A REVIEW ON COMPARISON OF REGULATORY REQUIREMENTS TO APPROVED DRUG DEVICE COMBINATION PRODUCTS IN EUROPE AND USA

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ABSTRACT

Combination products means a combination of Medicinal drug or device or biologics which are used for the treatment and prevention of wide range of disorder and medical conditions because when they use alone can only slow down or stop the progression of disease or injury. In order to tackle the clinical problems of the future, these products will be combined these are emerging and Morden day techniques for the drug delivery products. This article highlights on the legal basis of the current regulation in the USA regarding drugs, biologics and medical devices in general and will discuss the regulatory processes involved in getting a combination product into the Food and Drug Administration (FDA) approval processes. The role of Each centers for the regulation of this products and Combination product regulation in Europe is in its infancy and USA combination legislation has yet to be realised in the European Directives. In this article, the basic building blocks for a regulatory strategy in Europe are presented,. Description of various guidelines required for the authorisation of Drug device combination products and their Different regulatory environments and various development requirements in EU and US. Requirement of common regulatory approach or strategy in future for these products, which would result in easier and coast effective procedures for the regulation of combination products in the lucrative market in US and EU.

Keywords: Combination products, Europe Union, United States, Regulations, Medical Device, Drug products.
INTRODUCTION

Examples of combination products

- Monoclonal antibody combined with a therapeutic drug
- Device coated or impregnated with a drug or biologic
- Drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating; condom with spermicide
- Skin substitutes with cellular components; orthopaedic implant with growth factors
- Prefilled syringes, insulin injector pens, metered dose inhalers, transdermal patches
- Drug or biological product packaged with a delivery device
- Surgical tray with surgical instruments, drapes, and lidocaine or alcohol swabs
- Photosensitizing drug and activating laser/light source; iontophoretic drug delivery patch and controller

Global market of combination products

Recently, combination products are emerging as innovative medical products due to their contribution in advancing medical care and are thus expected to have major impact in the coming years. Moreover, these products offer several advantages which include reduced adverse side effects, improved patient compliance, controlled release administration of drug, and also provide targeted drug delivery.

The major product types in the market include drug eluting stents, infusion pumps, photosensitizers, orthopaedic combination products, wound care combination products, inhalers, transdermal patches and others which include intraocular implants and drug eluting beads. Various emerging technologies such as implants with drugs to permit faster healing, relief from pain and decreased morbidity currently form the major driver for the growth of this market.

The global drug device combination products market was valued at USD 66 billion in 2012 and is expected to grow at a CAGR of 7.9% from 2013 to 2019, to reach an estimated value of USD 115 billion in 2019.
Definition of combination products as per FDA

Combination products are defined in 21 CFR 3.2(e). The term combination product includes:

1. A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity.

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labelling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.

Classification of Medical devices as per FDA[^3]

Device Class and Regulatory Controls

1. Class I General Controls
   - With Exemptions
   - Without Exemptions

2. Class II General Controls and Special Controls
   - With Exemptions

[^3]: [URL to further FDA guidelines]
Without Exemptions

3. Class III General Controls and Premarket Approval

The class to which your device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If your device is classified as Class I or II, and if it is not exempt, a 510(k) will be required for marketing. All devices classified as exempt are subject to the limitations on exemptions. Limitations of device exemptions are covered under 21 CFR xxx.9, where xxx refers to Parts 862-892. For Class III devices, a premarket approval application (PMA) will be required unless your device is a pre-amendments device (on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device) and PMA's have not use. In that case, a 510(k) will be the route to market.

In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

All classes of devices are subject to General Controls. General Controls are the baseline requirements of the Food, Drug and Cosmetic (FD&C) Act that apply to all medical devices, Class I, II, and III.

Office of Combination Products

The FDA Office of Combination Products (OCP) was established on Dec. 24, 2002, as required by Sec. 204 of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). The law gives the Office broad responsibilities covering the regulatory life cycle of drug-device, drug-biologic and device-biologic combination products.

