Universidade de Lisboa

Faculdade de Farmácia

A Comparative Analysis of the 'Drug-Device Combination' Regulatory Aspects in the Europe Union, USA and Africa

Chidiebere Victory Diarachukwu

Dissertation supervised by Professor Ana Francisca de Campos Simão Bettencourt

Master in Regulation and Evaluation of Medicines and Health Products

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ABSTRACT

There has been an increase in the use of drug-device combinations, especially with the recent rise in health technology innovations, because of the increasing need for precise drug targeting, local administration and individualized therapy. These combinations are especially beneficial for patients suffering from life threatening diseases such as: multiple sclerosis, cancer, congenital malformations, diabetes and many more. This increasing complexity in health technology has led to even greater complexities in the regulatory requirements and because of this there is need to compare the regulation of these unique health technology across the globe to drive process development and then drive their early access to patients who need them, foster innovation and reduce duplication of work.

This thesis aims to compare how drug-device combinations are regulated across several regulatory agencies in the European Union (EU), the USA and Africa. This research was carried out by collecting data through the consulting different regulatory agencies and data search engines. Analysis of data collected resulted in a discovery of various ways through which the regulation of drug-device combinations can be improved across the different regulatory agencies involved

In the EU, the combination is regulated as either a drug or a device depending on their primary mode of action (PMOA), while ensuring that the other part conforms with regulatory standards, in the USA, the FDA assigns a center to handle their regulation depending on the PMOA, the assigned center consults other centers when and if need be. In Africa, there are a number of regulatory bodies, thus the regulation is less standardized. While some regulatory bodies regulate the different parts separately, regardless of the PMOA, some other regulate depending on the perceived PMOA of the combination product.

To exemplify the different regulatory pathways two case studies were discussed: Spermicide condom and Fe-doped brushite. This thesis analyzed the two drug-device combination products, detailing how they are regulated in the regions studied. Both are products that may pose unique regulatory challenges, being that it may be difficult to ascertain the exact PMOA and may be regulated, depending on the region on a case-by-case basis.

Findings made indicate that the different regulatory bodies across the different regions have different methods through which to regulate drug-device combination process and if we adopt a particular method across the different regions, then there would be the possibility of harmonizing the regulations to the point where a single marketing authorization issued by any of the regions would be all that is required to place the product in the market in these regions. This will reduce the burden of regulatory processes, save time and resources and lead to earlier access to the patients who are in need of them.

Keywords: regulation, drug-device combinations, innovation, process development, harmonization.

Declaration: I hereby declare that I have developed and written this work in strict accordance with the University of Lisbon's Code of Conduct and Good Practices. In particular, I declare that I have not engaged in any of the varieties of academic fraud which I hereby declare I am aware of, and I have followed the required referencing of phrases, extracts, images and other forms of intellectual work, fully assuming the responsibilities of authorship".

ACKNOWLEDGEMENT

I dedicate this work to the people who have supported me and held my hands throughout this journey.

Firstly, I would like to thank God for the strength and enablement. The road was long and tough to navigate through, but God saw me through, provided for me and has held my hands all through.

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Special appreciation also goes to my family: my parents, siblings, husband and daughter. Thanks for all the ideas and for pushing me not to give up. Thanks for the support, encouragement, provision and kind words, words fail me.

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ACRONYMS AND ABBREVIATIONS

AMA - African Medicines Agency
ANDA – Abbreviated New Drug Application.
BCS - Biopharmaceutics Classification System
BrC – Brushite Cement
BTIF - Bioequivalence Trial Information Form
CBER: Centre for Biologics Evaluation and Research
CDER: Centre for Drug Evaluation and Research
CDRH: Centre for Devices and Radiological Health
CE - Conformité Européenne
CECP – Clinical Evaluation Consultation Procedure
CHMP – Committee for Medicinal Products for Human Use
CMDh – Committee for Mutual recognition and Decentralized procedures for human medicines
CTD – Common Technical Document
DES – Drug-eluting stents
DOC - Declaration of Conformity
EAC - East African Community
EC - European Commission
ECOWAS - Economic Community of West African States
EDA – Egyptian Drug Authority
EEA – Euroean Economic Area
EMA – European Medicines Agency
EU - European Union
EUDAMED – European Database for Medical Devices
FAERS - FDA Adverse Event Reporting System
FDA – The US Food and Drug Administration
FDRC - Food and Drug Registration Committee
GHTF - Global Harmonization Task Force
GMP – Good Manufacturing Practices
IDDS – Implantable Drug Delivery Systems
IDE – Investigational Device Exemption
IGAD - Intergovernmental Authority on Development
IMDRF - International Medical Device Regulators Forum
IND – Investigational New Drug
IRB – Institutional Review Board
IVD – *In vitro* diagnostic devices
MA – Marketing Authorization
MCC - Medicines Control Council
MDD – Medical Devices Directive
MDR – Medical Devices Regulation
MRP – Mutual Recognition Procedure
NAFDAC - National Agency for Food and Drugs Administration and Control
NAPAMS - NAFDAC Automated Product Management and Monitoring System
NCO – Non-clinical Overview
NDA – New Drug Application

NMRA - National Medicines Regulatory Authorities
NOAELs – No-observed-adverse-effect-levels
NODCAR - National Organization for Drug Control and Research
NMRA - National Medicines Regulatory Authorities
OCP – The Office of Combination Products.
PMA – Pre-Market Approval
PMOA – Principal Mode of Action
QMS: Quality Management System
RFD - Request for Designation
RLD – Reference Listed Drug
SA – South Africa
SADC - South African Development Community
SAHPRA - South African Health Products Regulatory Authority.
SCoRE - Summary of Critical Regulatory Elements
SmPC – Summary of Product Characteristics.
SUSAR – Suspected Unexpected Serious Adverse Reactions
TFDA - Tanzania Food and Drugs Authority
UDI – Unique Device Identification
USA – United States of America
WAHO - West African Health Organization.
WHO – World Health Organization

1. INTRODUCTION

Medical devices according to World Health Organization (WHO) can be "any instrument, apparatus, implement, machine, appliance, implant, or reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination for a medical purpose". (1). A medical device is any article, instrument, machine or apparatus that is used in the treatment, prevention or diagnosis of illnesses or diseases or for detecting, correcting, modifying or restoring the structure and function of the body for health purposes and do not typically carry out their action through immunological, pharmacological or metabolic means but which may be assisted in its function by such means (2).

Drug-Device combination products are therapeutic and/or diagnostic products that combine drugs and medical device as a single product. They could be a combination of small molecule drugs and a medical device or even the large molecule biologics with a medical device (3).

They vary vastly in complexity (ranging from simple combinations to more complex drug-eluting stents (DES) and their method of combination (being impregnated or surface coated) and routes of administration. There are limitless forms in which drug-device combinations could come. They, therefore, often would require a unique regulatory approach which may also, vary across different geographical areas (4). Implantable Drug Delivery Systems (IDDSs) for example are classified under different categories from pharmaceutical and regulatory perspectives, due to their novelty and variety. This prevents application of uniform regulation, not only across regulatory bodies, but also, across different IDDSs (5).

Even though they are combination products, there is usually disagreement as to whether they should be registered as drugs, medical devices or combination products. Regulatory pathways exist for each component, independent of one another, but their regulatory pathway when brought together as a single product is less formalized.

Some types of drug-device combinations include:

i. Convenience kit or co-package: The drug or biologic and device component are provided individually as separate parts, but within the same package. E.g: empty syringes packaged together with drug or biologic (Figure 1).

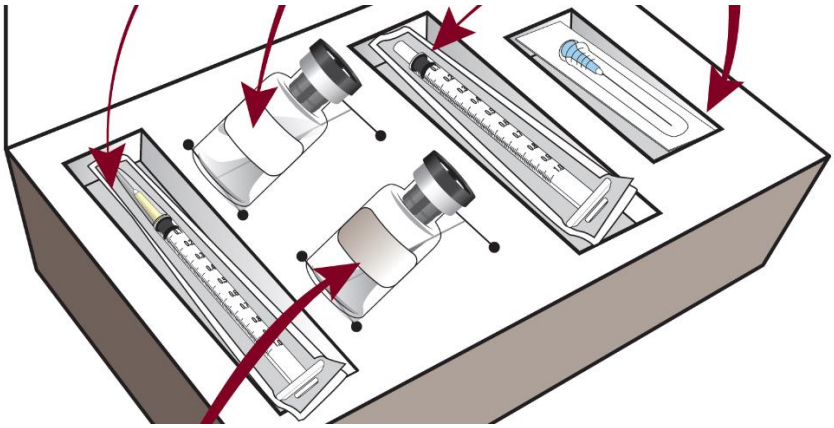

Figure 1: Illustration of empty syringes packaged together with drug or biologic (6).

ii. Pre-filled drug delivery device: The drug is filled into or otherwise combined with the device and the sole purpose is to deliver drug. E.g: auto-injectors, metered dose inhalers, nasal sprays.

iii. Pre-filled biologic delivery device: The biologic is filled into or otherwise combined with the device and the sole purpose is to deliver the biologic product. E.g: vaccines in pre-filled syringes, transdermal systems.

iv. Device coated, impregnated or otherwise combined with drug or biologic: the device here has additional function asides delivering the drug or biologic. E.g:

contact lens coated with drugs, live cells seeded in or on a device scaffold (Figure 2).

Figure 2: The INVOCELL culture device (7).

v. Separate products requiring cross-labelling like light activated drugs or biologics that are not co-packaged with device but labelled for use with a specific light source device.

vi. Possible combinations based cross labelling of separate products like drugs or biologics that use a particular device, while under development, but it is still unclear whether the final product will require the two to be cross-labelled.

vii. Drug-device-biologic products (8).

There has been an increase in the use of drug-device combinations, especially with the recent rise in health technology innovations, because of the increasing need for precise drug targeting, local administration and individualized therapy. There has also been an increase in scientific advice requests and marketing authorization applications in EU (9), USA and across the globe in general. This is because these combinations have been found to be very beneficial in patients undergoing regular, long-term drug therapy. It reduces the burden both on the patients and the entire healthcare system. For example, drug-eluting stents (Figure 3), which are small mesh tubes coated with medication (10), help

to lower plaque buildup in arteries are increasingly replacing bare-metal stents because they have the advantage reducing the probability of the arteries narrowing again. They also have the advantage of being less invasive, thereby reducing recovery time, in comparison to coronary artery bypass surgery (11).

Figure 3: Drug-eluting stents (12).

These combinations are especially beneficial for patients suffering from life threatening diseases such as: multiple sclerosis, cancer, congenital malformations, diabetes and many more (3). This increasing complexity in health technology has led to even greater complexities in the regulatory requirements and because these combinations contain two products that are regulated under different types of regulatory authorities, they can raise regulatory and policy challenges. Differences in regulating the different components impacts regulatory processes for all aspects of product development, including pre-clinical testing, clinical investigation, marketing applications, manufacturing, quality control, adverse effect monitoring, promotion and advertising, and post-marketing surveillance (13).

There is need for harmonization of regulatory processes for drug-device combination products in order to allow for early access to products, favorable marketing conditions, promotion of competition and reduction of unnecessary duplication, thereby fostering innovation.

