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Recapitulation of Modernize Medical Devices and Market-Oriented Economies in United Kingdom

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Abstract
The purpose of this study is to illuminate the importance of medical devices, regulatory requirements for the registration of medical device manufacturers in U.K. The controversy for companies developing and producing medical device is to update on the regulatory requirement and implement them in the process. Medicines and devices are regulated under European Union (EU) law, the regulatory regimens are very different, and some have argued that features of the pharmaceutical regime should be applied to medical devices in the current review of the medical device directives. The UK medical device market is third largest in Europe; the medical device trade is import-led, as most domestically manufactured products are exported to other markets. But two of these countries had different regulations to maintain the quality of medical devices marketing in their countries. The review will give a brief statement of the main points of regulatory requirements and registration of medical devices.

Keywords
Medical device, Regulations, Registrations, Approval.

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INTRODUCTION:

MEDICAL DEVICES

The term “medical device” means any instrument, apparatus, implement, machine, appliance, implant, and reagent for in vitro use, software , material or their similar or related articles, intended by the manufacturer to be used , alone or in combination , for human beings , for more of the specific medical purposes. The global medical device industry has experienced significant growth over the last five years and is expected to continue, reaching approximately US $ 302 billion in 2017 with a CAGR of 6.1% during next six years (2011-2017).these new segments are expected to improve the prospects for the market [1].

GLOBAL HARMONIZATION TASK FORCE (GHTF)

The Global Harmonization Task force (GHTF) was founded in 1993 by the governments and industry representatives of Australia, Canada, Japan, the European Union, and the United States of America. The purpose of GHTF is to encourage a convergence in standards and regulatory practices related to the safety, performance and quality of medical devices. WHO collaboration with the GHTF could facilitate access for developing countries (both those importing and those wishing to manufacture) to:

- Information on the major regulatory system for medical device
- Device approvals and health technology assessment from highly regulated markets
- Adoption of a single medical device nomenclature
- Innovative technology advances

1.8.3 REGULATORY BODY (MHRA)

The **Medicines and Healthcare Products Regulatory Agency (MHRA)** is a UK government which is responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Medicines and Healthcare products Regulatory Agency was formed in 2003 with the merger of the medicines control agency (MCA) and the Medical Devices Agency (MDA).

The MHRA is divided in to three main centers:

- The National Institute for Biological Standards and Control (NIBSC)
- The Clinical Practice Research Data Link (CPRD)
- MHRA Regulatory (the regular for the pharmaceutical and medical device industries)

AIMS OF MHRA: [2]

- Protecting public health through regulation, with acceptable benefit-risk profiles for medicines and devices.
- Promoting public health by helping people who use these products to understand their risks and benefits.
- Improving public health by encouraging and facilitating developments in products that will benefit people

OBJECTIVES OF MHRA: [3, 4]

- Safeguard public health through MHRA's primary role in ensuring that the products MHRA regulate meet required standards that they work and are acceptably safe.
- Carryout communication role through the provision of accurate, timely and authoritative information to healthcare professionals, patients and the public.

ROLES OF MHRA

- Assess applications for marketing medicinal products
- Assess applications to undertaken clinical trials
- Inspect the manufacturers and wholesalers of medicinal licensing
- Undertake post market surveillance including:
- Pharmacovigilance
- Quality defect monitoring
- Sampling and testing
- Product recalls

THE UNITED KINGDOM MEDICAL EQUIPMENT

The UK medical equipment market was valued at around $10.6 billion in 2018.It has a strong foundation of approximately 2,500 mostly small to medium sized companies around the country, with clusters of activity in areas such as the south east of England of the midlands. A large number of multi-national companies, including many of the leading U.S medical device manufacturers have head office or subsidiaries in the U.K.

The largest purchaser of medical equipment, the publicly funded National Health Service (NHS), accounts for approximately 85% of the country healthcare provisions [5].

