"A Review on Combination Products with Special Focus and Comparison of Regulatory Approval Process for Drug-Eluting Stents in USA and Europe"

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BY

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Semester VIII

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CERTIFICATE

*This is to certify that Project Work (BP812PW) entitled "**A Review on Combination Products with Special Focus and Comparison of Regulatory Approval Process for Drug-Eluting Stents in USA and Europe**" is the bonafide work carried out by **SHAH AAYUSHI** (19BPH003), **PATEL PRINCE** (19BPH082), **MODI VRAJ** (19BPH119), **PATEL YASHVI** (19BPH122) B.Pharm Semester VIII under my guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2022-2023. This work is up to my satisfaction.*

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CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B.Pharm. Project work (BP812PW) entitled ***"A REVIIEW ON COMBINATION PRODUCTS WITH SPECIAL FOCUS AND COMPARISON OF REGULATORY APPROVAL PROCESS FOR DRUG-ELUTING STENTS IN USA AND EUROPE"*** *Submitted by* ***SHAH AAYUSHI*** *(19BPH003),* ***PATEL PRINCE*** *(19BPH082),* ***MODI VRAJ*** *(19BPH119),* ***PATEL YASHVI*** *(19BPH122), B.Pharm. Semester VIII is a bonafide review/research work carried out by us at the Institute of Pharmacy, Nirma University under the guidance of Dr. Charmy Kothari. We are aware about the rules and regulations of plagiarism policy of Nirma University, Ahmedabad. According to that, the review/research work carried out by us is not reported anywhere as per best of our knowledge.*

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DECLARATION

We, ***SHAH AAYUSHI (19BPH003), PATEL PRINCE (19BPH082), MODI VRAJ (19BPH119), PATEL YASHVI (19BPH122),*** *students of VIIIth Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that our project work (BP812PW) entitled* ***"A REVIIEW ON COMBINATION PRODUCTS WITH SPECIAL FOCUS AND COMPARISON OF REGULATORY APPROVAL PROCESS FOR DRUG-ELUTING STENTS IN USA AND EUROPE"*** *is a result of culmination of our sincere efforts. We declare that the submitted project is done solely by us and to the best of our knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. We also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.*

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LIST OF ABBREVIATIONS

USA	The United States of America
EU	European Union
UDI	Unique Device Identification System
CDRH	Center for Device and Radiological Health
CDER	Center for Drug Evaluation and Research
DES	Drug Eluting Stent
EMA	European Medicines Agency
FD&C Act	Food, Drug and Cosmetics Act
MDI	Metered Dose Inhaler
DPI	Dry Powder Inhaler
TDS	Transdermal Delivery System
CAD	Coronary Artery Disease
PMA	Pre-Market Approval
USFDA	U.S. Food and Drug Administration
IND	Investigational New Drug Application
PMOA	Primary Mode of Action
MAA	Marketing Authorisation Application
MDR	Medical Devices Regulation
CE marking	Conformité Européenne
DDC	Drug Device Combination
GMP	Good Manufacturing Practices
IDE	Investigational Device Exemption
DMF	Drug Master File
LOA	Letter Of Authorisation
IVDR	In Vitro Diagnostic Regulation
MDD	Medical Devices Directive

1. ABSTRACT

Combination products have been tremendously advancing nowadays due to their efficiency and convenient use in treatment, but navigating the regulatory framework in the US and EU is complex and requires a thorough understanding to ensure compliance. There are four types of combination products in the US: drug with device delivery system, device coated or impregnated with a drug, biologic with device delivery system, and a product composed of two or more regulated medical products. Regulatory classes for drug-device combinations are determined by risk level, with class III products being the most high-risk and requiring strict oversight. In the EU, integral drug-device combinations must adhere to manufacturing, labelling, and UDI requirements to ensure conformity. The regulatory pathway for coronary drug eluting stents differs between the US and EU. The CDRH handles premarket review and regulatory responsibility for drug-eluting stents in the US, while the CDER evaluates the drug component's safety and efficacy. In contrast, the EMA oversees the regulatory process for drug-eluting stent in the EU, evaluating both the device and drug components. Compliance with regulations for combination products requires significant investment in time and resources and a thorough understanding of regulatory requirements in both regions.

2. INTRODUCTION TO COMBINATION PRODUCTS

- As set forth in section 503(g) of the FD&C Act and 21 CFR part 3, "a combination product is a product comprised of two or more different types of medical products. The drugs, devices, and biological products included in combination products are referred to as constituent parts of the combination product." [15]
- Under 21 CFR 3.2(e), combination products include:
- "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 (a single entity combination product, such as a prefilled syringe or drug-eluting stent);" [15]
- "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 (a co-packaged combination product, such as a surgical or first-aid kit containing bandages and an antiseptic drug);" [15]
- "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) (a cross-labelled combination product, as might be the case for a light-emitting device and a light-activated drug indicated for use together for treatment of a dermatologic condition);" or
- "Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (also a cross-labelled combination product)." [15]

3. DIFFERENT CATEGORIES OF COMBINATION PRODUCTS

The table-1 below has been created to identify and describe the 9 different types for a combination product.