2. AIMS AND RELEVANCE OF THE STUDY

Analysis indicates that the largest barrier to introducing a new kind of combination product is the determination of the regulatory centre that is to oversee its approval (4). This thesis, therefore, aims to compare the processes involved in the regulation of these types of products in the EU, USA and Africa which is important to drive process change and development.

2.1. Main objective

The main objective of the thesis is to compare the regulatory requirements and procedures involved with the registration of drug/medical device combinations in Europe, the United States of America and Africa.

To achieve the above main objective, the following it was necessary to follow these steps:

1. Literature and state-of-the-art review
2. Description and comparison of drug-device combination products in Europe, the United States of America and Africa.
3. Case study analysis
4. Proposal of amendments to the regulatory processes of the different regions

2.2. Methods

1. Data collection through computing keywords on:

- Search engines such as Pubmed or Mendeley
- Regulatory agencies; and
- Relevant associations (e.g: WHO, European Commission (EC)).

2. Interviewing people associated with relevant regulatory authorities.

Inclusion criteria: Information in English and Portuguese and mostly from 2019.

Exclusion criteria: Information from published articles or webpages over 11 years old. This exclusion criteria was chosen because I found a very helpful article on the use of spermicides from 11 years ago.

3. EUROPEAN UNION

3.1. REGULATION OF MEDICINES

The system of regulation of medicines in the EU is one that is unique, based on an integrated, closely coordinated regulatory network of National Competent Authorities (NCAs) in the member states of the European Economic Area (EEA) working together with the European Medicines Agency (EMA) and EC (14).

The EU-developed a harmonized system of laws regarding the authorization and safety supervision of medicines applies to its 27 member states plus 3 European Economic Area (EEA) countries, including Iceland, Liechtenstein and Norway(15). This regulatory system for medicines has many advantages to it including: the consistency of standards and use of best available expertise, better utilization of resources, harmonized scientific opinions, thereby improving patient's access to medicines. The EU has different procedures for the regulation of medicines depending on the kind of medicinal product: the centralized procedure, the mutual recognition procedure and the decentralized procedure; and the national procedure (15).

The Centralized Procedure

The centralized procedure falls under the Regulation (EC) 726/2004 (16) and allows the manufacturers to market the medicines throughout the EU to the patients and healthcare professionals after approval by the European Commission (EC) (16).

Advanced therapy medicinal products (gene therapy, somatic cell therapy and tissue-engineered products), orphan medicinal products and products for treatment of auto-immune diseases and other immune dysfunctions, viral infections, cancer, neurodegenerative disorders, diabetes are all regulated under the EU centralized

procedure (Figure 4). However, for some products, regulation under the centralized procedure is optional, for example: new active substances that do not fall under one of the compulsory classes, products that involve significant therapeutic, scientific and/or technical innovation and products for which it is in the best interest of the patients at the community level to be regulated through the centralized procedure (17).

The centralized procedure involves a single decision by the European Commission (EC), hence, a single marketing authorization valid in all member states. The European Medicines Agency (EMA) assesses the benefits and risks of a medicinal product and makes recommendations to the EC which then takes the decision on whether the product can be marketed in the EU. The decision is issued within 67 days of EMA's recommendation (18).

The EMA is responsible for the scientific evaluation of applications for the marketing authorization and providing scientific advice. The EMA has several Committees that handles pharmacovigilance and risk assessment and the scientific evaluation of the different classes of medicinal products including paediatric, herbal, orphan, veterinary, advanced therapy and other human medicinal products; and Working Groups consisting of working parties that oversee quality and safety assessment, scientific advice, quality review of documents, Summary of Product Characteristics (SmPC) and others (19).

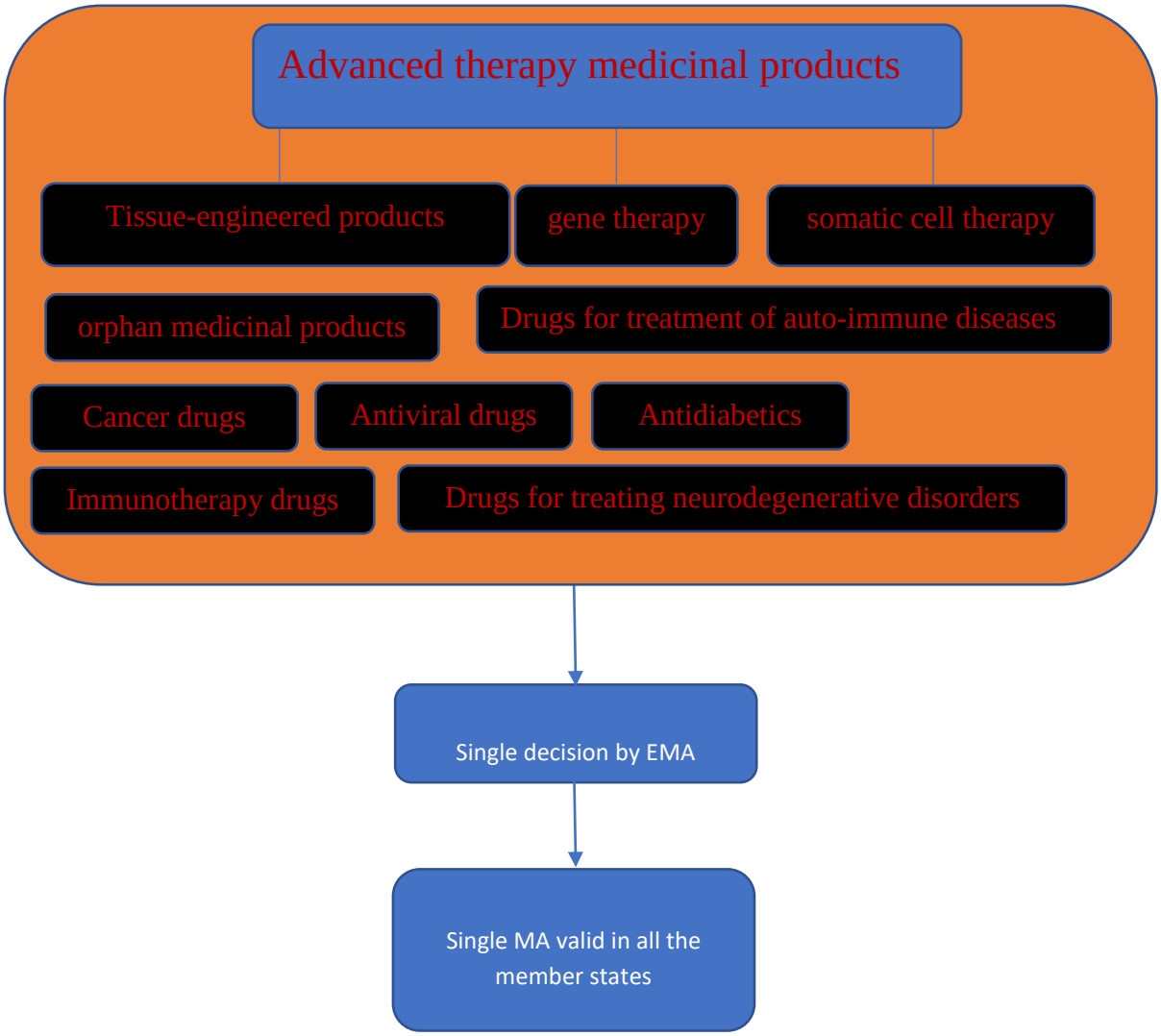

Figure 4: Centralized Procedure. MA, marketing authorization.

The Mutual Recognition Procedure (MRP) and the Decentralized Procedure

The regulation for this procedure (Figure 5) is established in Directive EU 2001/83/EC (20). The MRP involves the recognition of a pre-existing national marketing authorization by the concerned member states (20).

The decentralized procedure is similar to the mutual recognition procedure. The difference lies in the fact that it is applicable only for first time application for marketing authorization. It was introduced by directive 2004/27/EC (21) and is championed by the EMA (21), headed by an Executive Director and supervised by a Management Board.

Here, the company is allowed to submit application for marketing authorization in several member states simultaneously (the competent authorities of the reference member state and the concerned member states). After the approval of the draft assessment report, SmPC, labelling and patient information leaflet, as proposed by the reference member state, the other steps are identical to those of the mutual recognition procedure (20).

If there is disagreement on potential benefit-risk balance, based on submitted data between the reference member states and the concerned member states or between two concerned member states, the EMA's committee for mutual recognition and decentralized procedures for human medicines (CMDh) considers the issue and tries to reach an agreement in 60 days. If an agreement is not reached within that time frame, the reference member state will take the case to the Committee for Medicinal Products for Human Use (CHMP) for arbitration (20).

The National Procedure

This is applicable for manufacturers who want their product registered in only one member state. It is specifically for products that do not fall under the scope of centrally authorized products. Here, marketing authorization (MA) application is reviewed by the specific national competent authority of the member state where the MA is being applied for, following their own specific national procedure. After a national marketing authorization has been granted, the manufacturer can go ahead, if he so desires, to register the medicinal product in other member states, through the mutual recognition procedure (20).

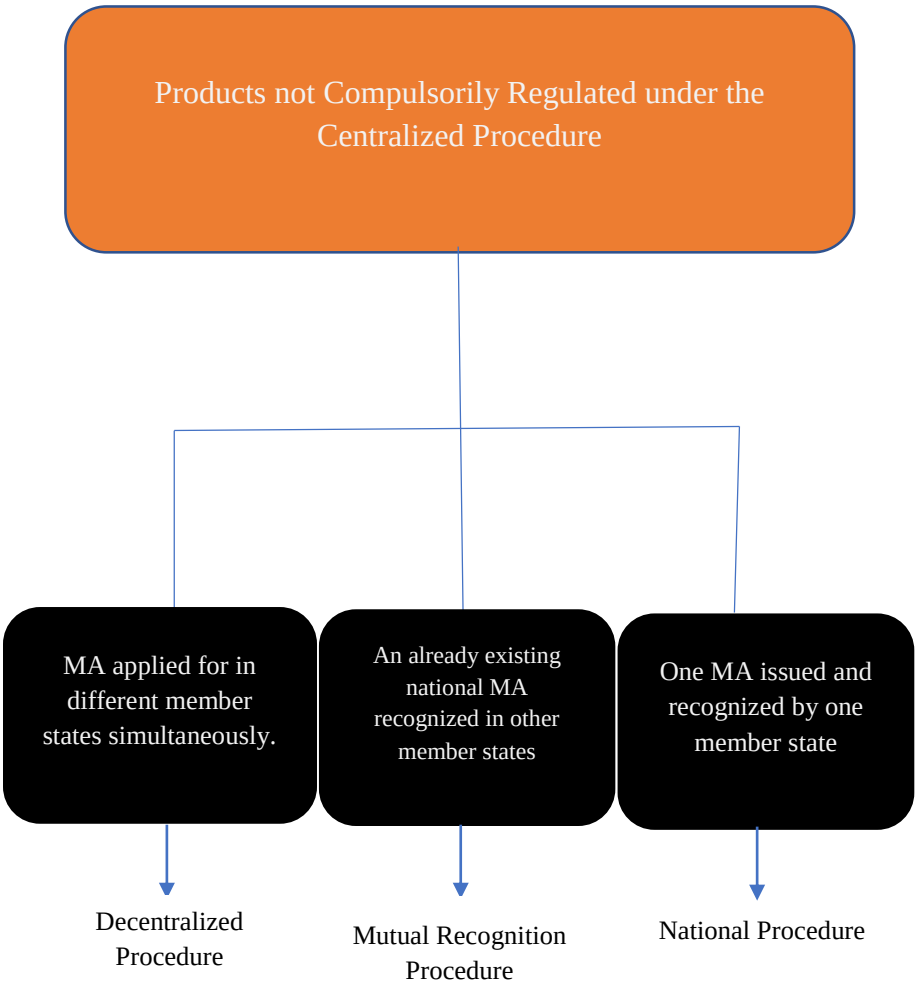

Figure 5: Procedure for products not compulsorily regulated under the centralized procedure.

