacturer of the device must give 60 days prior notice to MHRA before the device can be made available to a medical practitioner.
- Notification to MHRA can be made at the same time as a submission to MREC/LREC. – use Integrated [Research Application System \(IRAS\)](#).
- MHRA will send out formal acceptance of notification – starts the clock.
- Can proceed if no objection raised after this acceptance of application. MHRA will send out a letter approving or rejecting application.



Special circumstances

- Clinical **data** may be required where product is CE marked but a change in the intended use/performance claims of a device is proposed;
- One application can be used with variations to cover clinical investigation of several prototypes, provided patient risk not increased.



Special Circumstances

Products manufactured in-house in a health-care establishment and undergoing testing for POC **are out of scope**, *provided that the device is being manufactured and used on patients within the sole legal entity.*

Notify MHRA where the in-house manufacturer sees & intends a commercial medical application in results.



Special circumstances

Off-label" use

If a clinician uses a CE-marked device for a new "off-label" purpose which is unsupported by the manufacturer, then the clinician and the relevant healthcare establishment may take on the responsibilities of "the manufacturer" **if they see and intend a commercial application**, and must therefore fulfill all the requirements of a manufacturer as set out in the Medical Devices Regulations, including notification of a clinical investigation to the MHRA.

They may also take on liability with reference to the device being used "off-label".



Information required

Conforms to ER, except aspects under investigation

General admin information

Device details

- Name, description, intended purpose
- Classification, compliance with Harmonised standards
- Experience to date/manufacturing/packaging
- Biocompatibility
- Statements re; blood/tissues of animal origin

Clinical investigation plan

- Investigators brochure
- Principal investigator, locations, starting dates, duration
- Intended purpose and mode of action
- Informed consent docs & confirmation of insurance of subjects
- Ethics opinion
- Investigative parameters

Supportive documentation at manufacturer

Packaging/labelling



Safety Reporting



EU - Adverse incidents

- All AIs must be recorded and all serious AIs reported
- Serious AI
 - Death
 - Serious deterioration in health (*further defined*)
 - Foetal distress, death or congenital abnormality
 - Might have led to the above
- Report ASAP and not at conclusion of investigation
- Follow vigilance procedures for controls which are CE marked medical devices



End of clinical investigation

- Must notify MHRA when investigation comes to an end
- MHRA may request a final written report
- Must notify MHRA of early termination and provide a justification



Literature Reviews and Clinical Evaluation Report



Literature review

- Based on risk analysis
- Relevant to intended use
- Weighting of papers
- Market experience
- Validity of information & conclusions in the literature



Evaluation Report

Reports on the process of;

- Identifying the ER that require to be supported by clinical data
- Identifying available and relevant clinical data
- Evaluation of the suitability of the data for establishing safety & performance
- Identifying the need to generate any other clinical data to address outstanding issues
- Compilation of all clinical data and conclusions about clinical safety & performance



Evaluation Report

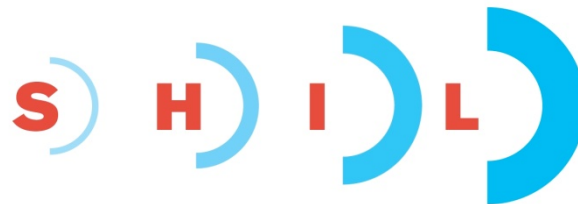
- Must be thorough and objective
- Discuss favourable & unfavourable data
- Must address clinical claims, adequacy of labelling & product information (IFU)
- Author to be relevantly qualified
- Include list of publications
- Risk/benefit assessment
- Conclusions
- **Keep updating with PMS data**



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bringing ideas to life



Guidance

<http://www.mhra.gov.uk/Howweregulate/Devices/MedicalDevicesDirective/Borderlinewithmedicines/index.htm>

- MHRA : [Bulletin 17](#) lists various products and whether they are considered medical devices or medicinal products.
- [MEDDEV 2.1/1](#) Definitions of "medical devices", "accessory" and "manufacturer"
- [MEDDEV 2.1/3 rev.3](#) Borderline products, drug-delivery products and medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative
- Additional guidance on specific products contained in the Medical Device Expert Group's 'Manual on borderline and classification in the Community Regulatory framework for medical devices'.



Guidance

MHRA Guidance documents

- [Guidance Note 1 - Guidance Notes for manufacturers on clinical investigations to be carried out in the UK \(updated Mar 2010\)](#)
- [Guidance Note 3 - Information for clinical investigators](#)
- [Guidance Note 5 - Guidance on biocompatibility assessment](#)
- [Guidance Note 17 - Guidance Notes for manufacturers on statistical considerations for clinical investigations of medical devices](#)

MEDDEV.2.7.1 Rev 3 Dec 2009 – Clinical evaluation : a guide for manufacturers and notified bodies

MEDDEV 2.12/2 – guidance on post market clinical follow up

Harmonised Standards

- BS EN ISO 14155-1; 2009, "Clinical Investigation of Medical Devices for Human Subjects-part 1: General Requirements", and
- BS EN ISO 14155-2:2009, "Clinical Investigation of Medical Devices for Human Subjects-part 2: Clinical Plan".

ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)