Table-1: description of categories of combination products [13]

Type	Description	Common Example(s)
1	Convenience Kit or Co-Package *Drug and device are provided as individual constituent parts within the same package*	Drug or biological product vials packaged with device(s) or accessory kits (empty syringes, auto-injectors, transfer sets), first aid or surgical kits containing devices and drugs
2	Prefilled Drug Delivery Device/ System *Drug is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver drug*	Prefilled drug syringe, auto-injectors, metered-dose inhalers, dry powder inhalers, nasal-spray, pumps, transdermal systems, prefilled iontophoresis system or microneedle "patch"
3	Prefilled Biologic Delivery Device/ System *Biological product is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver biological product*	Vaccine or other biological product in a prefilled syringe, autoinjector, nasal spray, transdermal systems or microneedle patch pre-loaded with biological product
4	Device Coated/ Impregnated/ Otherwise Combined with Drug *Device has an additional function in addition to delivering the drug*	Drug pills embedded with sensors, contact lens coated with a drug, drug-eluting stents, drug-eluting leads, condoms with spermicide, dental floss with fluoride, antimicrobial coated catheters/sutures, bone cements with antibiotics
5	Device Coated or Otherwise Combined with Biologic *Device has an additional function in addition to delivering the drug*	Live cells seeded on or in a device scaffold, extracorporeal column with column-bound protein
6	Drug/Biologic Combination	Antibody-drug conjugates, progenitor cells combined with a drug to promote homing

7	Separate Products Requiring Cross Labeling	Light-activated drugs or biological products not co-packaged but labeled for use with a specific light source device
8	Possible Combination Based on Cross Labeling of Separate Products	Drug/biological product under development utilizes a device, but unclear whether the final product will require that the two be cross-labeled
9	Other Type of Part 3 Combination Product (e.g., Drug/Device/ Biological Product) *Combination product not otherwise described*	All 3 articles are combined in a single product (e.g., a prefilled syringe containing an antibody-drug conjugate), device to manufacture a biologic also includes a drug or biologic in the kit, or the product contains two different combination product types (e.g., Type 1 and Type 2 are provided together

Some examples of above categories of combination products are discussed below in Table-2.

Table-2: Detailed information on examples of combination products

Product type	Mechanism	Treatment	Example
Drug eluting Stents	When compared to balloon angioplasty alone, the use of an endovascular stent, which minimizes vessel shrinking and recoil postintervention, reduces the likelihood of restenosis.	Used as a kind of therapy for coronary artery disease (CAD)	Sirolimus, often known as rapamycin, is arguably the most effective and well researched stent-released medication to date.
Orthopaedic device-based drug delivery	Placing orthopaedic hardware to mend and stabilize broken bones while they recover or to replace functionally whole tissues made of antibiotic-loaded polymer.	Surgical removal and soft tissue rebuilding are not required since PMMA or biodegradable beads resorb at controlled rates.	PEEK, Polylactide and its copolymer-based devices.
Transdermal Dosage Form (TDS)	The reservoir TDS consist of a semisolid substance in which the medication is	Drugs administered transdermally	They have been created for the delivery of hormone

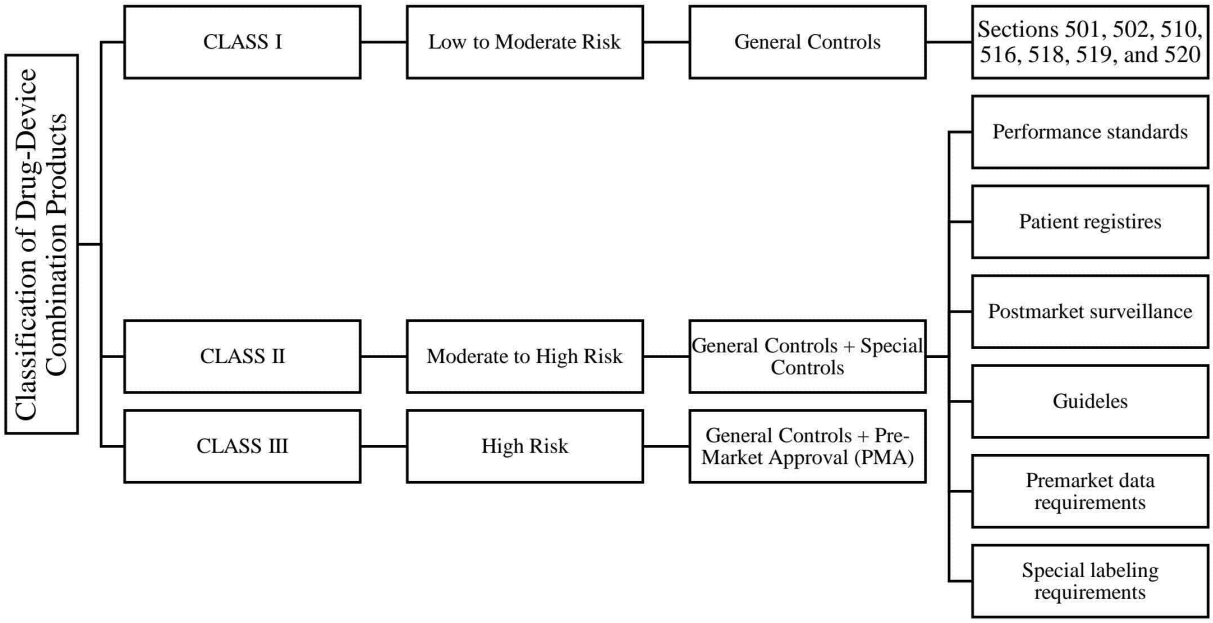
	suspended or dissolved, enclosed in a pouch that clings to the skin.	are used to manage and cure disorders like hypertension, motion sickness, discomfort, and migraines.	replacement therapy and contraceptives, as well as nitroglycerin, nicotine, testosterone, fentanyl, lidocaine, scopolamine, oxybutynin, and tacrine.
Intrauterine systems (IUS)	These reversible contraceptives include T-shaped polyethylene frames that retain medication over a lengthy period of time and are intended to deliver modest daily quantities of medicine into the uterine cavity.	Contraception is their major usage.	There are five different authorized brands: Paragard, Mirena, Kyleena, Liletta, and. Skyla.
Pre-filled Syringes	Drugs for parenteral use that are created as pre-filled syringes or sold in packages including a vial and a disposable syringe.	They are used in blood stimulants, therapeutic proteins, cardiac, diabetes, and autoimmune conditions for self-medication by the patients.	Depo-Provera (medroxyprogesterone acetate suspension), Risperdal Consta (risperidone intramuscular injection)