Responsibility

- Promptly assigning a centre with primary jurisdiction for a combination product;
- Ensuring the timely and effective premarket review of combination products by coordinating reviews involving more than one centre;
- Ensuring the consistency and the appropriateness of post market regulation of combination products;
- Resolving disputes regarding the timeliness of premarket review of combination products;
- Reviewing, modifying, revising, or (if appropriate) eliminating agreements, guidance documents, or practices specific to the assignment of combination products; and
• Submitting annual reports to Congress on its own activities and effects.

Requests for Designation (Rfd)¹

An RFD is also referred to as an applicant’s letter of request (see 21 CFR 3.2(j)). It is a written submission to OCP. RFDs generally request a determination of (1) the regulatory identity or classification of a product as a drug, device, biological product, or combination product, and/or (2) either the component of FDA that will regulate the product if it is a non-combination product, or which Agency Centre will have primary jurisdiction for premarket review and regulation if it is a combination product. A letter of designation, see 21 CFR 3.2(i), (alternatively referred to as a designation letter) is FDA’s formal response to an RFD and is a binding determination with respect to classification and/or centre assignment that may be changed under conditions specified in Section 563 of the FD&C Act and 21 CFR 3.9 in the regulations.

It is not necessary to submit an RFD for every product. We recommend submitting an RFD when the classification of a product or the Agency Centre to which it should be assigned is unclear or in dispute. Sponsors are encouraged to submit an RFD as soon as they have sufficient information for FDA to make a decision regarding classification or assignment of a product.

The RFD should be submitted before filing any investigational or marketing application for the product. This will avoid a potential stay of the review clock if the classification or assignment of the product under review is determined to be unclear or in dispute during the review process. See 21 CFR 3.10. This will also help you avoid expending unnecessary time and resources, by ensuring that whatever of the appropriate type and to the appropriate Agency component. If you have classification or assignment questions regarding multiple related products or product families that have different configurations, ingredients, and/or proposed uses or indications, we recommend submitting a separate RFD for each product.

Centres of Expertise

The FDA is structured into separate centres, each of which has expertise in particular industries. The three centres that carry the primary responsibilities for regulating combination products are the Centre for Devices and Radiological Health (CDRH), the Centre for Drug Evaluation and Research (CDER), and the Centre for Biological Evaluation and Research (CBER). Each of these centres has systems for reviewing new products before they are
introduced to the U.S. market. Prior to marketing a new product, the sponsor or manufacturer submits valid scientific studies demonstrating the product’s safety and effectiveness. How the new product is classified ultimately determines which centre will review it? The format for the submission, and the applicable regulations.

New medical devices may require a submission for premarket approval or a showing of substantial equivalence to an existing device [510(k)]; a new drug may require a new drug application or an application for an investigational new drug. After approval of the submission, the medical device manufacturer is subject to the Quality Systems (QS) regulation, whereas a drug manufacturer is subject to the Good Manufacturing Practice (GMP) regulation for drugs.

Although these two sets of regulations share common elements, the requirements placed on the manufacturers differ somewhat. For example, Quality System Regulation/Current Good Manufacturing Practices (QS/cGMP) are specified in the QS regulation (Title 21, Code of Federal Regulations, Part 820 [21 CFR 820]); current Good Manufacturing Practices for drugs are specified in 21 CFR 210. The QS regulation requires that a manufacturer send a medical device report to CDRH when a device caused or contributed to a death or serious injury. The drug cGMP includes a requirement that information about adverse drug experiences be sent to CDER’s Pharmacovigilance and Epidemiology Division.

**Definition as per EU**

The definitions of drug-device combination products represent rather two basic two-tiered approaches, drug delivery devices and devices incorporating medicinal substances with ancillary action, leading to two types of combination products and three possible regulatory authorisation pathways. In Directive 93/42/EEC.

It is stated in:

• Art. 1(3) “…for devices intended to administer a medicinal product..., that the device shall be governed by the present Directive,”

• “If, however, such a device… and the medicinal product form a single integral product which is intended exclusively for use in given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC. ….”

• In Art. 1(4) “Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of
Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, that device must be assessed and authorized in accordance with this Directive.”