The sector is also supported by firms offering associated goods or services, such as legal or regulatory proficiency, R and D facilities and logistical services. With the largest of the four administrations , NHS England, there are around 191 general practitioner – led (GP) clinical commissioning groups (CCG'S),which will receive combined funding of around two thirds of total NHS budget ($ 95 billion) in 2018/2019 to plan and commission NHS service for local patients ;10 ambulance trusts;60 mental health trusts; and 152 acute hospital trusts.

Wholesale medical supplies in UK: [6]

- ❖ Large central UK distribution facility
- ❖ High-quality medicinal products
- ❖ Long shelf life on test kits

LIFE CYCLE OF MEDICAL DEVICES: [7]

There are a number of different product development lifecycles used to design and develop medical devices with development usually containing the following steps: specification, design, development, testing manufacturing and subsequent to regulatory approval, product launch and post-market monitoring.

It is possible for medical device manufacturers to apply a variety of security development lifecycle. For example, the British standards Institution (BSI) recommends that manufactures consider following the good practices outlined in security standards developed for industrial automation and control system security; IEC 62443-4-1: product development requirements and IEC 62443-4-2: Technical security requirements. Basic safety standards for functional safety, utilized across other domains, now address cyber security throughout system lifecycles and recommend approaches to secure products, systems and networks. The lifecycle of medical devices includes two steps one is premarket and another one is post market in the premarket prototype, classification, clinical evaluation, competent authority, CE marking and in the post market post market survilienace, post – market clinical follow up. The lifecycle of medical device shown in Figure: 1