4. CLASSIFICATION OF DRUG-DEVICE COMBINATION PRODUCTS (USA & EUROPE)

➢ USA

The risk-based device categorization system for medical devices was established by the federal law (section 513 of the Federal Food, Drug, and Cosmetic Act). Each device is categorized into one of three regulatory classes—Class I, Class II, or Class III—based on the degree of regulation required to reasonably ensure its efficacy and safety. [12]

- From Class I devices to Class II to Class III, the limitations of regulation elevate as we move ahead, with Class III devices being subjected to the most amount of regulation and devices in Class I being liable to the least. The regulatory controls for each device class include: [12]



- Class III (critical risk): Premarket Approval (PMA) and general control
- Class II: General Controls and Special Controls (average to critical risk).
- Class I: General Controls (low to average risk)
- **General Controls:** Per sections 501, 502, 510, 516, 518, 519, and 520 of the FD&C Act, general controls are regulatory obligations. Unless specifically exempted by laws, all medical devices are subject to general controls. If a device

is exempt from 1 of the general restrictions, the classification rule for that device specifies this exception.

Table 3- Different section for general control of combination products according to FD&C Act [13]

SECTION	GENERAL CONTROLS
501	Adulterated Devices
502	Misbranded Devices
510	Registration of producers of devices
516	Banned devices
518	Notifications and other remedies
519	Records and reports on devices
520	General provisions respecting control of devices intended for human use

- **Special controls:** Regulations impose special restrictions on class II devices. FDA categorizes devices into class II when general controls alone cannot reasonably offer assurance of the device's safety and efficacy and when there is sufficient data to construct specific controls to do so.[13]
- Class III devices must have their **Premarket Approval Application (PMA) approved.**
- The FDA categorizes certain devices as class III devices if general controls and special controls are insufficient to reasonably assure the safety and efficacy of the device or if there is not enough information to make such a determination. Class III devices aim to safeguard or sustain human life, prevent human health disability, or if not pose a possible unreasonable risk of illness or injury. [13]

➢ **EUROPE**

There are dual kind of combination products:

1) **Integral**: The medical device and API form one single integrated product. [3]

Examples include: transdermal patches, pre-filled inhalers, pre-filled syringes and pens

Types of integral-

Class I-Non sterile

Class II a- sterile

Class II b- active device that are intended to administer or remove from the body.

Class III-implantable

2) **Co-packaged**: The API and medical device are two distinct goods that are combined in the same secondary package.[3]

Examples include a reusable insulin pen and a pain treatment pill delivery system with a controller.

5. GENERAL REGULATORY REQUIREMENTS OF USA AND EUROPE

- **USA**

Premarket Approval Pathway [14]

- DES are regulated under Class III devices hence they need to undergo a Premarket approval (PMA) procedure, although if in case there is a reference device available then a 510K premarket notification is applicable.
- According to FDA, PMA suffices the scientific evidence required to assure device safety and efficacy as per intended use. PMA approval by FDA is necessary before marketing the device.
- Whether an unclassified device requires a PMA or not can be known from searching the three-letter product code in the Premarket Approval (PMA) database and the 510(k) Premarket Notification database.

Requirements for PMA [14]

➢ PMA application
➢ Investigational device
➢ Exemption (IDE application)
➢ IND form 1571 (in case new drug is being used)
➢ Master files
➢ Letter of authorisation (LOA)

➢ Non clinical Engineering tests
➢ Toxicity studies ISO 10993
➢ Biological Evaluation of Medical Devices
➢ ISO13485
➢ Environmental assessment according to 21 CFR 25.