**Classification as per EU**

‘General’ medical devices are grouped into four classes as follows:
- **Class I** - generally regarded as low risk
- **Class IIa** - generally regarded as medium risk
- **Class IIb** - generally regarded as medium risk
- **Class III** - generally regarded as high risk.

Classification of a medical device will depend upon a series of factors, including:
- how long the device is intended to be in continuous use
- whether or not the device is invasive or surgically invasive,
- whether the device is implantable or active
- Whether or not the device contains a substance, which in its own right is considered to be a medicinal substance and has action ancillary to that of the device.

For the advanced therapies, a new type of combination product of cells or tissues containing devices was introduced and termed as, combined advanced therapy medicinal product. In 2006 the **Innovative Task Force (ITF)**[^7] was established as an internal EMEA horizontal cross-sectorial group.

The ITF brings together competences from the areas of Quality, Safety, Efficacy, Pharmacovigilance, Scientific Advice, Orphan Drugs and good practices compliance, as well as legal and regulatory affairs.

**Objectives of ITF**

Establish a discussion platform for early dialogue with Applicants in particular Small and Medium Enterprises (SMEs) to proactively identify scientific, legal and regulatory issues of emerging therapies and technologies. Address with relevant EMEA Committees and their Working Parties impact of emerging therapies and technologies on current scientific, legal and regulatory requirements. Identify early, the need for specialised expertise.

**Authorisation of Combination products**

A very few guidelines are available for the Combination products and their authorisation requirements are available from guidance available for drug and device. Different institutions such as representatives from national authorities, industry and trade association started
activities to harmonise requirements to authorise medicinal products or medical devices. Two major associations one is ICH developed in 1990 which assure the well-developed, safe, effective and high quality drug products and devices, and another one is The Global Harmonization Task Force (GHTF) developed in 1992 for regulation of medicinal devices. as per FDA:

The law provided that FDA assign a combination product to a lead agency centre based on the "primary mode of action" (PMOA) of the combination product, over time, FDA realized there were some combination products that did not have a clearly definable PMOA. To address these concerns, FDA set out definitions of mode of action and PMOA, as well as an "assignment algorithm" used to determine centre assignment when the PMOA cannot be determined with reasonable certainty. There is no special type of marketing application for combination products in US.

Combination products are either authorised as a drug, a biologic or a device. In the development programme three legal frameworks may be considered to collect the required data for a successful application for authorisation, since each of the above mentioned products have their own types of application for authorisation and QA regulations. The type of product and appropriate regulatory pathway defined by PMOA and designation of the product; will determine the specific requirements to place the combination product on the market.

"Mode of action" is the means by which a product achieves an intended therapeutic effect or action. "POMOA" is "the single mode of action of a combination product that provides the most important therapeutic action of the combination product." in another way, PMOA [9] is the "mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product." For example, if the PMOA of a drug-device combination product is attributable to its device constituent part, Centre for Devices and Radiological Health (CDRH) would have primary jurisdiction for the combination product, whereas if the PMOA of a drug-device combination product is attributable to its drug constituent part, Centre for Drug Evaluation and Research(CDER) would have primary jurisdiction.

In cases where FDA is unable to determine the most important therapeutic action with reasonable certainty, an "assignment algorithm" is used. First, FDA looks at historical
precedents to assign the combination product to the agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole. When there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole, FDA assigns the product to the agency competent with the most expertise related to the most significant safety and effectiveness questions presented by the combination product. For example, if the most significant safety and effectiveness issues presented by a drug-device combination product in this scenario were attributable to the drug constituent part, the combination product would likely be assigned to CDER.

**Combination Products Approved as Drugs or Biologics or device:**
The FD&C Act specifies in Section 505 the content of NDAs as whether (i) the drug is safe for use and effective in use, (ii) list of components, (iii) composition of such drug, (iv) a full description of the methods, and the facilities and controls used for, the manufacture, processing, and packing of the drug, (v) samples of the drug if requested by the Secretary and (vi) specimens of the labelling for the drug. Further on, the 21CFR314 “Application for FDA Approval to Market a “new Drug” specifies the content of a new drug application (NDA) in Section 314.50 and Section 314.126 which provides the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs by adequate and well controlled studies in human.