The Comparison between the different procedures is listed in Table 1.

Table 1: Regulatory Procedures in the EU.

Regulatory Procedure	Differences	Kind of Products Regulated	Principal Regulatory Authority
Centralized	A single decision is made by EMA on the issuance of marketing authorization valid in all the member states.	Advanced therapy medicinal products, orphan medicinal products, products for treatment of auto-immune diseases and other immune dysfunctions, viral infections, cancer, neurodegenerative disorders, diabetes. Drugs with new active substance not belonging to the above class and drugs that involve significant innovation and drugs of which it is to the best interest of the patients to be regulated through the central procedure, may or may not be regulated through the central procedure.	EMA
Mutual Recognition Procedure	An already existing national marketing authorization is recognized in other member state	Drugs that do not fall into the category compulsorily regulated through the centralized procedure.	Reference member state's national regulatory authority
Decentralized	First time application for a marketing authorization is made simultaneously in more than one member state	Drugs that do not fall into the category compulsorily regulated through the centralized procedure.	National regulatory authority of the different member states
National procedure	Marketing authorization application is made in only one member state	Drugs that do not fall into the category compulsorily regulated through the centralized procedure.	The national regulatory authority of the member state where the marketing authorization application has been made.

3.2. REGULATION OF MEDICAL DEVICES

The Medical Devices Regulation (MDR (EU 2017/745) (19) applies since 26 May 2021. Before 2021, it was governed by the Medical Device Directive (MDD 93/42/EEC) (19) on medical devices and (MDD 90/385/EEC) (22) on active implantable medical devices (22). The new EU MDR focuses on a life-cycle approach rather than a pre-approval phase only approach by using a comprehensive Quality Management System (QMS). This is to ensure that products put on the market consistently deliver good quality, performance and safety (23).

Some of the major changes are related to the following:

1. The definition of medical device has now been expanded to include the following: products aimed at performing prediction and prognosis and products without any direct medical intent such software, cosmetic implants and sterilization products.
2. Reclassification of devices such as surgical meshes and spinal disc replacement implants to class III and increased assessment for *In vitro* diagnostic IVD medical devices.
3. More rigorous procedures for the assessment of class III devices by the notified bodies
4. Stricter designation of roles and requirements for the notified bodies to ensure they have the required capabilities and competencies.
5. Improved availability of clinical investigation data. The results of clinical investigations will be available on the European database for Medical devices (EUDAMED).

6. Improved traceability by Unique Device Identification (UDI) number and implant cards for certain implantable devices (24).

According to the EU MDR 2017/745 (22), medical devices are “products or equipment intended for a medical purpose (22). The medical purpose is usually achieved by physical means and not through metabolic or pharmacologic means”.

The *In Vitro* Diagnostic Devices (IVDs) Regulation EU 2017/746 (22) applies since 26 May 2022. It repeals Directive 98/79/EC (22) of the European Parliament and of the Council on in vitro diagnostic medical devices (22). This new regulation has brought improvement to several aspects of IVD regulation, including:

1. A broader and clearer IVD definition and classification system, now expanded to include software, prognostic and diagnostic devices and devices for near-patient testing designed for use for healthcare professionals outside the laboratory and also companion diagnostics, which are devices meant to be used in combination with a specific drug (25).
2. Augmentation to the criteria for the designation of notified bodies and their oversight procedures.
3. Stringent rules for manufacturers regarding compliance to ensure patient safety and strengthening of vigilance and post-marketing surveillance requirements (25).

Both medical devices and IVDs are regulated at the national level, but the EMA is also involved in the regulatory process, giving scientific advice and providing technical guidance.

The majority of medical devices and IVDs can only be put in the market after they have been Conformité Européenne (CE) marked. Examples that do not need to bear CE mark are custom-made devices, systems and procedure packs, medical devices for clinical

studies and IVD for performance studies(26) CE marking documents shows that it has passed the conformity assessment and that they meet the legal requirements of demonstrating safety and intended performance. The conformity assessment usually involves an audit of the manufacturer's quality system and where applicable, a review of technical documentation from the manufacturer on the safety and performance of the device. This conformity assessment is carried out by member state-appointed notified bodies. The notified bodies would require the opinion of specific expert panels before issuing a conformity certificate, for some specific high-risk devices such as class III implantable devices, class IIb active devices intended to administer or remove medicines from the body and class D *in vitro* diagnostic devices (22). These expert panels provide opinion on the notified body's assessment of the manufacturer's clinical file for class III implantable and class IIb active devices, this is called the Clinical Evaluation Consultation Procedure (CECP) (22). As of the 27th of February 2023, manufacturers of high-risk devices in the EU to take part in a Pilot run by the EMA that enables expert panels to provide scientific advice for these manufacturers. In some other cases, the notified bodies will seek scientific opinion from the EMA before issuing a conformity certificate (27).

3.3 REGULATION OF DRUG-DEVICE COMBINATION

As previously mentioned, (Chapter 1 – Introduction) drug-device combination products are products that combine a medicinal product with a medical device component and are intended to elicit therapeutic or diagnostic effects. Under the EU MDR, however, there is no formal legal definition for these kinds of products, there is only a description of the regulatory pathways for the different kinds of drug-device combinations (28). Due to the complexities associated with drug-device combinations, in terms of technology and innovation, these sorts of products would often require greater coordination and interaction between the various stakeholders (3). In the EU, the stakeholders involved include: the EMA, the national competent authorities (for the drug component) and the notified bodies designated by the European Commission for the device component.

In EU, drug-device combinations are often regulated either as a drug or as a medical device depending on its primary mode of action (Figure 6).

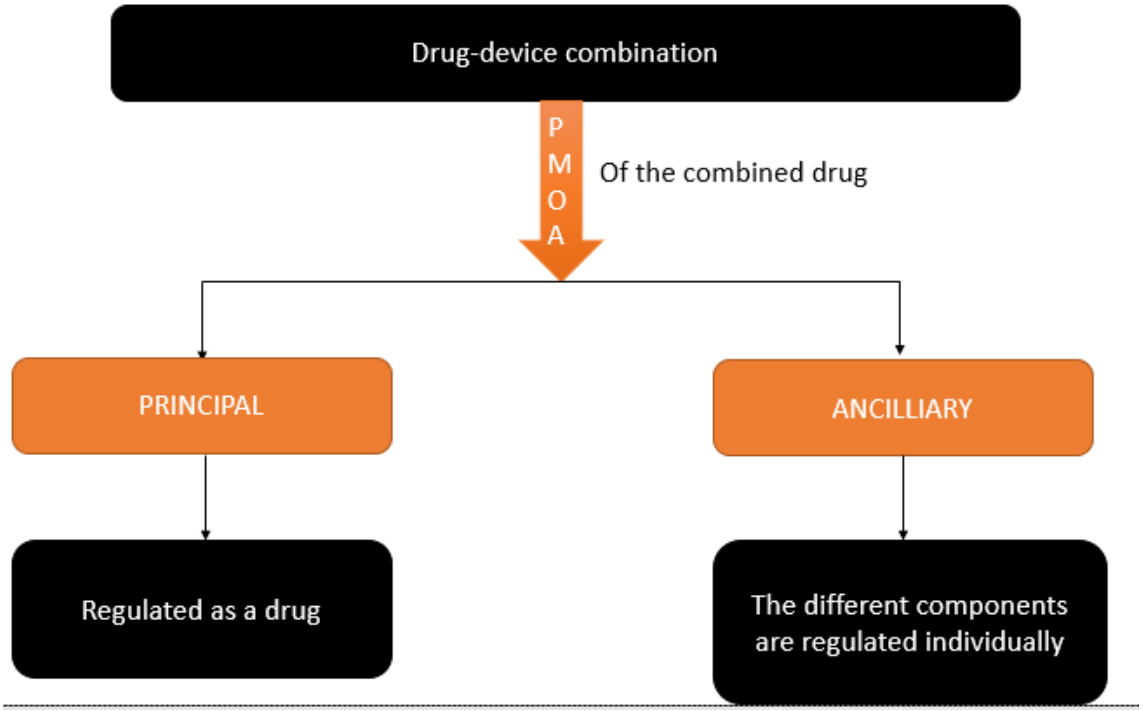

Figure 6: Regulation of Drug-Device Combinations based on principal mode of action.

For example, a drug-device combination in which the sole purpose of device component is to deliver the drug which will elicit the desired therapeutic effect of the drug-device combination, would be regulated as a drug under the pharmaceutical regulation Directive 2001/83/EC (28) or Regulation EC 726/2004 (28), while a drug-device combination, wherein the role of the drug component is ancillary, just providing support to the device component, would be regulated as a medical device. In these cases, the device component must be CE marked and a scientific opinion must be given by a medicines authority before a notified body can issue a certificate for the drug-device combination product (28).

According to MDR Articles 1(8) and 1(9), there are two types of drug-device combinations:

1. Drug-device combination product where the medical device incorporates the drug component and if the action of the drug component is principal, is regulated as a drug.
2. Drug-device combination products where the device is used to deliver the drug and placed in the market in such a way that they form a single integral product which is intended for use exclusively in the combination and not reusable. They are governed either by Directive 2001/83/EC (29) or Regulation EC 726/2004 (29) as applicable.

For IVDs to be used together with a drug product that falls under the scope of centrally authorized products, the EMA gives scientific advice on the suitability of the IVD with the drug. For medical devices that contain systemically-absorbed substances, the notified body seeks the scientific opinion of the national competent authority, while the EMA provides scientific opinions on the compliance of the systemically-absorbed substance to the requirements of directive 2001/83/EC-Annex I (22). Products for which it is not clear whether they are medicinal products or medical devices, hence uncertainty on which regulatory frame work applies called borderline products for example Gold implants used for the treatment of arthritis and arthrosis, which have recently been found to also exert systemic actions in the treatment, the notified body decides how to classify such products on a case-by-case basis depending on the products composition, mode of action and intended purpose, either as medicines or medical device, then they are regulated as such (30).

