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Review article

THE AUTHORIZATION FOR MARKETING OF DRUG ELUTING STENT IN SRA COUNTRIES

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Abstract

Drug Eluting stents are those stents made up of metal which has a layering of drugs like paclitaxel, everolimus and anti-proliferative drugs to do the widening of the arteries which are narrowed. Since the year 2016, the use of drug eluting stent has increased due to its benefits which shows reduces in the occurrence of stent restenosis. The global market of drug eluting stent is expected to reach the revenue of $5614.6 Million by 2024. As the drug eluting stent comes under high-risk medical device, its regulation is very stringent in developed countries like USA and EU, while its regulations tend to become tough in developing countries like India. In USA, DES requires investigational new drug approval for drug and pre-market approval for device which approximately takes 180 days for final market approval of the device. In EU, the DES is required to go through the entire CE marking process and then it can be marketed in the European Union. In India, the device needs to get approval from central licensing authority which is done by stringent device testing. Although the regulatory authorities of various countries process to bring such lifesaving high risk medical devices into the market can be difficult, they also need to develop activities to increase the transparency and effectiveness of the entire process.

Key words: Drug Eluting stents, USFDA, CDSCO, EMA, Comparison, Medical Device

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Introduction

Percutaneous coronary intervention has rapidly evolved, marking a remarkable technological advancement in this century. Previously, surgical bypass grafting was the sole method for coronary revascularization. The field has progressed since the initial use of a basic balloon dilation catheter to relieve angina.

Evolution of Coronary Revascularization: Historically, coronary revascularization was achieved through surgical bypass grafting. The introduction of balloon angioplasty, known as plain old balloon angioplasty (POBA), facilitated intracoronary lumen enlargement. However, POBA led to restenosis and heart tissue degradation. To address these challenges, metallic stents were developed.

The Era of Drug Eluting Stents (DES): To mitigate the limitations of metallic stents, drug eluting stents (DES) were introduced. DES, a type of peripheral or coronary stent, releases drugs gradually to inhibit cell proliferation, preventing restenosis and clot formation within stented arteries.

Global Market and Key Players: The global DES market is projected to exhibit a 5.4% CAGR, potentially reaching $5,614.6 million by 2024, spanning regions including North America, Europe, Asia Pacific, and the rest of the world. Notable players in this field include Abbott Laboratories, Boston Scientific Corporation, Medtronic PLC, and others.

USFDA Regulations and Classification: In the United States, DES is classified as a combination product, subject to USFDA regulations. Clinical trial data establish that the uncoated stent primarily maintains vessel lumen efficacy, with the drug component playing a secondary role in preventing restenosis.

Market Outlook: The DES market in the USA was valued at $5.63 billion in 2018, with a projected CAGR of 5.67% leading to an anticipated value of $8.27 billion by 2026. North America's high DES use (42%) is attributed to the rising prevalence of heart disease. In Europe, market growth is expected at a CAGR of 7.3% from 2018 to 2024.

Medical Device Industry in India: India's medical device industry is valued at USD billion, experiencing a growth rate of 15.8% CAGR. Positioned as the 4th largest market in Asia, it is expected to reach USD 50 billion by 2025, solidifying its global standing. (1)

Drug-Eluting Stents (DES)

A coronary stent, resembling a tube, is inserted into a coronary artery that supplies blood to the heart. Its primary function is to maintain open arteries, aiding in the treatment of heart disease through Percutaneous Coronary Intervention (PCI) or angioplasty. This technique opens blocked coronary arteries without the need for open-heart surgery.

Components of DES: A drug-eluting stent comprises three key components: 1.) Platform 2.) Drug 3.) Drug polymer. Each of these elements plays a crucial role in DES functionality.

1. Platform: Early-generation DES utilized stainless steel platforms with a coarse texture. Contemporary DES employ various alloys like cobalt chromium or platinum chromium, offering corrosion resistance. These stents, with a thickness of up to 60 µm, possess enhanced radial strength.
   Thicker platforms delay full exposure and heighten the risk of sub-acute thrombosis. Research indicates that thinner platforms facilitate better endothelialization. Flexible stents with thinner platforms improve crossability. (Pravesh Kumar Bundhun)
   Stent designs are based on a chronological ring-building method, consisting of a series of elastic Z-shaped structural elements. Present stents are fashioned through laser cutting of metallic tubes. (Pravesh Kumar Bundhun)

2. Drug: First-generation drugs like paclitaxel and sirolimus are commonly employed. Paclitaxel inhibits microtubule formation during mitosis by attaching to beta-tubulin subunits. Its high lipophilicity enables stent attachment without polymer use.
   Sirolimus, a potent immunosuppressant, impedes protein synthesis, cell cycle progression, and migration. Its anti-restenosis effectiveness stems from improved kinetics and a broader therapeutic index.

3. Polymer and Coating: The polymer coating influences drug release and availability. Polymer composition may trigger inflammatory reactions.
   Initial DES using durable polymers caused arterial wall irritation, prolonged vascular healing, stent thrombosis, and late stent restenosis.

4. Polymer-Free DES: Inflammation often results from polymer coatings on stents, which can be circumvented by directly releasing antiproliferative drugs from the stent surface. Polymer-free stents allow rapid drug elution, impacting therapeutic effects.
   To mitigate these challenges, stent manufacturers employ various methods to reduce elution rates, categorized as: smooth surface, microporous, nanoporous, and drug-filled stents.