**Table 4.1FDA centres and approved product category**

<table>
<thead>
<tr>
<th>Primary FDA Approval Centre</th>
<th>FDA Consulting Centre</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDRH (device)</td>
<td>CDER (Drug)</td>
<td>Bone cement containing antimicrobial agent, Cardiac pacemaker lead with steroid coated tip, condom or diaphragm with contraceptive or antimicrobial agent, drug eluting stent, dental device with fluoride</td>
</tr>
<tr>
<td>CDRH (device)</td>
<td>CBER (biologics)</td>
<td>Spinal fusion cage with recombinant human bone morphogenic protein catheters that deliver angiogenesis gene to heart muscle</td>
</tr>
<tr>
<td>CBER (biologics)</td>
<td>CDRH (device)</td>
<td>Plasmaphoresis devices- blood banking equipment</td>
</tr>
<tr>
<td>CDER (Drug)</td>
<td>CDRH (device)</td>
<td>Photo activated drug with proprietary light source, oxygen tank for therapy, prefilled syringe, transdermal patch</td>
</tr>
<tr>
<td>CDRH (device)</td>
<td>None</td>
<td>Device that calculate drug dosages, Glucose monitor device/insulin pump combination - Drug delivery pump and/or catheter infusion pump for implantation Iontophoreses device, Nebulizer etc.</td>
</tr>
</tbody>
</table>
Table 4.2 Comparison between Device and Drug/Biologic product regulatory Process

<table>
<thead>
<tr>
<th>Review requirement</th>
<th>Device</th>
<th>Drug/biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>can use prototype in clinical trial.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Product life cycle</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Ease of in vitro assessment</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Influence of physician technique on result</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ability to visualise performance after use</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Number of full-scale clinical studies usually required</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Number of regulatory classes</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Extent of clinical data required</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Average number patients in clinical trial</td>
<td>Hundreds</td>
<td>Thousands</td>
</tr>
<tr>
<td>Average time to FDA approval once all required testing complete and submitted for review</td>
<td>90 days 2 to 5 years</td>
<td>7 to 10 years</td>
</tr>
<tr>
<td>510(k) PMA (include IDE study), NDA /BLA (pharmaceutical) (include IND studies)</td>
<td>Low moderate to high</td>
<td>High</td>
</tr>
<tr>
<td>510(k) PMA, NDA /BLA (pharmaceutical)</td>
<td>$300,000-$500,000</td>
<td>$200 million-$300 million</td>
</tr>
</tbody>
</table>

Regulations and directives required for combination products as per EU

There is no particular guidelines for the regulation of combination products in EU. Combination products are authorised either as a medicinal products or medicinal device and their development and marketing authorisation applications requirements are derived from medicinal device and drug legislation and guidelines.

Table 4.3 For Combination products as a Medicinal Products

<table>
<thead>
<tr>
<th>Regulations for Authorisation and supervision of Medicinal products for human use in European community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directives</td>
</tr>
<tr>
<td>Medicinal products or medicinal biological products</td>
</tr>
<tr>
<td>Directive 2001/83/EC amended by Documentation required for Marketing</td>
</tr>
</tbody>
</table>
---|---
Directive 2001/20/EC | Good clinical practice for clinical trial

For Combination products as a Medicinal Device

European regulatory path
Within Europe, there is no regulatory agency dedicated to defining specific regulatory paths for combination products. European approval requirements place greater emphasis on safety and performance; and although clinical efficacy requirements are included, they are not necessarily as robust as those in the U.S. Devices in general are classified based on a number of rules described in the Medical Devices Directive, which builds on the concept of a risk-based approach related to the device’s duration of use, invasiveness, and associated hazards. A product can only be regulated as a medicinal (whether drug or biologic) or a device. Once approved for market, a product can be sold anywhere in the European Economic Area (the original 15 EU countries and after May 2004, the additional 10 new member states, plus Iceland, Liechtenstein and Norway). Other countries throughout the world also accept the CE mark.