As a general principle, however, in any drug-device combination, the suitability of the device component for its intended use must always be assessed, taking into account the quality aspects and its combination with a particular medicinal product. The complexity of the device, relevant patient characteristics and clinical setting where the device is intended to be used also form a part of the regulatory process (31). The medicinal product dossier of such drugs that are intended to be combined with medical devices should include a full evaluation of the medical device in terms of: quality target profile, critical quality attributes and overall control strategy of the drug (32).

In drug-device combinations where the device component has no CE marking or is considered a high-risk device (sterile class I, measuring class I, class IIa, class IIb or class III medical device), there is need to obtain an opinion regarding the safety and performance from a notified body (according to MDR/745) (29). However, if the device component is already CE marked, then a declaration of conformity will be submitted alongside a copy of the CE certificate issued by the appropriate notified body (29).

Documentations needed to be obtained by the notified body opinion would include:

i. A general description of the device component, stating its intended purpose, intended users, intended patient population and the medical conditions to be diagnosed, treated or monitored with the device.
ii. A description of the accessories for the device component and other devices and products which do not constitute a part of the device but are meant to be used in combination with it.
iii. A description of the key functional parts of the device component
iv. A description of raw materials used in the manufacture of the key functional parts and those making direct or indirect contact with the body

v. Warnings and contraindications.

vi. Principles of operation and modes of action.

vii. Precise identity of the controlled documents offering evidence of conformity.

viii. A general safety and performance requirements checklist highlighting all the requirements that apply to the device component and an explanation as to why the others do not apply.

ix. A summary of methods used to demonstrate conformity with the General safety and performance requirements and a summary of results showing conformity.

x. Details on the methods adopted to meet the safety and performance requirements, including a verification and validation of the methods adapted to meet these requirements.

xi. Technical specifications such as features, dimensions and performance attributes, of the device component, including any variants, configurations and accessories that would typically appear on the product specification.

xii. Identification of harmonized standards, common specifications or other solutions applied to meet the applicable requirements.

xiii. Instructions for use, product and packaging insert (33).

Any change that could affect the intended use of a device or its safety and performance characteristics may cause a variation in the marketing authorization application requirement and might require additional notified body opinion (33).

The process of registering a drug-device combination in the EU is done in such a way that the device component is registered according to EU MDR, while the drug component

is registered with the competent authority or the EMA, depending on whether centralized or decentralized approaches are to be followed.

Quality Management System (QMS) for Drug-Device Combination in the EU

Under EU MDR, the QMS for the constituent parts of the combination are managed separately. Management of modifications to the device component is done according to MDR, while changes to the drug component is managed under the drug QMS The EU MDR has very specific expectations of the components to be safe, efficacious and usable (34).

EU Vigilance Surveillance Aspects of Drug-Device Combinations

For drug-device combinations regulated as drugs, the MDR vigilance requirements are not applicable, but it is recommended that the manufacturer incorporates all technical knowledge and processes into their quality management system, for easy access to information required to handle, evaluate and investigate aspects of the safety and quality of the drug-device combination when there are device-related complaints. There are however, no clear recommendations for the reporting of device complaints with potential impact on drug delivery (33).

For drug-device combinations regulated as drugs, the labelling and UDI requirements of the MDR are not applicable. Therefore, it is not required that a device component related UDI should be applied to the packaging or labelling. The labelling of these sort of drug-device combination products should be done according to the labelling requirements of medicinal products (33).

In general, however, regardless of the kind of drug-device combination, changes to an already approved drug-device combination are categorized based on risk to public

health and the impact on the drug component's quality, safety and efficacy and any changes to be made to the content of the marketing authorization application must be done in accordance with the EC regulation EU1234/2008 (35).

The EU regulation seeks as much as possible to adhere to the guidelines developed by the Global Harmonization Task Force (GHTF) for the regulation of medical devices and its follow-up initiative the International Medical Devices Regulators Forum, in order to promote global convergence of regulations and subsequently promote a higher level of safety and protection worldwide and accessibility. Especially, in the areas of common technical documentation, general safety and performance requirements, unique device identification (UDI), classification rules, conformity assessment procedures and clinical investigations (36).

The EMA MDR describes 3 different types of drug-device combinations:

Integral: here, the drug component and the medical device form a single product. Example: pre-filled syringes, nasal sprays

Co-packaged: the drug component and the medical device are separate but included in the same package. Example: oral administration device

Referenced: In this case, the manufacturer of the drug component refers to a medical device to be used with the drug but marketed separately from the drug (37).

4. THE UNITED STATES OF AMERICA

4.1. REGULATION OF MEDICINES

The regulation of medicines in the USA is done according to The Federal Food Drug and Cosmetic Act. The US Food and Drug Administration (FDA) oversees medicines regulation in the USA. The FDA is involved in all stages of drug lifecycle. The cycle which begins at the research and development stage, comprising of preclinical and clinical trials, wherein the FDA is in constant communication with the applicant, and also receiving updated information after each stage. However, the review process of the new drug application may not start until the application is fully submitted with the exception of drugs accepted under the rolling review status, wherein the application and review process can be carried out in sections (38).

Federal law in the US prohibits drugs without an approved marketing authorization application from being transported across state lines, with an exception made for drugs which their Investigational New Drug (IND) Application has been approved. This exception allows the IND to be distributed, without restriction across the different FDA centres (39).

Prior to the submission of an IND application, extensive pre-clinical studies must have been carried out on the drug, both *in vivo*, in test animals, and *in vitro*, to demonstrate enough safety and efficacy to warrant testing in humans (40). The IND application must contain information in these three main areas: 1. Animal Pharmacology and Toxicology Studies. 2. Manufacturing information. 3. Clinical protocols and investigator information The core non-clinical component of the IND application is the Non-Clinical Overview (NCO), which together with other supporting documents and study reports in the Common Technical Document (CTD), demonstrates, biological activity, disposition and

toxicology of the IND, from which the starting dose for clinical study is derived, based on the No-observed-adverse-effect-levels (NOAELs) in the most sensitive species (40). There are two types of INDs: those for commercial use and those for research purposes, and three pathways for filing their application: as an investigator IND, an emergency use IND or a treatment IND. The investigator IND application is submitted by a physician, who has initiated and conducted investigations on the new drug or an already approved drug for a new therapeutic indication or new patient population, for immediate administration or dispensing, under the direction and supervision of the physician.

The emergency use IND allows the FDA to authorize the use of a drug in an emergency situation that doesn't allow enough time for the IND application to be made in accordance to the regulation 21CFR, sec. 312.23 or sec. 312.20. It is used for patients who do not meet an existing study protocol criteria or if an approved study protocol does not exist.

The treatment IND application is submitted for drugs that have shown promise for serious or immediately life-threatening conditions while the final clinical work is concluded and reviewed by FDA (39).

In order to avoid issuance of suggestions, mandatory changes or clinical holds on the application, thereby saving time and effort, the FDA encourages investigators to seek early consultation with the appropriate new drug division before submitting a formal IND application. This consultation is done through the Pre-Investigational New Drug Application Consultation Program. In addition to this consultation program, the FDA also provides investigators with guidance documents that provide investigators with necessary data and materials for the IND application (38).

Phase 0 clinical trials represent the first-in-human exploratory trials and can be carried out while awaiting the review of the IND application. It is usually carried out in a very

small number of subjects, usually a cohort of 10-15 patents, with a dose level of less than one percent of the dose that has been shown to elicit a clinical effect and administration schedules not expected to show any toxicity. The duration of dosing is expected not to exceed one week. The phase 0 trial is carried out to determine if the drug engages the expected target in humans, thereby being likely to produce similar therapeutic effects as have been seen in the animal models. After the approval of an IND application, an investigator may then proceed to carry out Phase Ia, Ib, II and III clinical trials. After a successful completion of the phase III clinical trials, the drug sponsor can file a New Drug Application (NDA) with FDA, through its CDER (38).

In the USA, NDAs are approved by the FDA, through three different pathways: i. 505(b)(1) NDAs; ii. 505(b)(2) NDAs; and iii. 505(j) abbreviated NDAs (ANDAs). The pathway used in the approval of the drug would depend on the active ingredient, administration route, clinical indication, already approved products, drug formulation, and many other factors.

The 505(b)(1) NDA submission pathway is used for drugs that have been discovered and developed with sponsor-conducted studies. These are often new drug molecules that have not previously been registered in the US. The 505(b)(2) NDA submission pathway is for drugs that already have full and well-established safety and effectiveness report, including non-clinical information required for drug approval. Here, some of the information provided for the NDA approval come from studies not carried out by the applicant. This submission pathway was created to reduce unnecessary duplication of efforts and studies (41). This is a hybrid between the 505(b)(1) and the ANDA (42). Brand-named drugs can either be approved through a 505(b)(1) or a 505(b)(2).

The 505(j) ANDA does not contain clinical study, but are required to contain information demonstrating that the drug under review is bioequivalent to a Reference Listed Drug (RLD). This is the submission pathway for most generic drugs (43).

After the approval of an NDA by the FDA, the drug can be distributed across the US

Pharmacovigilance

Collection of safety data begins during preclinical studies and continues all the way through to the clinical settings. In the USA drug manufacturers are required by the FDA to carry out ongoing safety evaluations and periodically review and analyse their safety databases. This allows for early detection of potential public health threats. For suspected serious unexpected adverse reactions (SUSARs), the post-marketing safety reports must be expedited, but for non-serious or serious expected adverse effects, the post-marketing safety reports are filed quarterly after the first three years of approval and thereafter, filed annually. SUSARs are reported to the sponsors who then determine if the SUSAR is reasonably unexpected and then reports to the FDA, electronically through the FDA Adverse Event Reporting System (FAERS) database (44) within a specified time period: Within 15 days for domestic and foreign SUSARs and quarterly for the first 3 years, then annually for serious and expected, non-serious and unexpected and non-serious and expected adverse events (45). The manufacturers are also required to examine reports and literature from other countries. Adverse events can be reported by patients directly to manufacturers or health care providers through direct submission registries. Reporting to national registries is compulsory for the manufacturers, but voluntary for healthcare professionals (44).

4.2. REGULATION OF MEDICAL DEVICES

Device regulation by the FDA only began in 1976 after it was discovered that faulty devices could lead hundreds and thousands of deaths and injuries. This led to the enactment of the Medical Device Amendments Act, the same year, by the congress (46). The US FDA through its Centre for Devices and Radiological Health (CDRH) is the institution responsible for regulating medical devices in the USA (47). Medical devices are regulated based on the potential risk they pose and are classified as such into class I, II and III, with class I being associated with the lowest risk and class III, with the highest risk, with corresponding rigor of regulatory process. Class I devices are subject to General Controls (simple compliance to manufacturing guidelines). Class II devices are subject to additional special controls (special labelling, performance standards and post marketing surveillance). Class III devices are subject to the most rigorous regulatory process and require a pre-market approval (PMA) (46).

All medical device manufacturers and distributors must register their organization with the FDA and verify registration information yearly (Table 2). Foreign manufacturers that wish to market their device in the US must have a US agent. The details of the agent must be submitted electronically on the FDA Unified Registration and Listing System (FURLS System) and will undergo an automated process to that they consent to be an agent to that establishment. The duty of this agent is to: assist FDA in communications with the foreign manufacturer, respond to questions concerning the manufacturer's devices to be marketed in the US, assist FDA in scheduling appointments for the inspection of the foreign establishment, receiving information and documents from FDA on behalf of the foreign manufacturer in any case the FDA is unable to contact them directly (48).