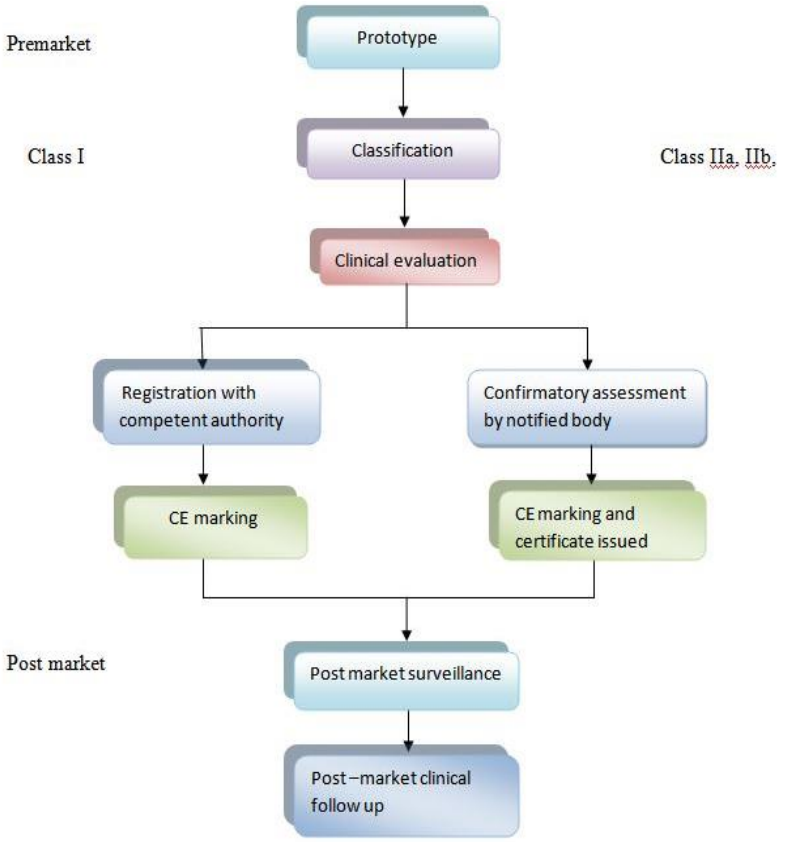

Figure: 1 Lifecycle of Medical Devices

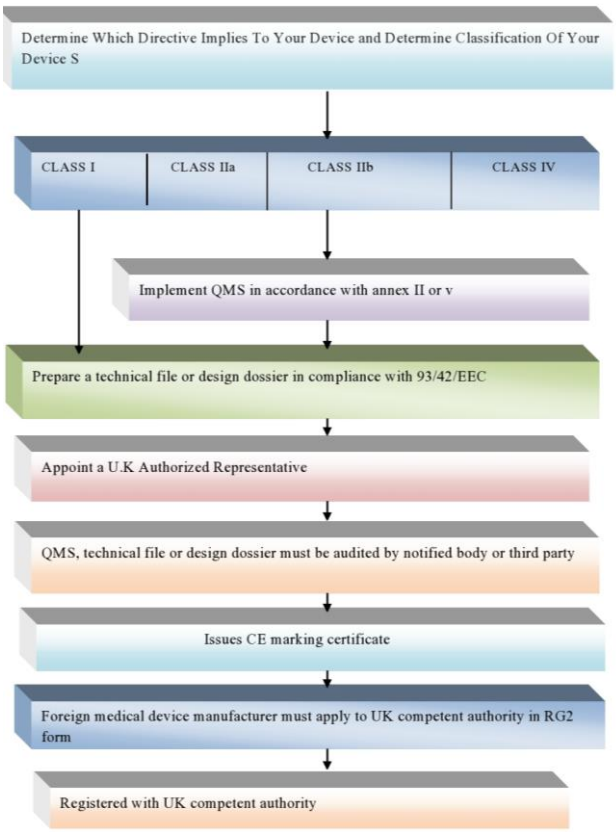

Figure: 2 Registration Processes of Medical Devices in U.K [14 15]

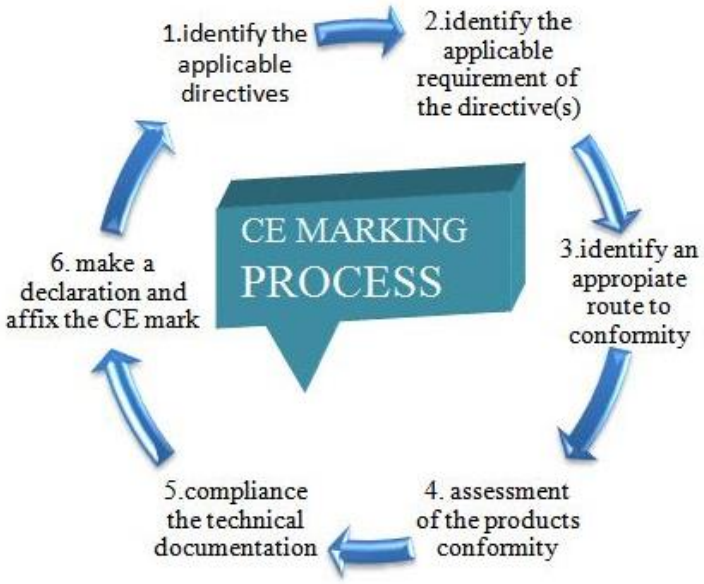

Figure: 3 The CE Marking Process [16]