A medicinal product cannot be CE-marked. It can only be marketed through submission of a Marketing Authorization Application (MAA) either to the governmental authority in a single country, referred to as the Competent Authority, or to the European Medicines Evaluation Agency (EMEA; London), a centralized agency that can authorize a medicinal product throughout the EU. The equivalent of a Competent Authority in the U.S. is the FDA. The two different paths – one of which results in a CE mark (medical device) and the other with a Marketing Authorization (medicinal product) – Have resulted in the same product from different manufacturers who chose different routes to approval, being CE-marked in one instance as a medical device and in another instance approved as a medicinal product. Additional confusions arise when a product from a single manufacturer is CE-marked as a medical device but is still considered a medicinal product in some countries.
Before placing a medicinal product onto the market of European Member States an authorisation under one of two or three kind of market authorisation application (MAA) is required: the decentralized procedure (DCP), mutual recognition procedure (MRP) or the centralised procedure (CP). The MAA will be reviewed by one of the governmental agencies with mutual recognition by the National Competent Authorities of concerned MS or by the central European agency, EMEA. The centralized procedure, which is solely performed by the EMEA, is mandatory for biotechnology products and certain therapeutics which allows marketing of medicinal products in all European MSs with a single license. However, in the case when the medical device and medicinal product form a single integral product, the Competent Authority responsible for the evaluation of the medicinal product would consult, if necessary.

**General Development Considerations**

Combination product development typically focuses on the scientific and technical issues raised by the particular product being developed. For a combination product, these scientific/technical issues will ordinarily reflect the combination product itself as well as its constituent parts. When combining products such as drugs or biologics and devices that are customarily developed using different regulatory paradigms, certain critical developmental issues, such as the interaction of the drug/biologic and device constituents, may not be readily apparent. Existing guidance documents are generally excellent starting points for considering the types of issues raised by the constituent parts of a combination product, but often they will need adaptation to fully address the combined nature of a combination product. For example, guidance for preclinical evaluation of drugs/biologics differs from the preclinical/non-clinical studies conducted for devices. When developing a combination product, it is likely that neither isolated approach would fully address the relevant preclinical development questions for both constituents as well as for the combination product as a whole. Instead, FDA recommends that developers consider the scientific and technical issues raised by the combination product and its constituents and propose an approach that appropriately addresses these issues without requiring duplicative or redundant studies.

In many circumstances, the development considerations depend on the type of combination product. When the combination product is comprised of constituents that are chemically, physically or otherwise combined or mixed and produced as a single entity, developers should consider and, as appropriate, evaluate the potential for a broad range of
drug/biologic/device interactions. For example, for a drug eluting stent, the mechanical attributes of the polymer coating system that contains the drug substance are important for stent deployment, drug release, biocompatibility, and stability. For some combination products, the constituents may have synergistic effects that should be evaluated. In the context of these studies, it is appropriate to discuss approaches to avoid duplication/redundancy and to develop strategies to streamline the overlapping aspects of development.

Innovative new technology may also challenge existing approaches for product development. For example, a new device used to deliver a drug/biologic to a new area of the body that was previously inaccessible might make it necessary to develop new methods to determine the effect of such localized/targeted delivery, particularly when it results in higher exposure to that target than when the drug is systemically administered. Likewise, innovative technologies such as nanotechnology or live cellular products may lead to the development of new manufacturing methodologies or unique safety issues not associated with products manufactured in other ways.

**Drug Delivery system**

Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery systems. Today, drug delivery companies are engaged in the development of multiple platform technologies for controlled release, delivery of large molecules, liposomes, taste-masking, oral fast dispersing dosage forms, technology for insoluble drugs, and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon, and Trans mucosal routes.
ICH guidelines harmonised by three countries like Japan, US and Europe for the prevention of unnecessary duplication of animal studies and clinical trials by following international standards.