➢ EUROPE

Conformity assessment of device

The European legal framework for medical devices was altered by the Regulations on Medical Devices (Regulation (EU) 2017/745) and on In Vitro Diagnostic Devices (Regulation (EU) 2017/746) by introducing new responsibilities for EMA and national competent authorities in the assessment of specific categories of medical device. [1]

- The Medical Devices Regulation went into force on May 26, 2021. Manufacturers must adhere to the regulation when introducing new medical devices to the market. The Active Implantable Medical Devices Directive 90/385/EEC and the Medical Devices Directive 93/42/EEC have both been abolished. [1]

- Requirements to be fulfilled by combination product manufacturers have changes since the previous medical devices Directive was super ceded by a new MDR in May 2021.[1]

- Earlier for a DDC having medicinal product as the PMOA, a Marketing Authorization Application (MAA) was to be submitted in accordance with notice to Applicants V2B3. [1]

- Meanwhile under the MDR, along with a MAA a separate NBOp opinion is required. If this step is not addressed appropriately, it can amount to high costs and time of approval. [1]

- CE marking in accordance with European legislation is an integral part of marketing a DDC product in Europe, as it confirms the product compliance with regulations, safety and performance. [1]

- Under the MDR, Article 117 is applicable for those DDC products which are regulated as medicinal product. [1]

- This article mandates that manufacturers CE-mark any component of a device that is non-reusable or designed just for use in a specific DDC, including any device component of a medical product. They must include the appropriate paperwork in their marketing authorization dossier. [1]

- The manufacturer must provide the GSPRs published by a Notified authority for the conformance of device components in its DDC if the device parts are not CE certified. Usability data must be included in the DDC submission to European regulators in order for the notification body to examine the device component(s). [1]

- The Annex I of MDR covers all the requirements related to instructions of usage, labelling, manufacturing, design, performance and risk under the GSPRs which acts as proof of conformity during regulation of DCC products. It is the responsibility of manufacturer to identify and attach evidence for all the important GSPRs during submission.[1]

- As described in the Annex II of MDR, in NBOp submission a technical file consisting required amount of documentation as provided in the guidance on structure and content of submitting file5 is given by TeamNB for CE marking of medical devices. [1]

Requirements of MAA Submission [3]

I. Manufacturing process - Must comply with GMP and detailed according to MAA

II. Controls - Acceptance criteria of finished DDC product are based on the stability data, industry standards, Available release, experiments and target population.

III. Validation - The proof of robustness of manufacturing process for continually producing the DDC up to desired standards must be included in the MAA.

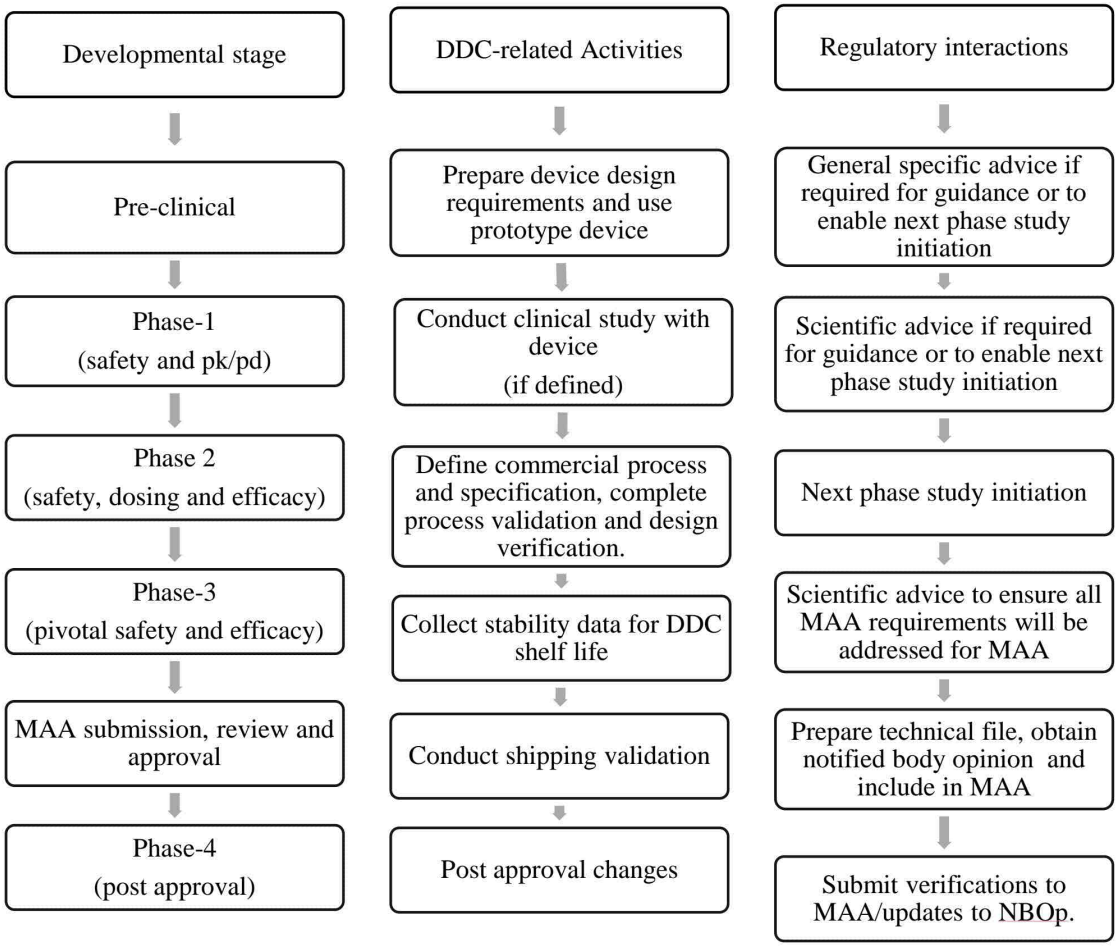
IV. Stability - In-use procedures, assigned shelf-life and its maintenance along with shipping conditions should be mentioned in the MAA.