Some class I and class II medical devices which are exempted from PMA application, require premarket notification (510(k)) submission (49) and as such, cannot be distributed in the USA without authorization from FDA in the form of a clearance order (Table 2). Which is a letter specifying that the device is Substantially Equivalent (SE), safe and as effective as existing legally marketed devices. For a device to be marked as substantially equivalent to another one, manufacturer must demonstrate equivalence to an already existing legally marketed device called a Predicate. The equivalence is usually demonstrated in terms of proposed use, safety, effectiveness and other standards such as: biocompatibility, manufacturing process, labelling, energy consumed or delivered and many other applicable standards. A device will be marked as substantially equivalent to another device if it has the same proposed use with the same technological features as the predicate or if it has the same proposed use with different technological features but doesn't raise different questions of safety and effectiveness and the information provided by the supplier is sufficient enough to validate that the device is at least as safe and as effective as the already existing legally marketed medical device (50).

The premarket approval application is to be submitted by manufacturers of class III devices and devices that cannot be substantially classified as a class I or class II or for class II devices where substantial equivalence cannot be demonstrated due to lack of a suitable predicate or FDA's rejection of the 510(k) submission. (Table 2). This is subject to approval or rejection by the FDA, based on risk evaluation. Devices for which a Pre-marketing approval application has been submitted must receive FDA approval in the form of a private license before the onset of any kind of marketing activity. After the FDA has granted their approval or rejection, information is published on their website providing the data on which their decision was based allowing the interested parties the opportunity to petition FDA within 30 days for reconsideration of their decision.

Investigational new devices can be used pre-approval to gather evidence of safety and effectiveness. It allows the manufacturers to lawfully use the device for clinical study without forcing all the FDA requirements required for device commercialization. Through the Investigational Device Exemption (IDE), results from the IDE studies are used to support Pre-Market Approval Applications. For investigational devices associated with significant risk, all the clinical studies carried out must be approved by FDA and reviewed by the Institutional Review Board (IRB). While studies on the devices associated with less risk are approved only by the IRB (51).

The quality system of the FDA according to Regulation 21 CFR Part 820 specifies the regulatory requirements in terms of methods, facilities and controls to be used for the entire lifecycle of the device (51, 52) in other for manufacturers to produce devices that consistently meet the safety and efficacy requirements and that have consistent specifications.

The labelling of devices is done according to FDA's 21 CFR Part 801. It includes specifications for general device labelling, use of symbols, labelling of *in vitro* products, general electrical products and investigational devices, unique device identification and good manufacturing practices (51).

For early detection and correction of problems leading to adverse events associated with the use of a device, the device manufacturer must report to the FDA if the use of the device has just led to death or serious injury or the device has just developed some serious malfunction that may lead to death or serious injury (51, 53).This report is done using the form 3500A. Importers must report to the FDA and the manufacturer in case of death or serious injury and only to the manufacturer in case of only serious injury. Healthcare facilities must report to FDA and manufacturers if they suspect that the defects in a

particular device could potentially lead to injury or death and may on their own volition, through MedWatch, report to the FDA of any malfunction to devices (51).

Table 2: Medical device regulation in the US and the classes of devices to which they apply.

Regulation	Device class
Establishment Registration and Medical Device Listing (21 CFR Part 807)	All medical devices
Premarket Notification 510(k) (21 CFR Part 807 subpart E)	Some medical devices exempted from pre-market approval
Premarket Approval (21 CFR Part 812)	Class III devices, devices that cannot be substantially classified as a class I or class II and class II devices for which substantial equivalence cannot be demonstrated
Investigational Device Exemption (21 CFR Part 812)	Applies to every class of medical devices
Quality System Regulation (21 CFR Part 820)	Applies to every class of medical devices
Labelling (21 CFR Part 801)	Applies to every class of medical devices
Medical Device Reporting (21 CFR Part 803)	Applies to every class of medical devices

4.3 REGULATION OF DRUG-DEVICE COMBINATIONS

According to FDA 21 CFR 3.2. Drug-device combination includes:

i. Products that combine a drug and a device, a biologic and a device or a device--drug-biologic complex and produced as a single entity.

ii. Drug-device, biologic-device or a device-drug-biologic complex packaged together in a single package or as a unit.

iii. Approved drugs and biologic products packaged separately from a medical device and according to their investigational plan or proposed labelling are packaged, for instance to reflect a change in indication, dosage form, strength or route of administration.

iv. Investigational drugs or biologics packaged separately from an investigational device but are intended to be used together to achieve the intended use, indication or effect (54).

The status of a combination product is determined by the FDA, through the Office of Combination Products, according to the Regulation 21 CFR Part 3 Product Jurisdiction (55). This regulation contains the processes through which FDA will determine based on its Principal Mode of Action (PMOA) (55,56) whether the Centre for Drug Evaluation and Research (CDER), the Centre for Devices and Radiological Health (CDRH) or the Centre for Biologics Evaluation and Research (CBER) will be responsible for carrying out pre-marketing review and post-marketing control of the product (55).

The Office of Combination Products (OCP) is responsible for developing regulations and guidance for combination products in the US. It is the principal office for dealing with combination product reviews for FDA reviewers and pharmaceutical manufacturers. It doesn't review the products directly but does it by assigning the combination product to

the appropriate FDA centre based on the primary mode of action of the product. When the primary mode of action is as a drug, the CDER will handle its review, when the primary mode of action is as a biologic, the CBER will handle its review, when the primary mode of action is as a medical device, the CDRH will handle its review (55) (Figure 7).

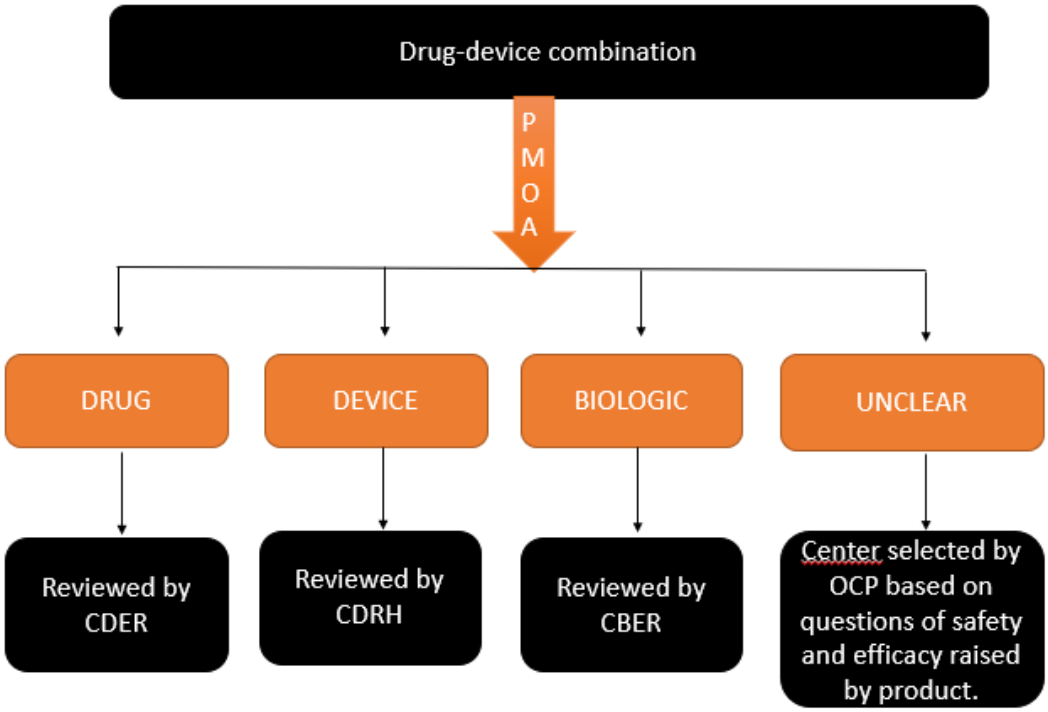

Figure 7: Regulation of Drug-Device Combination Based on Principal Mode of Action in the USA.

However, in some situations, it is impossible to determine with absolute certainty which component of the combination will contribute to a greater extent, the overall therapeutic effect of the product. In this case, FDA, through the OCP will assign the combination product to the FDA component that regulates other combination products that present similar questions of safety and effectiveness with regards to the combination product as a whole. If such product that raises the same questions of safety and effectiveness does not yet exist, the OCP will assign the combination product to the FDA component with

the most expertise related to the most significant questions of safety and efficacy raised by the product. The centre reviewing a particular product can collaborate with other centres if some other constituents of the product lie outside their jurisdiction (56, 57).

If the classification of the product as a drug, device, biologic or combination product is unclear, a sponsor can file a Request for Designation (RFD) with the OCP to argue in favour of a particular centre reviewing their product. However, there must be enough reliable data available for the FDA to understand the product and uncover its primary mode of action (55).

The OCP is responsible for writing down combination product guidance documents, clarifying regulations and co-ordination of reviews of products involving more than one agency centre. They ensure consistency and appropriateness of post-market surveillance, resolve disagreements on timelines of pre-market reviews, and revise agreements, guidance documents and combination products-specific practices (56).

Quality Management System (QMS) for Drug-Device Combination in the US

According to FDA 21 CFR part 4, it is expected that the combined use of the components of the combination be considered throughout the QMS, including the change management (58). The lead centre will co-ordinate review of combination product changes while consulting with other centres as needed. Regarding the safety efficacy and performance of combination products, the FDA is more focused on the drug component and have yet to clarify the essential performance requirement for medical devices (30).

USA Surveillance Aspects for Drug-Device Combination

In the USA, post-market surveillance reports are driven by application type and applicant type. Application-based reporting is supplemented with specific reporting from each of the other constituent parts of the combination product. If a reportable event occurs on a combination product having a constituent part similar to a constituent part of a US-marketed combination product, it is required that such event be reported in the US. Regardless of whether it is the device part or the drug component (30). A manufacturer must submit a report no later than 5 days of becoming aware of a reportable event associated with the combination product (59).

Irrespective of the Primary mode of action, the manufacturer must meet the requirements of 21 CFR 820:100 Corrective and Preventive Actions. Under the US 21 CFR 4B regulations and guidelines, there is intent to ensure comprehensive reporting consistent with the underlying requirements called out in the rule associated with each of the components (27).

5. AFRICA

As of March 2022, only Nigeria, Egypt, Ghana, South Africa and Tanzania have been classified by the World Health Organization (WHO) as having effective regulatory systems on the African continent, all having a WHO maturity level of 3. It was on March 2022, according to the WHO that the medical products regulatory agencies in Nigeria and Egypt had reached maturity level 3, which means that these national bodies have been found to function well and could be eligible for inclusion into the transitional WHO Listed Authorities, a list that will comprise the world's regulators of reference – that is, regulatory authorities that should be globally recognized as meeting WHO and other international standards". Nigeria has reached maturity level 3 for medicines and imported vaccines, while Egypt has reached a maturity level 3 for locally produced and imported vaccines regulation (60). A streamlined regulatory process across Africa would make it easier for manufacturers to bring their products into the African market, thereby increasing patient access to safe health products (61).