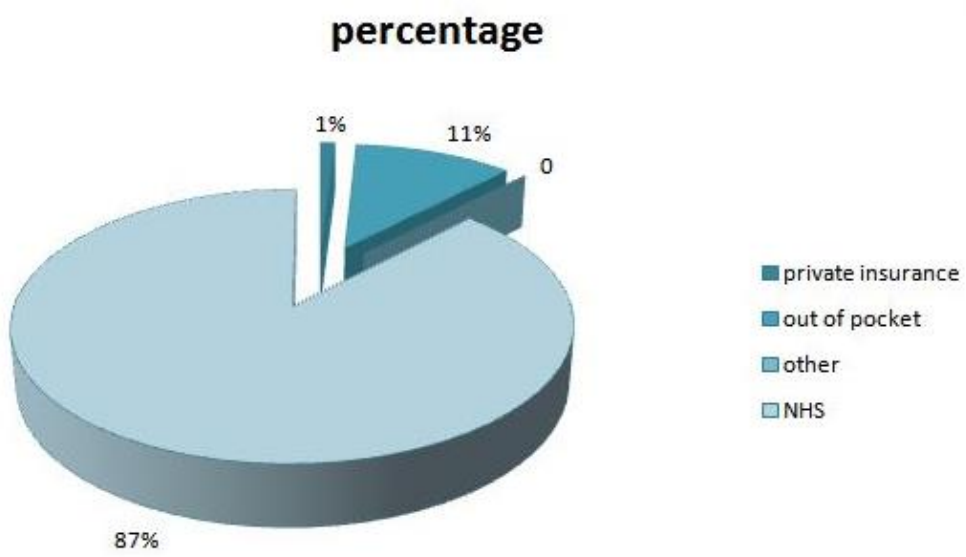

Figure 4: Sources of Funding Healthcare in U.K

1.8.2 MHRA CLASSIFICATION OF GENERAL MEDICAL DEVICES:

Likewise, the MHRA [8] has classified medical devices in to three groups

1. General medical devices
2. AIMD
3. In vitro diagnostic medical devices, the table1 has shown in below:

Table: 1 Classification of Medical Devices

CLASSES OF DEVICE	RISK LEVELS	REQUIREMENTS	EXAMPLES
Class I	Low risk	Premarket notification	Dressings
Class II a	Low –medium risk	Certification by notified body	x-ray film
Class II b	Medium-high risk	Certification by notified body	Blood bags, contact lens care products
Class III	High risk	Certification by notified body	Bone cement, cardiac stents.

Table: 2 Regulations of Medical Devices in UK

S.NO	REQUIREMENTS	U. K
1)	Regulatory body	The Medicines and Healthcare Products Regulatory Agency (MHRA)
2)	Regulations	Directive 93/42/EEC (The general medical devices), medical device regulations (MDD)
3)	Definition of medical devices	Article 1.2 of directive 93/42/EEC (The general medical devices)
4)	Classification	According with the Annex II, III, IV, V, VI, VII of these MDD based on risk level class I, IIb, IIa, III
5)	Regulatory requirements	UK authorized agent
6)	Types of submission	Understanding the UK regulatory process Obtaining CE mark
7)	Device application	Submission to obtain CE mark Registration certificate submission RG2 form Headed designation letter
8)	Documents required	RG2 form CE marking certificate Technical file
9)	QMS	ISO 13485:2003
10)	Certifications	CE marking certificate, registration certificate.

THE REGULATION OF MEDICAL DEVICES IN UNITED KINGDOM

The system by which medical devices are CE marked for use, introduced and monitored is set out in the medical device Directives of the European Union (EU): a complex system of legislation which is currently undergoing major revision [9] There are three directives relating to the following: active implantable devices (e.g. cardiac pacemakers) (90/385/EC), most other medical devices (93/42/EC) and in vitro diagnostics (used on substances produced by the body) (98/79/EC).

If you are a manufacturer based in the UK and you intend to supply medical devices in the UK or Europe, then you need to be aware of the following regulations

- The medical device regulations 2002 (SI 2002 No 618, as amended)
- The general product safety regulations 2005 (SI 2005 No 1803)

Regulation 2017/745 on medical device and regulation 2017/746 on in-vitro diagnostic. Devices are officially published in the official journals of the European Union on 5th may 2017.The MDR and IVDR constitute a consequential development and strengthening of the existing regulatory system of medical devices in Europe and will replace the original directives which have been in place for over 25 years.

The MHRA is the UK national competent authority and is the authority legally delegated by the European Commission to regulate the medical devices. These are currently regulated under three separate EU directives on medical devices (93/42/EEC), active implantable medical devices (90/385/EEC) and in vitro diagnostic medical devices (98/79/EEC), all of which are undergoing revision as regulations [10].

The competent authority's main roles concerning medical devices are to designate and audit notified bodies (organizations accredited by member states to assess medical device),ensure that manufacturers comply with the regulations, issue guidance on particular medical devices, evaluate adverse incident reports, and approve clinical investigations of marked devices not marked with the 'Conformite Europeenne (CE) mark.

These regulations are safety regulations under the consumer protection act 1987 and as such, the MHRA can investigate any business activity that is covered by these regulations in accordance with the consumer rights Act 2015[11].