V. Manufacturers of integrated DDC goods that are regulated as medical products are required to follow certain guidelines in order to comply with the relevant labeling standards. As a result, packaging does not require a UDI associated to the device component.

VI. The appropriate information, such as the device manufacturer, CE marking, must be included on either the device itself or its packaging for co-packaged combination items where the device component is required to have a CE mark and adhere to MDR criteria. The entire outside package should have this information.

The MDR standards, which dictate that labelling information such as device maker, UDI, and CE mark shall be supplied on the device or its packing container, are followed for co-packaged DDC items when device component is CE marked. Information about pharmaceutical products, such as the patient information booklet, product labeling, and SmPC, shouldn't contain it. In addition, there must be no mention of device vigilance reporting in the information on medical products. [3]

Regulatory pathway for DES in Europe [3]



6. REGULATORY PATHWAY FOR CORONARY DRUG ELUTING STENT

- **USA**

The MOA for modern DESs where the device element maintains open and unobstructed coronary vessels, while the drug component improves the safety and efficacy of the uncoated stent by preventing restenosis. After thorough consultation with CDER, CDRH has been assigned with the pre-market review and regulatory duties for these coronary drug-eluting stents. [7]

Application Process: [7]

I. Product classification

Coronary DES are Class III devices that must submit and get premarket approval (PMA) applications before being commercially marketed in the US. To be considered for approval, the pre-market approval application must contain or reference reliable scientific data that provides a rational assurance of the effectiveness and safety of the drug-eluting stent when used according to its designated use.

II. Investigational Device Exemption (IDE) Application:

According to 21 CFR 812.3(m), which defines a serious risk, The FDA has mandated that the submission of an Investigational Device Exemption application is necessary for drug-eluting stents and they are not exempted from this requirement.

Before starting human clinical research in the United States, the sponsor must get FDA clearance for an Investigational Device Exemption (IDE) application if one is necessary.

Sponsors of these studies are required to comply to:

- Investigational Device Exemption regulations (21 CFR 812) 104
- Regulations governing institutional review boards (IRB) (21 CFR 56)
- Informed consent (21 CFR 50)

The FDA advises sponsors to communicate before filing an Investigational Device Exemption (IDE) application in order to get informal advice on development. For a DES, pre-submission contacts can be general or narrowly focused on things like engineering testing, CMC testing, or clinical protocols.

III. IND application

To completely characterise potential toxicities, non-clinical and clinical assessment of the API singularly (not given through a stent, for example) may be necessary.

An IND application must be submitted in order to conduct human studies of an experimental drug in the US. The prospective use of the medicine is planned to be integrated with a stent, and this should be made clear in the IND application.

IV. PMA Application

An application of Pre-Market Approval must give enough assurance of the completed drug eluting stent's effectiveness and safety in order to be approved.

Considering the significant volume of nonclinical data generally required and the relatively lengthy primary endpoint timeline for a DES, it may be advisable for applicants to consider utilizing the Modular PMA application program. (e.g., one year or longer).

A modular pre-market approval application is a collection of distinct portions, which are to be turned in sequentially when they are finished. The components come together to form an entire application.

The advantage of the modular approach is that it allows the applicant to identify and address any deficiencies pointed out by the FDA in a particular section earlier in the review process, as opposed to a conventional PMA application, where the entire application is submitted in one go.

V. Master Files

The information in the master file may be used by a third-party applicant with the holder's consent to aid the application of the third party to the FDA, though the master file's contents are still the holder's property.

If a third-party applicant fails to include a letter of authorization from the MAF or DMF holder, allowing the FDA for reference to the master file to lead to the application, FDA will not consider the MAF or DMF as supportive evidence for the application.

VI. Letter of Authorization

The original LOA should be provided to the DMF, and copies of the LOA should be submitted with the initial IDE and subsequent PMA applications.