5.1. REGULATION OF MEDICINES

There is no harmonized system of medicines regulation in Africa as is seen in Europe, different countries have their different regulatory authorities which varies in level of development, with some countries having minimal to no regulatory body in place. Therefore, describing regulation of medical products in Africa, would mean describing regulation of these products in each country as a single entity which would not allow an exhaustive description (61).

Nigeria, South Africa, Tanzania, Egypt

Nigeria: In Nigeria, the National Agency for Food and Drugs Administration and Control (NAFDAC) is responsible for the regulation of medicines placed on the market, according to sections 5 and 30 of the NAFDAC Act (CAP. N1, LFN) 2004 and section 12 of the Food, Drug and Related Products Act (Cap. F33, LFN) 2004(Table 3). NAFDAC ensures that all the drugs placed in the market meet the quality, safety and efficacy requirements throughout their lifecycle. A certificate of registration valid for 5 years is issued for products authorized for marketing in Nigeria and may be renewed after the 5-year validity period (62). No medicine can be sold or manufactured in Nigeria without satisfactory evidence that such product has been manufactured according to Good Manufacturing Practices (GMP). Post-approval, a certificate of analysis would be submitted to NAFDAC and after review of the post-approval documentation, NAFDAC would inspect the production facility and carry out laboratory analysis to verify the results on the certificate of analysis. If product is finally approved, a Notification of Registration is issued and if not approved, compliance directives will be issued instead (62).

South Africa: With the recent amendments to the Medicines Act, the South African Health Products Regulatory Authority (SAHPRA) has replaced the Medicines Control Council as the principal regulatory authority for medicines and health products in South Africa (63). The registration of medicines in South Africa is governed by the provisions and requirements of The Medicines Act, including the regulations and the published guidelines (64). SAHPRA requires that all pharmaceutical manufacturers, wholesalers and importers be licensed to manufacture, sell or import medicines.

In South Africa, guidelines issued by SAHPRA are meant to be complied with by the manufacturers, wholesalers and importers (63). All manufacturing and quality control

sites involved in a dug product manufacture must be GMP compliant prior to the submission of an application for registration. GMP compliance is demonstrated through a GMP certificate or an equivalent manufacturing license. All new registration applications would require a completed Summary of Critical Regulatory Elements (SCoRE), a document designed to reduce evaluation time of applications by providing an extensive summary of the application. If a biostudy has been included in the application, a Bioequivalence Trial Information Form (BTIF) is filled out and submitted, otherwise, a Biopharmaceutics Classification System (BCS)-based biowaiver. SAHPRA adopts the EMA format for Professional Information and Patient Information Leaflets (64).

Applications are submitted on a CD, DVD or USB, with supporting paper documents. The applications go through a screening process to confirm of all SAHPRA's requirements ensuring that only high-quality dossiers move on to the evaluation phase. The evaluation phase involves the assessment of the quality, safety and efficacy of the medicine, after which the application is approved or denied by the Medicines Control Council (MCC). (64)

Tanzania: Tanzania has two National Medicines Regulatory Authorities (NMRAs), namely the Tanzania Food and Drugs Authority (TFDA) and the Zanzibar Food and Drugs Board (65).

The Minister of Health is responsible issuing regulations that govern the control of medicines and other health-related products (66). Manufacturers, wholesalers and distributors of medicinal products must carry out their activities according to 'The Tanzania Food, Drugs and Cosmetics Act of 2015 (CAP. 219)' and must hold a license issued by TFDA(Table 3). This does not apply in some situations such as: products prepared in a pharmacy, according to a doctor veterinarian or dentist's prescription and

under the supervision of a pharmacist; products prepared in a hospital or pharmacy according to a formula in an official pharmacopeia and intended for patients served by that pharmacy or hospital; products intended to be used in research and development studies; and medicinal products including alternative medicines formulated by a pharmacist, doctor, veterinarian or traditional health practitioner registered under the Traditional and Alternative Medicines Act, for a particular patient or on behalf of another pharmacist, doctor or veterinarian (67).

Application for registration of a medicinal product is made in both hard and electronic copies, accompanied by the supporting documents, including a dossier and must include the particulars of a representative with appropriate knowledge of all aspects of the product, who will be responsible for communicating with the TFDA. Application for registration must comply with technical requirements stipulated by the TFDA and data demonstrating the safety, quality and efficacy of the products must be provided (67).

After the evaluation of an application, the TFDA presents their results and recommendation to the Technical Committee for Registration of Medicinal Products for deliberation. The outcome recommendation of their deliberation is then presented to the Director General of TFDA for final approval. The Director General then rejects or approves the product with a full registration status or offers recommendation, approving the product with a provisional registration status, specifying the conditions that need to be fulfilled by the applicant to acquire full registration. The newly registered product will be added in the Government Gazette list of registered products and fully registered products are issued a certificate of full registration, valid for five years except otherwise stated, and a certificate of provisional registration valid for not more than three years (67).

The TFDA requires the marketing authorization holder to conduct post-marketing surveillance and safety studies biennially, in order that can analyse the benefit-risk profile and ensure the product is safe enough to remain on the market. Depending on the outcome of the safety studies, the marketing authorization may be revoked, suspended or retained. Failure to submit the result of the study would lead to a suspension of the marketing authorization (67).

Egypt

The Egyptian Drug Authority (EDA) is the Egyptian national competent authority, in ensuring safety, effectiveness and quality of pharmaceutical products. The law governing the regulation of medicines in Egypt is the Pharmacy Act of 1955 (Table 3) (68).

Marketing authorization is only given for a product if a certificate of compliance is obtained for said product from the EDA's National Organization for Drug Control and Research (NODCAR) (69). Manufacturers must obtain a general manufacturing operational licence for their manufacturing facility from the Industrial Development Authority and the facility must be registered in the industrial registered, then they must obtain a manufacturing license from the EDA (70).

Marketing authorization is only given for a maximum of 12 medicinal products containing similar active ingredients, including the innovator brand and specifications, according to Ministry of Health Decree 425/2015. Generally, only one imported brand is allowed for a particular active ingredient and a maximum of 5, for products involving complex technology, not commonly found in Egypt (70). To obtain an MA, the applicant must first ascertain that there is still a vacancy for the registration of such medicinal product by submitting an enquiry to the EDA and if there is no vacancy, the request is registered on a waiting list. If there is a vacancy however, the next step would be to submit documents determining the commercial name and price of the product, after which the

application is reviewed by several EDA committees after the submission of a marketing authorization application, accompanied with required supporting document (70).

The website from the Egyptian Ministry of Health contains information on registered medicines and regulatory processes. However, the website was not accessible outside Egypt (69).

Products for which marketing authorization is granted are issued a certificate of registration valid for 10 years. The regulation of biological products is done separately, under Ministry of Health Decree No. 297/2009 (68, 70).

Pharmacovigilance is carried out according to Ministry of Health Undersecretary Decree No. 2/2010 The MA holder is required to have a system for collecting, analysing and assessing adverse effects and must report any adverse effect not more than 15 days of becoming aware of them (70)

Table 3: Comparison between the regulatory processes involved in the registration of medicines in Nigeria, South Africa, Tanzania and Egypt.

	Nigeria	**South Africa**	**Tanzania**	**Egypt**
Regulatory body	NAFDAC	SAHPRA	TFDA	EDA
Regulation	sections 5 and 30 of the NAFDAC Act (CAP. N1, LFN) 2004 and section 12 of the Food, Drug and Related Products (Registration, et.c) Act (Cap. F33, LFN) 2004.	The Medicines Act	The Tanzania Food, Drugs and Cosmetics Act of 2015 (CAP. 219)	The Pharmacy Act of 1955
Validity of Certificate of Registration	5 years	5 years	5 years	10 years

5.2 REGULATION OF MEDICAL DEVICES

Nigeria: NAFDAC regulates medical devices in Nigeria under the provisions of Act CAP F33 LFN 2004(Table 4) (71). The medical device classification system in Nigeria is a risk-based system, dividing devices into four classes (A-D) with A posing the lowest potential risk and D the highest (72).

For foreign medical device manufacturers, the first step towards registering their products in Nigeria would be to appoint a local medical device authorized representative. Before the submission of application for registration, the brand name of the device must be registered with the Trademark Registry of the Ministry of Industry, Trade and Investment (73). All medical device applications are submitted through the NAFDAC Automated Product Management and Monitoring System (NAPAMS) portal. The application is accompanied with supporting documents like GMP letter, certificate of compliance, clinical evaluation report and other necessary documents (71). Technical documents, such as Declaration of Conformity (DOC), certificate of compliance product dossier (for *in vitro* diagnostics) and clinical evaluation report with statistical data, for novel medical devices must be submitted in an electronic format. For imported devices, a DOC must be submitted, to attest that the medical device complies fully with the essential principles of safety and performance as is documented on the DOC. The DOC should contain, at least the following information:

A. A statement that the device complies with the essential principles for safety and performance and has been classified according to the classification rules,
B. A global medical device code and term for the device,
C. Date from which the DOC is valid,
D. Name and address of the device manufacturer and

E. The name, position and signature of the responsible person who has been authorized to complete the DOC on behalf of the manufacturer.

After successful screening of the application and review of supporting documents, an import permit is issued electronically via the NAPAMS website, for the importation of samples for laboratory testing.

Products for which document review, production facility inspection and laboratory analysis results are satisfactory, are presented for the Food and Drug Registration Committee (FDRC) approval meeting. An electronic Certificate of Product Regulation is issued for the approved product (74). The timeline from when application of registration is accepted by NAFDAC to the time of issuance of a registration number for a device is 120 days, but the clock stops ticking when a compliance issue is raised by NAFDAC (75). All product registration certificates are valid for 5 years and can be renewed after that (74).

South Africa: South Africa (SA) has an established formal regulatory process for medical devices which includes all essential components recommended by WHO. Medical devices are regulated by the SAHPRA under the Medicines and Related Substances Act of 2015, Act No, 1417 and General Regulations Relating to Medical Devices and *In vitro* Diagnostic Medical Devices (Table 4). All medical devices, except custom-made devices must be registered with the SAHPRA and all manufacturers and importers must obtain a license from SAHPRA (61). SA uses a risk-based system in their classification of medical devices. The system designates 4 levels of risk: Class A, B, C, D, with Class A being associated with the lowest risk and Class D, with the highest risk. The pre-market approval process for Class A devices includes a demonstration of conformity by passing a Conformity Assessment Body and Declaration of Conformity, while class B to D devices are required to meet the IMDRF's essential principles for

medical devices and demonstrate conformity by passing a Conformity Assessment Body and DOC. Passing the conformity assessment may require clinical testing, ensuring risk management and outlining procedures for quality assurance techniques and sterility (61).

In SA, medical device manufacturers and importers must present evidence that their products conform to safety and performance standards. Their products must also conform to the IMDRF's established list of essential principles for medical devices including *in vitro* diagnostic devices (61).