If you are a manufacturer based in the UK and you intended to supply medical devices in the UK or Europe then you need to be aware of the following regulations: The regulation of medical devices in UK as shown in below Table: 2

- The medical devices regulations 2002(SI 2022 No 618, as amended)
- The general product safety regulations 2005(SI 2005 No 18)

MEDICAL DEVICE REGISTRATION IN UNITED KINGDOM

Definition: A medical device is any apparatus, software, material, or other article whether used alone or in combination, including the software intended by the manufacturer to be used specifically for diagnostic and/or therapeutic purpose and

necessary intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment, or alleviation of disease.
- Diagnosis, monitoring, treatment, alleviation, or compensation for an injury or handicap.
- Investigation, replacement, or modification of the anatomy or of a physiological process; [12].

Examples ranges from simple devices such as Tongue depressors, medical thermometers, and disposable gloves to advanced devices such as computers which assist in the conduct of medical testing, implants, and prostheses [13].

To market within the UK, a medical device must have rational CE marking. A CE mark is a sign of confirmatory with the European Union's medical device regulations allows the medical devices to be marketed within the European Union. A CE mark is valid up to 5 years. The timeline for the medical device registration process can vary depending on the class of the device. For class I devices the registration process typically does not make more than one week. for higher classes, the timeline is dependent on product type and contract with notified body. The registration process shown in the Fig 2.

REQUIREMENTS FOR THE COMMON SUBMISSION FORMAT FOR THE REGISTRATION OF MEDICAL DEVICES IN UK

1) CE MARKING: Notified body is required for the registration of class IIa and class IIb medical devices in U K.

2) FORM RG2 FOR GENERAL MEDICAL DEVICES: For the registration of medical devices manufacturer should apply in FORM RG2 "general medical devices.

3) HEADED DESIGNATION LETTER:

The letter should state the full name and address of the AR and that they are the designated EU authorized representative based within the UK, under the Medical Devices Directive 93/42EC.

4) HEADED CANCELLATION/TERMINATION LETTER:

In the case of an overseas manufacturer employing a new AR, the MHRA will require a copy of the letter from the overseas manufacturer, to be old AR terminating their services, and the date the service or contact is due to end.

5) CHANGE OF COMPANY NAME:

We can establish whether the allocation of a new registration number is appropriate any registration where there has been change of company name, including becoming a limited company, will need confirmation in writing starting whether there has been or has not been a change in the legal entity of the business e.g. enough changes to the operations or structure of the company, as to be wholly different to the previous registration.

What is CE marking?

CE marking is the medical device manufacture's claim that a product meets the essential requirements of all relevant European medical device directives. The directive outlines the safety and performance requirements for medical devices in the European Union (EU). The CE marking process shown in figure 3

THE EUROPEAN CE MEDICAL DEVICE APPROVAL PROCESS:[17]

STEP1:

Determine which EU medical device directive applies to your device 93/42/EEC-Medical device directive (MDD) or 90/385/EEC –Active implantable medical device directive (AAMD).

STEP 2:

Determine classification of your device using Annex IX of the medical devices directive (MDD): Class I (non-sterile, non-measuring),Class I (sterile, measuring),Class IIa,Class IIb, Class III/AIMD.Active implantable medical device are typically subject to the same regulatory requirements as Class III devices.

STEP 3:

For all devices except class I (non-sterile, on-measuring), implement Quality management system (QMS) in accordance with Annex II or V of the MDD. Most companies apply the ISO 13485 standard to achieve QMS compliance. For Class I (non-sterile, on-measuring), a QMS is not formally required. PMS procedure is required, though not audited by a notified body (NB).

STEP 4:

For classes I through IIb, prepare a technical file that provides detailed information on your medical device, and demonstrates compliance with 93/42/EEC. All devices require will require clinical data. Most of these data should refer to the subject device. For Class III/AIMD devices, prepare a design dossier. Clinical studies are required for class II b and III implants, through existing clinical data may be acceptable. clinical trials in Europe must be approved by a European competent authority.