An LOA may give FDA the authority to discuss and/or reference information from one regulatory submission in support of other submission.

- **EUROPE**

Drug-eluting stents are subject to EMA regulation as medical devices and must adhere to the EU's In Vitro Diagnostic Regulation (IVDR) and Medical Device Regulation (MDR). The safety, functionality, and quality standards for medical devices, including drug-eluting stents, are outlined in the MDR and IVDR. [4]

Drug-eluting stents must go through a thorough evaluation procedure by the EMA in order to be commercialized in the EU. Clinical trials are used to evaluate the device's efficacy and safety, and laboratory testing is done to make sure it adheres to the necessary standards. Once a drug-eluting stent has received EMA approval, the EU can market and sell it. [4]

The EMA nevertheless continues to monitor the efficacy and safety of medical devices. Percutaneous coronary intervention benefits are typically reduced by restenosis. Stents are used to treat arterial injuries in medicine, but they don't deal with the process of intimal thickening that might happen as a side effect. Therefore, some individuals may continue develop restenosis even after having stents and the greatest medical treatment possible. [4]

DES are combination items made up of medical devices and drugs, and because the drugs serve a secondary purpose to the device, they are still considered medical devices under Council Directive 93/42/ EEC.

To ascertain the safety, quality and efficacy of the medicinal substance integrated as a medical device, the Notified Body must consult one of the Member States' competent authorities or the EMEA, according to the medical device legislation. According to the Medical Devices Directive and its associated Guidelines, clinical data must be used to demonstrate a medical device's clinical performance and safety in the case of implanted, active implantable, and Class III devices. [4]

Clinical data can be based on any of the following and are pertinent to the many aspects of the device's clinical safety and performance. [4]

I. Information that has been made public or unpublicized about the device's market performance, or information on a comparable product whose comparability to the questioned product may be proved;

II. Prospective clinical examinations of the impacted device;

III. findings from a clinical investigation(s) or other investigations of a comparable device that were published in the scientific literature and showed equivalence to the subject device.

Depending on the understanding of the auxiliary medical component, many options can be recognized, such as: [6]

1. The applicant asserts: "The medicinal substance of the combination is known to the competent authority and already registered in the Community in the context of a DES for a specific indication."

a) Comparative medicinal substance release characteristics (A).

i. same stent material with the same polymer material (A1)

ii. same stent material with different polymer material (A2)

iii. different stent material with same polymer material (A3)

iv. different stent material with different polymer material (A4)

b) Variables in the release properties of therapeutic substances (B)

2. The proper authorities are aware of the combination's medicinal product, but it is unregistered in the context of a drug eluting stent. (C);

3. The combination medicine includes a unique active ingredient that the Competent Authority is not familiar with, either as a drug or in relation to a DES. (D)

Regulatory process of drug eluting stent in European union [6]

The regulatory process for drug-eluting stents (DES) in the European Union is overseen by the European Medicines Agency (EMA). The EMA is responsible for evaluating

and approving all medicines and medical devices that are intended for use in the European Union.

CE marking for drug eluting stent [6]

If the device is a Class III device, a Notified Body must carry out either an audit of the full quality assurance system or an "Annex III examination", coupled with one of the assessments 1, 2 or 3 (above) provided for Class IIa devices. The Annex III examination is a procedure whereby the Notified Body ascertains whether or not a representative sample of the device production satisfies the Directive.

If, however, the manufacturer opts for a Notified Body to carry out an audit of the full quality assurance system then they must also submit a design dossier for examination.

Alternatively, the manufacturer may opt for an Annex III examination, but this can only be coupled with either assessment 1 or 2 (above) provided for Class IIa devices.

Final steps to CE mark: [6]

Manufacturers of Class IIa, Class IIb and Class III devices must wait to receive a certificate from the Notified Body. For all devices, once the relevant assessment has been successfully completed (and the certificate received, as applicable) the manufacturer may place the CE mark on their medical device and then put their device on the market.

The CE mark must be easily visible, readable and permanent. If a Notified Body has been involved in the assessment procedure, then the Notified Body's number must also be shown alongside the CE mark.

Specifically, drug-eluting stents fall under Class III devices, which are considered high-risk medical devices and require the most rigorous evaluation process. The regulatory process for DES involves several steps:

Regulatory Process of DES in European Union [6]

Preclinical studies: Before a DES can be tested in humans, it must undergo preclinical studies. These studies evaluate the safety and effectiveness of the stent in animal models.

Clinical trials: Once preclinical studies are completed, the DES is tested in clinical trials. These trials involve testing the stent in humans to evaluate its safety and effectiveness. The trials are conducted in several phases, with each phase involving increasing numbers of participants

Regulatory submission: Once clinical trials are completed, the manufacturer of the DES submits a regulatory dossier to the EMA. The dossier includes data from the preclinical studies and clinical trials, as well as information on the manufacturing process, quality control measures, and labeling

EMA evaluation: The EMA reviews the regulatory dossier and conducts its own assessment of efficacyy & safety of the DES. The evaluation is conducted by a team of experts who assess the data and make a recommendation on whether the DES should be approved.