ICH Guidelines are mainly concern with QUALITY, SAFETY and EFFICACY

Guidelines required for Medical Device in US and EU
Sector of Medical device has to follow the international initiative for the pre and post approval requirements. The GHTF represents an international initiative of representatives from medical device regulatory authorities and trade associations in EU, US, Canada, Japan and Australia to promote harmonisation and standardisation of regulatory requirements for medical devices.

International Medical Device Regulators Forum (IMDRF)
The International Medical Device Regulators Forum (IMDRF) was conceived in February 2011 as a forum to discuss future directions in medical device regulatory harmonization. It is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force on
Medical Devices (GHTF), and to accelerate international medical device regulatory harmonization and convergence.

**Guidelines for Combination Products in US**

There are mainly two guidelines for the Combination products, one is discussing the technical and scientific information required for Marketing Application and another is GMP.

Some of the important perspective which are studied for combination products like

- Manufacturing considerations
- Clinical investigation
- Drug Device interactions
- Stability data
- Pre-clinical testing
- Biocompatibility studies
- PK studies.

**Current Good Manufacturing Practice (CGMP)**

The following current good manufacturing practice regulations and other applicable standards are codified for products that may be constituent parts of a combination product:

- Current good manufacturing practice (cGMP) regulations for finished pharmaceuticals, or drug products (21 CFR Parts 210 and 211). Drug products not subject to these regulations (e.g., bulk drugs or active pharmaceutical ingredients) must still meet the current good manufacturing practice general standard required by the statute.
- Quality system (QS) regulation for devices (21 CFR Part 820).

The biological product regulations, 21 CFR Parts 600-680, may also apply to the manufacture of drugs that are also biological products along with the drug cGMP provisions. FDA has not promulgated current good manufacturing practice regulations specifically for combination products. Until it does so, each constituent part (i.e., the drug, device, or biological product) remains subject only to its governing current good manufacturing practice regulations when marketed separately, see 21 CFR 3.2(e)(3) and (4), and when manufactured separately as constituent parts of a combination that will later be combined, see 21 CFR 3.2(e)(1) and (2).

For example, if a drug is marketed that is intended for use only with an approved individually specified device that is also marketed separately, the drug constituent must comply only with 21 CFR Parts 210 and 211, and the device constituent must comply only with 21 CFR Part
820. Similarly, during the time of separate manufacture (i.e., before drug and device combination products are produced as a single entity or are co-packaged) 21 CFR Parts 210 and 211 apply only to the drug constituent, and 21 CFR Part 820 applies only to the device constituent.

However, for combination products that are produced as a single-entity or are co-packaged, see 21 CFR 3.2(e)(1) and (2), both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together. The rest of this section refers only to situations when combination products that are produced as a single entity or are co-packaged as defined in 21 CFR 3.2(e)(1) and (2) are joined together.

Guidelines for Combination Products in the EU
There are three types of medical devices incorporated into combination products:

- Devices for the administration of medicines (e.g., empty single-use syringes and reusable spoons or droppers). These items are regulated by the medical device regulations.

- Devices that combine with a medicinal product to form a single, integral product designed to be used exclusively in the combination—e.g., prefilled syringes. These products are not reusable and are subject to Directive 65/65/EEC in the EU. In addition, the relevant essential requirements of Annex 1 of Medical Devices Directive 93/42/EEC apply to safety- and performance-related features of such devices. This means that the combination is assessed by the drug regulatory authorities, and the device also needs to meet the essential requirements of the Medical Devices Directive. This is usually satisfied by the use of a CE mark.

- Devices incorporating a substance, which, if used separately, may be considered a medicinal product. In addition, the substance (the drug) is liable to act upon the body with action ancillary to that of the device—e.g., a heparin-coated catheter. In this case, the medical device assessment authority (notified body) assesses the combination product, and the drug information is sent by the notified body to a drug regulatory authority for assessment of that specific section. The drug regulatory authority must verify the safety, efficacy, and usefulness of the drug.
DOSSIER CONSULTATION

Table 4.4 Two types of applications are required for the assessment of the Documents submitted

<table>
<thead>
<tr>
<th>Bibliographic data application</th>
<th>New active substance applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known medicinal substances are concerned with well-established medicinal use within the Community for at least ten years.</td>
<td>Medical substance is none established.</td>
</tr>
<tr>
<td>Safety and Efficacy data may not require if required than use of literatures like textbooks</td>
<td>Comprehensive data is required in full applications.</td>
</tr>
</tbody>
</table>

At the time of developing device or products these data are required in consultation dossier.