STEP 5:

If you do not have a location in Europe, appoint an Authorized Representative (EC Rep). Located in Europe. The EC Representative should be qualified to handle regulatory issues. Place EC REP name and address on instructions for use, outer packaging, or device label.

STEP 6:

For all devices except class I(non-sterile, on-measuring),your QMS and Technical file or design

dossier must be audited by a notified body , a third party accredited by European authorities to audit medical device companies and products.

STEP 7:

For all devices except class I(non-sterile, on-measuring),you will be issued a European CE marking certificate for your device and an ISO 13485 certificate for your facility following successful completion of your notified body audit.ISO 13485 certification must be renewed every year.CE marking certificates are typically valid for 3 years.

STEP 8:

Prepare a Declaration of Confirmatory, a legally binding document prepared by the manufacturer stating that the device is in compliance with the applicable Directive. You may now affix the CE marking.

STEP 9:

All class I devices must be registered with the competent authority where you or your EC REP is based. Some EU member's states require additional registration of class IIa, IIb, or III devices that are placed on their markets.

STEP 10:

For class I(non-sterile, on-measuring),annual NB audits are not required. However, you must perform CER updates and PMS activities. For all other classes, you will be audited each year by a notified body to ensure ongoing compliance with 93/42/EEC or 90/385/EEC. Failure to pass the audit will invalidate your CE marking certificate .you must perform CER updated and PMS activities.

INVITRO DIAGNOSTICS MEDICAL DEVICES:

In vitro diagnostics medical device means any medical device which is a reagent, reagent product, calibrator, control material, kit instrument, apparatus, and piece of equipment, software 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 tissues donations, rived from the human body .

FOUR CATEGORIES OF IVDs: [18]

These categories are, in order of increasing perceived risk:

- General IVDs, i.e. all IVDs other than covered by Annex II and IVDs for self-testing as blood gas analyzers', therapeutic monitoring reagents and tissue processors.
- IVDs for self - testing (a device intended by the manufacture to be able to be used by lay persons in a home environment excluding self-test devices covered in Annex II.
- IVDs in Annex II list B of the directive: which, amongst others, includes reagents products for rubella, toxoplasmosis and phenylketonuria as well as devices for self-testing for blood sugar.
- IVDs in Annex II list A of the directive :which includes reagents and products for HIV I and II ,Hepatitis B,C and D,and reagent products for determining ABO systems and anti-cell including those used to test donated blood plus tests for screening CJD.

THE OVERVIEW OF MEDICAL DEVICE INDUSTRY AND HEALTHCARE STATISTICS IN U.K

United Kingdom medical device industry: The UK medical device market is the third largest in Europe, beyond Germany and France, and the sixth largest in the world. It was valued at $9.5 billion in 2015.In 2015; there were approximately 3000 medical manufacturers in UK. The UK manufacturers lie in Orthopedic but also in imaging, diagnostics, and cardiovascular devices [19]. The UK comprises England, Scotland, Wales and Northern Ireland. Since 1998, a process of devolution has given decision – making powers over healthcare provision and purchasing medical technologies to the developed governments of Scotland, Wales and united Ireland. Hence the healthcare systems in these parts of the UK have developed differences over the past 10+ years [20].

The department of health (DOH) registers products, whereas the 'National Health Service 'assesses and buys the vast majority of medical devices in the UK. The NHS is a department of the governments DOH – the NHS is funded from general taxation (76%), national insurance contributions (15%) and user chargers (5%).Other sources of funding come from private health insurance (1%), out of pocket payments (11%) and other sources such as charitable donations, etc (<1%) it is shown in the fig :4

CONCLUSION:

The overview of regulatory requirements and registration process of medical devices of U.K has their own requirements and regulations that allow them to maintain a level of control over their medical devices effectively and efficiently. The controversy for companies developing and producing medical device is to update on the regulatory requirement and implement them in the process. Regulation of these devices has also advanced due to the requirement for a steady regulatory perspective. To reduce these errors, designers need to follow a human factors engineering approach to address the true user needs for device operation and, through regular device evaluation throughout the design process, to ensure that these needs are

encompassed in to the device design in an economical fashion.

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