Approval: If the EMA approves the DES, it is granted a European Union-wide marketing authorization. This allows the manufacturer to market and sell the DES throughout the European Union

Post-marketing surveillance: Once the DES is on the market, the EMA monitors its safety and effectiveness through post-marketing surveillance. This involves collecting and analyzing data on the use of the DES in clinical practice to identify any safety concerns or issues with its effectiveness.

In summary, the regulatory process for drug-eluting stents in the European Union involves preclinical studies, clinical trials, regulatory submission, EMA evaluation, approval, and post-marketing surveillance. The process is designed to ensure effectiveness and safety for use of DES in patients.

7. APPROVED CORONARY DRUG ELUTING STENTS BY FDA AND EMA

- **USA**

The given below Table-4 discusses approved DES in USA with descriptive product characteristics.

Table-4: Approved coronary drug eluting stents in USA [14]

Company	**Stent Name**	**Drug Instilled**	**Metals used**	**Polymer Used**	**Maximum Guide Wire[inch]**	**Introducer Size[F]**	**Stent Diameter (mm)**	**Stent length[mm]**	**Delivery System Length [cm]**
Medtronic Vascular (2022)	Resolute Onyx Zotarolimus Eluting Coronary Stent System	Zotarolimus	cobalt alloy and platinum/iridium alloy	polymer Biolinx coating	Less than or equal to 0.014	≥ 5	2.0-5.0	8,12, 15,18, 22,26,30,34,34	140
Biosensors International USA, Inc. (2022)	Biofreedom Drug covered Coronary Stent	Biolimus A9	316L stainless steel metal stent	-	Less than or equal to 0.014	≥ 6	2.25-4.2	8, 11, 14, 18, 24, 28	142

Svelte Medical Systems, Inc. (2021)	SLENDER Sirolimus-Eluting Coronary Stent Integrated Delivery System	Sirolimus	Cobalt-chromium alloy metal stent	PEA	Less than or equal to 0.014	≥ 5	2.25-3.50, 4.0	8, 13, 18, 23, 28, 33, 38	145
	DIRECT Sirolimus-Eluting Coronary Stent Rapid Exchange Delivery System				0.014		2.25-3.50, 4.0	8, 13, 18, 23, 28,	139
Boston Scientific Corporation (2020)	Ranger Paclitaxel-Coated PTA Balloon Catheter	Paclitaxel	-	-	0.014/ 0.018		4,5, 6, 7	30, 40, 60,80,100, 120,150,200	

Boston Scientific Corporation (2020)	SYNERGY Everolimus Eluting Platinum Chromium Coronary Stent System	Everolimus	platinum-chromium metal stent which is	poly(lactic-co-glycolic acid) (PLGA).	Less than or equal to 0.014	≥ 5, ≥6	2.25-5.0	8, 12, 16, 20, 24, 28, 32, 38, 48	144

- **EUROPE**

The given below Table-5 discusses approved DES in Europe with descriptive product characteristics.

Table-5: Approved coronary drug eluting stents in Europe [20]

Company	**Stent Name**	**Drug Instilled**	**Metals Used**	**Polymer Used**	**Maximum Guide Wire[inch]**	**Introducer Size[F]**	**Stent Diameter (mm]**	**Stent length[mm]**
Abbott (2009)	Xienc Prime BTK	Everolimus	Cobalt Chromium	Fluorinated copolymer	0.014	4	2,5,3,3,5,4	28,38
Alvimedica (2013)	Cre8 BTK A	Amphilimus (sirolmus + fatty acid)	Cobalt Chromium	No Polymer	0.014	4	2.25–4.5	8 to 46
Biosensors International (2008)	BioMatrix Flex BTK Drug-eluting Peripheral Stent z	Biolimus A9 pharmaceutical ingredient	Stainless steel	Biodegradable polymer layer	0.014	5, 6	2.25- 4	36, 33, 8, 11, 18, 24, 14, 28

Boston Scientifc Corporation (2016)	Eluvia Drug-eluting Vascular Stent System	Paclitaxel	Nitinol	Polymer-based & biocompatible	0.035	6	6–7	40 to 150
Boston Scientifc Corporation (2016)	Eluvia Drug-eluting Vascular Stent System	Paclitaxel	Nitinol	Polymer-based & biocompatible	0.035	6	6–7	40 to 150
Concept Medical (2020)	Abluminus DES+	Sirolimus	Cobalt Chromium alloy L605	Adjustable biodegradable matrix	0.014	5	2.25-4.0	8 to 40
Cook Medical (2009)	Zilver PTX	Paclitaxel	Nitinol	No Polymer	0.035	6	5–8	40 to 140
iVascular Angiolite (2017)	BTK	Sirolimus,	CoCr L605	Biostable Fuorinated acrylate	0.014	5	2.0-4.5	39, 19, 29 34, 14, 16, 24,

Table-7: CE marking for approved coronary drug eluting stents in Europe [20]