- Description of the method of manufacturing medicinal substance
- Control of starting material
- Qualitative and quantitative test data carried out for the control of medicinal substance
- Stability data
- Toxicity data
- Pharmacokinetic and pharmacodynamics data
- Local tolerance
- Labelling information
- Clinical evaluation data.

Design Dossier

Design dossiers are extensive technical documents that demonstrate a manufacturer’s product meets the requirements of relevant regulations. They include test reports, risk management reports, assessments of clinical evaluations, biological evaluations and other reports that need to be reviewed by a Notified Body before they may be approved.

General Requirement to Conduct Clinical Trials in the US and the EU

Clinical data are most required information for the authorisation of drug or device medical products in any country but approaches and objectives are differ within countries.

Table 4.5 General Requirement to Conduct Clinical Trials in the US and the EU

<table>
<thead>
<tr>
<th>IN USA</th>
<th>IN EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>For IND application mainly focus on New drugs and supports for its developments</td>
<td>They follow the Directive 2001/20/EC and clinical trial application (CTA) mainly focus</td>
</tr>
</tbody>
</table>
Investigational New drug application and its exemption

The Investigational New Drug (IND) Application is a formal notification by the study sponsor to the FDA that a drug or biologic will be used in a clinical investigation. The IND Application is a summary of the investigational plan.

- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
- The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent set forth in 21 CFR 50.
- The investigation is conducted in compliance with the requirements of 21 CFR312.7

Investigational Device Application and its exemption

An Investigational Device Exemption (IDE) allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data.

Permits the device to be shipped lawfully for the purpose of conducting investigations of the device.

Table 4.6 Three Types of Studies described in IDE regulations at 21 CFR 812

<table>
<thead>
<tr>
<th>IDE Exempt</th>
<th>Significant Risk (SR)</th>
<th>Non-Significant Risk (NSR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not subject to IDE regulations</td>
<td>Subject to IDE Regulations (21 CFR 812)</td>
<td>Subject to IDE Regulations (21 CFR 812)</td>
</tr>
<tr>
<td>No IDE application required</td>
<td>FDA approved IDE application required (21 CFR 812)</td>
<td>No IDE application required (assumed to have an approved IDE after IRB approval 21 CFR 812)</td>
</tr>
</tbody>
</table>
CONCLUSION
The regulatory environment for drug-device combination products in the US and the EU is an implicit part of the legislations and guidelines to regulate and classify drugs and devices. There is a separate guideline for combination products whereas no specific guidelines for combination products they are either regulated as a device or drug in USA these products are regulated as a Drug-Device combination and in EU they regulated as fix combination products.

The concept of combination products could probably be applied easier to new drugs and devices and advanced technology with the general US definition while in EU there is no specific combination products guidelines so it is specific and in detailed so regulation is accurate but not well compatible with new technologies.

In US identification of primary mode of action for intended purpose and for the selection of regulatory pathway for any products there are certain tools like ICA, published RFD play a vital role but in EU situation is different At present, there is no central decision-making to indicate which regulatory route should be followed in case of doubt some EU guidance is available through the MEDDEV 2.1/3.

Currently there is no convergence between US and EU for regulation and development of the combination products Due to the different regimes in the US and EU, companies would need to set up different in-house procedures and teams to understand and comply with the differing regulatory demands. Also, types and sizes of clinical trials and the information on the drug and device elements of their products required for regulatory approval and market entry would be different.

To date there is no common approach between these two countries for combination product regulation which results in complexities in this area so a global response and common approach will result in simplification and relieve coast and could also be useful in the areas of clinical trials, post-market vigilance and health technology assessment, and could result in streamlining of pre-market requirements for companies, and a standardising of documents needed to be filed for combination products.
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