They employ extensive post-market controls including: inspection according to quality management systems procedures and guidelines, seizure of expired and unregistered devices, reporting of adverse events and control of labelling and advertising.

Tanzania: The TFDA is responsible for regulating the safety, quality and performance of medical devices in Tanzania. The regulatory provisions in Tanzania are stipulated in Food, Drug and Cosmetics (Control of Medical Devices) Act of 2015 (Table 4). In Tanzania, medical device manufacturers and importers must present evidence that their products conform to safety and performance standards. Their products must also conform to the IMDRF's established list of essential principles for medical devices including *in vitro* diagnostic devices (61). Tanzania Medicines and Medical Devices Authority (TMDA) is an Executive Agency under the Ministry of Health, Community Development, Gender, Elderly and Children (MOHCDGE). TMDA is responsible for regulating safety, quality and effectiveness of medicines, medical devices and diagnostics (76).

In Tanzania, just like in Nigeria, medical devices are classified into 4 (class A to D), depending on the level of potential risk they pose, with class A posing the potential lowest risk and class D the highest (Table 4). When a device belongs to two classes, the class

representing the higher risk will apply. When a class A device poses very low potential risk, it may be exempt from registration (77).

To register a class B to D device, the applicant must provide information regarding risk assessment of the device and measures adopted to reduce said risk, according to the requirements of ISO 1497, list of countries which the device has been used and any associated problems or recalls in those countries, in case of IVDs manufactured from or incorporating materials of biologic origin, the biological safety of the device is evaluated, in case of a near-patient IVD, detailed information on investigational testing, conducted on human subjects under conditions similar to conditions of intended use, must be provided (77).

The application for the registration of a medical device is carried out by the manufacturer or a local representative, in case of foreign manufactured devices. The application is submitted with other supporting documents, depending on the class of the device. When the TFDA determines that the device meets the safety and performance requirements, a certificate of registration is issued, which is valid for 5 years, unless it gets revoked or suspended before then. The results from post-marketing surveillance are submitted biennially including any adverse events (77).

Table 4: Comparison between the regulatory processes for medical devices in Nigeria, South Africa and Tanzania.

	Nigeria	South Africa	Tanzania
Regulation	Act CAP F33 LFN 2004.	the Medicines and Related Substances Act of 2015, Act No, 1417	Food, Drug and Cosmetics (Control of Medical Devices) Act of 2015
Classification	Risk-based system, divided into four classes (A-D) with A posing the lowest potential risk and D the highest.	Risk-based system, divided into four classes (A-D) with A posing the lowest potential risk and D the highest.	Risk-based system, divided into four classes (A-D) with A posing the lowest potential risk and D the highest.
Format for submission of application documents	Electronic format		
Validity of Certificate of Registration	5 years		5 years

Egypt: To manufacture or import medical devices in Egypt, manufacturers or importers must be registered with EDA (70). Approval of a medical device registration application would require compliance with the Central Administration of Pharmaceutical Affairs division of the Egyptian Ministry of Health. The registration process is controlled by a special committee, made up of experts from different fields of medical expertise that study the medical device. Their key task is to review and approve application, focusing more on their intended use and ascertaining whether there is a real need for it, as it concerns the target patients. (71)

5.3 REGULATION OF DRUG-DEVICE COMBINATIONS

Regulation of drug-device combinations in Africa varies based on country and regional harmonization initiatives. Some of the challenges of regulating drug-device combinations in Africa are:

- The lack of a harmonized and standardized regulatory framework for drug-device combinations across different countries and regions (78).

- The difficulty of classifying drug-device combinations based on their principal mode of action (PMOA), especially for innovative and complex products that may have multiple or changing modes of action (79)

- The limited capacity and resources of many National Medicines Regulatory Authorities (NMRAs) in Africa to perform the core regulatory functions, such as quality control, post-marketing surveillance, pharmacovigilance and clinical trials oversight (78)

Notwithstanding, there are also some opportunities and initiatives to improve the regulation of drug-device combinations in Africa, such as:

- The treaty for the establishment of the African Medicines Agency (AMA) on the 5th of November 2021, which would aim to harmonize and strengthen NMRAs in Africa (80).

- The African Medicines Regulatory Harmonization Initiative, which supports regional economic communities to harmonize their regulatory requirements and procedures (81).

- The African Vaccines Regulatory Forum, which facilitates information sharing and collaboration among NMRAs on vaccine regulation (82).

- The Network of Official Medicines Control Laboratories, which provides quality control testing and training for NMRAs in Africa (83).

- The WHO Prequalification Scheme, which assesses the quality, safety and efficacy of medical products for priority diseases (65).

Some regions in Africa have come together to create a harmonization initiative (the African Medicines Regulatory Harmonization) in order to foster uniform regulatory processes. Some of these include: East African Community (EAC), Economic Community of West African States (ECOWAS), Intergovernmental Authority on Development (IGAD) and South African Development Community (SADC) (Figure 8). The main aim of this collaboration is to be able to rely on the work of one another and to reduce marketing authorization timeline, through the issuing of a single MA, valid in all the member states as seen in the EMA's centralized procedure (84).

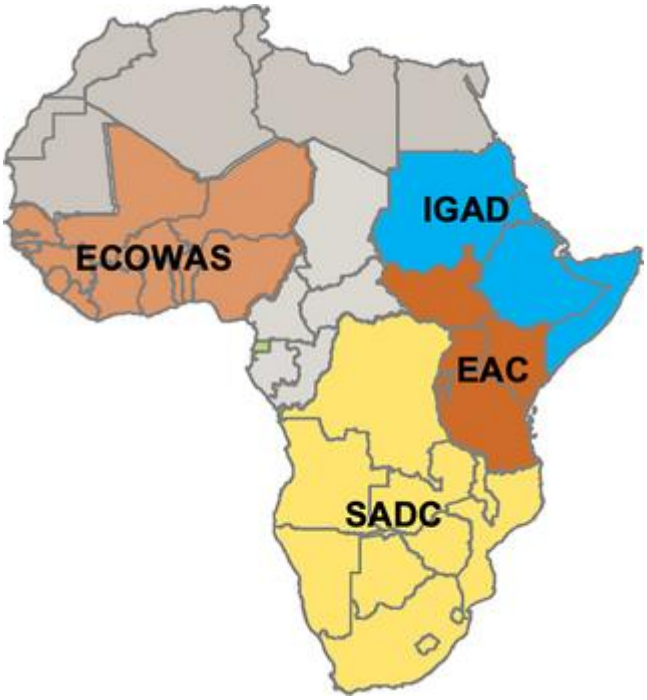

Figure 8: The map of Africa indicating the regions included in the regulatory harmonization initiative (84).

Differences of the Regulatory aspects between the East African Community (EAC) and the Economic Community of West African States (ECOWAS) are described in Table 5.

Table 5. Summary of the main differences in Regulatory Aspects between two of the regional harmonization initiatives (EAC and ECOWAS).

Regulatory Aspect	EAC	ECOWAS
Conformity Assessment System	Based on the European CE Mark, which indicated that essential requirements of Safety, quality and Performance are met	Based on WHO guidelines, which provide a set of recommendations and best practices for regulating medical devices.
Kinds of devices covered	All medical devices, drug-device combinations, *in vitro* diagnostics and health software	Medical devices only, excluding *in vitro* diagnostics and health software
Classification System	Risk-based from class A to D (highest to lowest potential risk)	Risk-based from class I to IV (highest to lowest potential risk)
Registration System	Centralized: All applicants can submit their applications and pay their fees electronically, through a single online portal	Decentralized: Applicants must submit application and pay required fees to the different regulatory authorities individually and may involve manual or paper-based procedures.

Assessment Committee	Presence of a regional joint assessment committee, consisting of experts from their different member states and other stakeholders. Joint assessments are carried out and regional certificates of conformity are issued.	Absence of similar mechanism for joint assessments and regional certificates.
Post-market surveillance and Pharmacovigilance	Established guidelines for the different aspects including adverse events reporting, recalls, inspection and audits	Guidelines are established for the different aspects, but with less detail and specificity
Monitoring body	Monitored and evaluated by the EAC secretariat and EAC-MRH steering committee, which oversee the implementation and enforcement of the framework and guidance and feedback to the member states and stakeholders	Monitored and evaluated by the West African Health Organization (WAHO) and the ECOWAS Medicines Regulatory Harmonization Steering Committee, which plays similar roles for their member states and stakeholders.

Both frameworks are aligned with the international standards and best practices for regulating medical devices. However, they may have some differences or gaps in terms of their scope, approach and implementation. Therefore, there is a need for further

harmonization and coordination among the regional frameworks to ensure consistency and efficiency in regulating combination medical devices in Africa. The implementation and enforcement of these frameworks depend on the commitment and capacity of each country or region to adopt and apply the harmonized guidelines and standards (78).

Nigeria: NAFDAC regulates drug-device combinations either as a drug or a medical device, since the procedures for regulating drugs and devices are fundamentally the same.

South Africa: In South Africa, combination products are regulated by SAHPRA under the Medicines and Related Substances Act 101 of 1965 (as amended).

According to guidelines issued by SAHPRA for the registration of combination products, Combination products may be defined as products that consist of any combination of a medicine or scheduled substance and a medical device; or two or more medical devices; or two or more medicines or scheduled substances.

In the Southern African Development Community (SADC) to which South Africa belongs (85) combination products are regulated by the SADC Pharmaceutical Programme, which aims to harmonize the regulation of medicines and health technologies among the SADC Member States (Angola, Botswana, Comoros, Democratic Republic of Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Tanzania, Zambia and Zimbabwe (85)). This programme has developed guidelines for the registration of combination products, which define them as products that consist of any combination of a medicine and a medical device; or two or more medical devices; or two or more medicines.

Tanzania: In the East African Community (EAC), to which Tanzania belongs (85), combination products are regulated by the EAC Medicines and Health Technology Regulatory Harmonization (EAC-MRH) Project, which aims to harmonize the regulation

of medicines and health technologies among the EAC partner states, including Burundi, Kenya, Rwanda, South Sudan, Tanzania and Uganda (85). The EAC-MRH project developed guidelines for the registration of combination products, defining them as products that consist of any combination of a medicine and a medical device; or two or more medical devices; or two or more medicines.

Egypt: There is no separate regulation for drug-device combination products in Egypt. The device and drug components are regulated separately according to the general guidelines for regulating each component (70).

6. CASE STUDIES

6.1. Spermicide Condoms

Introduction

The use of spermicides as a contraceptive method, dates back to thousands of years. Several active ingredients can be used in their formulation, but the most used ingredient is nonoxynol-9 (86), which works by preventing the movement of the sperm.

A spermicide condom is a barrier contraceptive worn on the penis during sexual activity, it is a thin sheath typically made from latex and coated with a spermicide, a chemical which kills sperm, preventing it from getting to the uterus, inhibiting their chances of getting to an egg (87).

Even though no current evidence suggests that spermicides increase the contraceptive or STI-protective effect of the condoms (87) the intended purpose for combining spermicides with condoms is for synergistic effects.