Product Name	CE Mark Indications
Xienc Prime BTK	Treats claudication or Critical limb ischemia caused by Infrapopliteal artery occlusive lesions by improving peripheral luminal diameter. Arterial diameter ranges from 2.25 to 4.25 mm
Cre8 BTK A	Peripheral/BTK
BioMatrix Flex BTK Drug-Eluting Peripheral Stent	Indicated for treating occlusive lesions above the ankle and below the BTK that cause critical limb ischemia; Diameter of artery- 2.25 to 4 mm
Eluvia Drug Eluting Vascular Stent System	SFA and/or PPA
Abluminus DES+	Indicated for AMI and DM
Abluminus NP	For treatment of increasing luminal diameter in patients with bleeding risks, or additional risks. Coronary arteries diameter- from 2.25 to 4.00 mm and lesion length ≤ 36 mm
Zilver PTX	Above-the-knee femoropopliteal arteries
BTK	Indicated for chronic and acute arterial lesions in the lower limbs below the knee, as well as popliteal and Infrapopliteal lesions with reference vessel diameters between 2-4.5 mm, Increases arterial diameter and improves blood circulation.

8. Comparative study of Drug Eluting Stents

USA	EUROPE
Regulatory Authority: Centre for Drug Evaluation & Research and Centre for Device & Radiological Health[12]	Regulatory Authority: European Medicines Agency (EMA)[1]
Regulated under class III medical devices.[13]	Regulated under class III medical devices.[1]
Considered as single entity combination product (Drug + device = primary mode of action)[15]	Considered as medical device with medicinal product.[1]
• Pre-market approval (PMA) method if no predicate available • Pre-market notification 510k method (has to provide clinical trial documents of safety and efficacy) • In case of new device, along with PMA filing, investigational device exemption filing also need to be done.	• If the DES is new device, the manufacturer has to go with Decentralised approval process. Also need to show safety of the device. • Application has to be sent to any of the notified bodies (NB) of EU. • NB will check the documents in accordance with European standards. • Establishment of the facility will be checked. • If the device passes the audits, CE is granted and the device can be marketed across entire Europe.
Application Fees:[14] 510(k): 12,745 USD (10,41,616 INR) PMA: 374,858 USD (3,06,36,207 INR) PMA, PMR: 441,547 USD (3,60,86,532 INR) Annual Fee for Periodic reporting: 13,120 USD (10,72,264 INR)	**Application Fees:[19]** (a) MDR technical file & guidance = $4500 (INR 3,15,000) (b) Ancillary medicinal substance additional fees to (a) = $2000 (INR 1,40,000) (c) Risk Analysis Support with Usability Files additional fees to (a) = $1000 (INR 70,000) (d) Clinical Evaluation additional fees to (a) and (c)= $7999 (INR 5,59,930) (e) PMS + PMCF + PSUR additional fees to (a), (c) and (d) = $3000 (INR 2,10,000)

	(f) Complete=Notified=Body Coordination till Technical FileApproval additional fees to (a), (c), (d) & (e) = $5000 (INR 3,50,000)
Documents[7] -510K application or PMA application -Investigational device exemption (IDE application) -IND form 1571 (in case new drug being used) -Master files -Letter of authorisation (LOA) -Non clinical Engineering tests -Toxicity studies ISO 10993 -Biological Evaluation of Medical Devices. -ISO13485 -Environmental assessment according to 21 CFR 25	**Documents[19]** -Europe follows ISO 10993 Biological Evaluation of Medical Devices for toxicity Studies. Toxicity study documents must include the following - Tests for Genotoxicity, Carcinogenicity & reproductive toxicity - Tests for in vitro cytotoxicity
USFDA has prepared a guidance document on engineering tests required for drug eluting stent where they have precisely mentioned the key attributes which need to be tested on DES. (Non-Clinical Engineering Tests and Recommended Labelling for Intravascular Stents and Associated Delivery Systems - Guidance for Industry and FDA Staff.)[7]	
- Market approval takes 180 days or even more.	- Approval is significantly faster.

9. CONCLUSION

Before marketing medical devices, safety and effectiveness are top priorities for all nations. In the US, the Drug Eluting Stent (DES) is considered a single entity medical device combining drug and device components, with clearance overseen by regulatory agencies such as the CDER and CDRH. The US regulatory framework is the most restrictive, requiring well-planned and controlled clinical investigations. The cost of FDA clearance is higher in the US than in Europe, and they have an application called an investigational device exemption (IDE) for new high-risk devices. In contrast, Europe has a decentralized process for marketing medical devices, overseen by the European Medicine Agency, with a requirement for a CE mark on every device. With the recent update to the Medical Device Regulation (MDR), Europe now has a quicker approval process than the US. It is imperative for all countries to prioritize finding safer and more effective alternatives to DES, given the frequent adverse events linked to the drug's polymer. The primary goal of selling medical products should be to provide the public with the best and most efficient care, not commercial uniformity. It is important to have clear and understood rules for the production and usage of DES. To make sure that the underprivileged groups may benefit from therapy, DES prices should be reduced. Medical device approval processes ought to be quicker. In order to maintain peace, the regulatory systems of the US and Europe should also work together by sharing ideas and counsel.

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