One simple polymer-free design involves embedding the drug directly into the stent's smooth metal surface. Absent polymer or perforations regulating drug release, solubility, drug dispersion, and coating thickness govern elution rates. Micro and nanoporous systems involve surface abrasion, creating gaps or cuts for drug placement. Microporous stent surfaces feature pits and micron-scale openings, established through micro abrasion. (2) (Table 1)

Table 1: Polymer types and names

Types of Polymers	Polymer name
Biocompatible durable polymer coatings	Vinylidene fluoride hexafluoropropylene polymer C10–C19–polyvinylpyrrolidone polymer
Fluorinated copolymers	vinylidene-fluoride hexafluoropropylene copolymer (reduce protein adsorption, platelet adhesion and thrombus formation)
Three different polymers mixture	C10, C19 and polyvinyl pyrrolidone
Biodegradable Polymers	Polylactic (PLLA, PDLLA), polyglycolic (PGA) and polylactic-co-glycolic (PLGA)copolymers

Comparison of Regulations of DES between USA, EU and India (3-6)

Here are some key elements of difference between the regulation of DES of USA, EU and India. This comparison will give a basic idea on how the DES is regulated. (Table 2)

Discussion

All the nations will first look upon the safety and effectiveness of any medical device before marketing it in their country. Coronary artery disease is the most dreaded disease in the entire globe which is characterized by lipid retention and plaque formation in the wall of the artery. Obstructive coronary artery lesion will lead to the inability of the heart to pump blood which will ultimately lead to myocardial infraction. In US, the DES is considered as the single entity medical device which comprise of drug and the device hence the regulatory authorities are Centre for drug evaluation and research (CDER) and centre for device and radiological health (CDRH). US regulatory system is the most stringent regulatory system, as they require a well-designed controlled clinical study. Cost wise too USFDA is higher than Europe and India. Also, USFDA has specific application called investigational device exemption (IDE) for those devices which are carrying very high risk and which are very new to enter the market. Europe on other hand, consist of European medicine agency as its regulatory authority and they have notified bodies as a third-party audit of each state. Europe only follows decentralized procedure for market application of medical device. Also, there is a unique mark called CE mark (conformity European) which all the medical device needs to have which are marketed in Europe. Also, time taken for approval is less than US. Recently Europe has updated its medical device regulation and now it is known as Medical Device Directive (MDD). Along with Europe, India also came up with new medical device regulation on January 2018. Earlier the rules in India for medical device were not taken seriously and were not followed. But after the enforcement of new medical device regulation, the rules are made mandatory to follow. In Indian regulation CDSCO centre for drug standard control organization under drug controller general of India, is considered as the regulatory authority. Under them comes central licensing authority (CLA) for DES. India is less time consuming in terms of approval and also cost is very low compared to US and Europe. In terms of testing and clinical evaluation, US, Europe and India, all have almost same criteria to be evaluated and controlled.

Conclusion

Recognizing the common adverse event related to the polymer of drug and finding more effective substitute must be the common goal of all the countries of the globe. The decision to market the device must not be driven from a need to standardize commercial rules but rather to provide the best and effective treatment to the population. Also, USA, EU and India must make a proper and understandable guideline on the use or manufacturing of Drug eluting stent. The prices for DES must also be made low so that the poor community can also take the benefit of the treatment. The timeline for approval of the device must be made shorten. Moreover, all the three nation’s regulatory system should come together and work by giving suggestions and advice, so that a harmony is maintained.

Table 2: Comparison of Regulations of DES between USA, EU and India

	USA	EU	India
Regulatory Authority	Centre for Device &Radiological Health (CDRH) and Center For Drug Evaluation &Research (CDER).	European Medicine Agency (EMA).	Central licensing authority (CLA)is responsible for regulation, under DCGI, CDSCO.
Classification	Class III medical device	Class III medical device	Class IV medical device
Considered as	Single entity combination product (Drug + device = primary mode of action)	Medical device with medicinal product	Medical device
Application Method	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 Decentralized 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.	Getting Loan License to manufacture (if the same device is already in market) Application in Form MD-7 or MD – 8 or Test license to manufacture for clinical investigation, test, evaluation, examination, demonstration or training for each distinct medical device MD-27 or Form MD-29. Also, permission from the central government in Form MD-22 by the sponsor before starting the investigation. Grant of test license in given in form MD-27
Application fees	PMA 510(k) $11,594 (INR 8,11,580), PMR $3,40,995 (INR 2, 38,69,650) Annual fee for periodic reporting = $11,935 (INR 8,35,450)	(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 File Approval additional fees to (a), (c), (d) & (e) = $5000 (INR 3,50,000)	Manufacturing license or loan license for Drug Eluting Stent INR 50,000. Permission to conduct Pilot clinical investigation INR 1,00,000. Permission to conduct Pivotal clinical investigation INR 1,00,000. Certificate to export each distinct medical device INR 1000. For foreign investors Import License for drug eluting stent (class D) =$2000 (1,40,000 INR). Different types of drug eluting stent each= $1000 (70,000 INR)
Document	-510K application or PMA application -Investigational device exemption (IDE application) -IND form 1571 (in case new drug being used) -Master files -Letter of authorization (LOA) -Non clinical Engineering tests -Toxicity studies ISO 10993 - Biological Evaluation of Medical Devices. -ISO13485 -Environmental assessment according to 21 CFR 25.	-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	-Power of Attorney -Undertaking from authorized agent -Constitution details of domestic manufacturer or authorized agent -Site or plant master file -Device master file (DMF) -Checklist of essential principles for demonstrating conformity to the essential principle of safety and evaluation performance of the medical device
Market approval time	Takes 180 days or even more.	Here approval is significantly faster.	Approval is faster.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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