Nonoxynol-9 acts by interacting with the lipids in the membrane of the acrosome and midpiece of the sperm. It lyses the sperm membrane, acrosome, neck and midpiece of the spermatozoa, loosening and detaching them, which results in immobilization and subsequent death (88).

REGULATION OF SPERMICIDE CONDOMS IN THE EU

In the EU, there is no definition for a drug-device combination, they are regulated based on their primary mode of action. In the case of a spermicide condom, because the drug and device components work synergistically to achieve contraception, it is not clear what the primary mode of action is, therefore, the different components of the combination will be regulated individually.

The condom, being a medical device, upon demonstrating satisfactory safety and performance would be CE-marked, indicating conformity to regulatory standards. Condoms would be classified as class 'Is' medical devices because although they are low risk medical devices, they are required to be sterile, but when incorporated with a spermicidal agent becomes a class III device, according to MDCG 2021 – 24 Annex 4, Rule 14, which states that devices that incorporate as an integral part, a substance which if used separately acts as a drug, are classified as class III devices (89).

The drug aspect of the combination, nonoxynol-9, will be regulated through the decentralized or mutual recognition procedure, since it doesn't fall under the class compulsorily regulated through the centralized procedure. A marketing authorization will be issued when the drug has demonstrated safety, efficacy and quality.

Regulation of Spermicide Condoms in the USA

FDA classifies condoms as class II medical devices. When combined with a spermicide, the ensuing product is a drug-device combination, since it contains a device and a drug, packed as a single unit.

The FDA office of combination products will first determine which of the centres will be responsible for reviewing the product, according to regulation 21 CFR Part 3. Since it is

not possible to determine with great certainty, which mode of action contributes the greatest to the overall effect of the combination, FDA will assign the product to the centre that that regulates other products presenting similar questions of safety and effectiveness with regards to the combination product as a whole, such as other barrier contraceptive methods combined with spermicides, for example diaphragms, cervical caps and sponges combined with spermicides (90). The primary centre designated for the product review can then consult other centres, if they require their expertise. In this case, the sponsor can also argue in favour of a particular centre by filing an RFD with office of combination products, providing enough data for FDA to uncover its principal mode of action.

Regulation of Spermicide Condom in Africa

In Nigeria, South Africa and Tanzania, probably the regulatory authorities will regulate spermicide condoms as medical devices, because the spermicide part may be considered just as being an adjunct to the device.

In Nigeria, medical devices and drugs are basically regulated the same way, necessary application documents are filed with NAFDAC and when they are deemed satisfactory, samples are tested and if they meet regulatory requirements, would be issued a certificate of registration.

In Egypt, the separate components of the combination are regulated individually.

6.2. Fe-Doped Brushite

Brushite cements (BrC) are bioceramics made from calcium phosphate. They are widely used in bone and dental tissue engineering. They have become more widely used than many other calcium phosphate ceramics due to their osteoinductivity, injectability and moulding properties. Even though Brushite has a lot of desirable properties, there was need to increase their clinical application which has led to the modification of their chemical properties by adding trace elements known as dopants. Trace elements which have typically been used as dopants with brushite include magnesium, silicon, zinc, which have been used to improve their mechanical properties, some even has some antimicrobial properties (91).

In recent times, iron has been used as a dopant for brushite cement. It was initially used for its antimicrobial properties (when the iron used is in the form of iron oxide). Iron in the form of iron oxide when combined with brushite cement has also shown inhibitory effect on bone tumour development (91). Studies have been carried out to check for biocompatibility when bone cements doped with iron are used as bone fillers for the filing sites of bone tumour removal (92).

Regulation of Fe-Doped Brushite in EU

Because Fe-doped brushite can act as an anti-tumour agent, the manufacturer could argue in favour of the primary mode of action being a drug, with the bone cement being only a delivery system for the drug, which is the iron-oxide nanoparticles. He could also argue in favour of the bone cement being the principal component of the combination, stating that the iron-oxide is just an adjunct to improve the mechanical properties of the bone cement. In this case, the different components of the combination will be regulated individually.

In the case where the combination is regulated as a drug, this will be done through the centralized procedure Regulation EC 726/2004 (28), since the product is used in tissue engineering, has potential anti-cancer properties and involves significant innovation. This might be the fastest and most hassle-free method for getting the product to the market, as it would involve a single decision by the EMA and a single marketing authorization valid in all the EU member states. After a positive benefit-risk analysis, the EMA makes recommendations to the EC, which would then decide within 67 days whether the product can be marketed in the EU.

If argument is made in favour of marketing the product as a medical device, the 2 components of the combination will be regulated individually, with the drug component being regulated under the centralized procedure and the device component, being regulated as a class III implantable device, where it would have to meet the legal requirement of safety and performance. Due to the fact that it is a high-risk implantable device, the notified bodies would require the scientific opinion of expert panels in a process called the Clinical Evaluation Consultation Procedure, before issuing a conformity certificate.

Regulation of Fe-Doped Brushite in the USA

In the USA, given that it is unclear which mode of action of the product is primary, the OCP would decide the primary centre that would handle the review of the product, based on questions of safety and efficacy raised by the product. The centre that in times past has reviewed products that raise similar questions of safety and efficacy, would be the centre assigned by the OCP to review this product.

As usual, the manufacturer could argue in favour of a particular centre handling the review of the product by filing a ‘request for designation’ but would have to proof beyond

reasonable doubt why that centre should handle the review by providing sufficient reliable data for the understanding and uncovering of its primary mode of action. If the manufacturer successfully argues in favour of the product being a drug, the CDER will handle its review, if in favour of a medical device, then the CDRH handles its review.

Regulation of Fe-Doped Brushite in Africa

In Africa generally, there is no standard regulation for drug-device combinations and are often regulated on case-by-case basis. In Nigeria, the regulation of drugs and devices typically follow the same procedure, however analysis carried out by NAFDAC to determine suitability of products might defer. In the case of Fe-doped brushite, it may be suggested that NAFDAC will regulate the components as different entities and manufacturers would have to submit different application documents for the device part and the drug part after relevant application documents are submitted and are deemed satisfactory by NAFDAC, NAFDAC would then analyse the product, using the analytical methods involved in drug regulation for the drug component and the methods for analysing medical devices for the device components.

In South Africa and Tanzania, it may be suggested that Fe-doped brushite would be regulated the same way as it would be in Nigeria.

In Egypt, as a standard procedure, the Fe-doped brushite would be regulated as if they were individual components. The device component must show compliance to standards set by the Central Administration of Pharmaceutical Affairs division of the Egyptian Ministry of Health. The registration process will be controlled by a special committee, made up of experts from different fields of medical expertise that would study the medical device and ascertain whether there is a real need for it.

The drug part would be regulated by the EDA's NODCAR. It must be well established first of all that there are not more than 12 different products similar to it. The regulatory agency will then analyse for its conformity to the legal requirements of safety, quality and efficacy according to Egyptian Pharmacy Act of 1955.

7. Conclusions and future perspectives

To allow for new, innovative health technology to get to the patients quicker, while still consistently maintaining quality, safety, effectiveness and performance, there is need for constant improvement by the regulatory authorities to reduce regulatory burden while maintaining due process.

Drug-device combination products pose unique regulatory challenges, because they contain two distinct health technologies, regulated differently depending on the NRA and the individual regulatory protocols are not always suitable for a product that combines both as a single entity. The major problems regulators face due to this unique technology include: issues with classification, because it is difficult in some cases to determine the PMOA, selecting a suitable single regulatory pathway and establishing appropriate pre- and post- authorization requirements (93).

The uniqueness, regulatory complexity and hence long regulatory timelines associated with these kinds of products discourage manufacturers, hence stifling innovation, reducing patients' access to their much needed therapy. There is therefore need for harmonization of regulatory processes when it comes to combination products.

In the EU, there is no actual definition for combination products and such, are regulated either as a drug or a medical device, depending upon the primary mode of action. For the component which is ancillary in action the requirements for safety, quality and efficacy or performance must be met. This has its limitation, as there are some products that cannot easily be classified as drugs or medical devices. Usually, such products would be classified by the notified body on a case-by-case basis. This process will further lengthen the already long regulatory time frame. It will be advisable that the EU agrees on a definition for drug-device combination products and includes co-packaged products in

that definition. It will be advisable that the regulation of these products be done in a manner that there is a regulatory body to handle the regulation of these unique products, which would include experts from all the necessary fields of science, required for the proper regulation of drugs and medical devices. This is to say that there should be experts skilled in the regulation of medicines and ones skilled in the regulation of medical device within the same regulatory body. This way, there would be no need to classify the products either as devices or drugs and would eliminate the problem of not knowing how to classify certain products. While this would cost the government a lot of funds to start up, in the long run, it will be beneficial to the patients, manufacturers, regulators and even the government, as this would foster innovation, competition and quicker access by patients, due to the reduction in regulatory timelines that would follow.

In the USA, drug-device combinations have been well defined, with inclusions as to what is classified as drug-device combination and what is not. The regulation of drug-device combination is handled by the office of combination products, which then determines the centre that will handle the review of the product, depending on the PMOA. Depending on expertise required, the different centres can collaborate with one another and if the PMOA is unclear, the sponsor would have to file an RFD to argue in favour of a particular centre to review the product, providing enough reliable data as basis for the product to be reviewed by the chosen centre. The USA is more advanced in their regulation of combination products as they have successfully classified it as a different health technology and assigned a regulatory body (The OCP) to be in charge of these kind of products, to write regulatory guidelines for them and co-ordinating the review products which have undergone inter-centre collaborations in their regulatory process. However, the issue of conflicting PMOA still arises. If one centre would be assigned to the review of all drug-device combination without prejudice to the PMOA, or if there would be a

particular centre dedicated to the review of combination products whose PMOA is unclear, then this would solve the issue of having to file an RFD, which I believe adds to the regulatory timeline.

Regulation of drug-device combination in Africa is diverse, as Africa is a large, diverse continent in all ramifications. Regulations vary from country-to-country to varying degrees of advancement, with some countries not even having a regulatory body, as such the definition of drug-device combination products as well as their regulation varies from country-to-country. However, the regulatory systems in Africa are actively seeking reform, with different regions of the continent coming together to create a uniform regulation for health products. This, is a step in the right direction, as it would foster innovation in Africa and allow earlier access of patients to health products. Of the African countries reviewed in this thesis (Nigeria, South Africa, Tanzania and Egypt), only Egypt has a clear description of how drug-device combinations are regulated. Their component parts are regulated separately. While this works, it may be time-consuming and create greater regulatory burden especially as more sophisticated products may be difficult to regulate this way. Other African countries reviewed basically regulate these products on a case-by-case basis either as a drug or medical device. It is advisable that regulatory bodies in Africa create a well-defined structure for regulating drug-device combination products, adopting a system like what is obtainable in the USA.

In conclusion, if all the regulatory authorities across the world come together and adopt a method for regulating drug-device combination products as is obtainable in the USA and there is a world-wide harmonization, where what we have in the EU mutual recognition system is carried out, then we as a people would have reached the height of advancement in regulation of drug-device combinations.

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