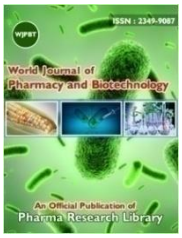

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Post Marketing Surveillance Requirements of Drug and Medical Devices Stents

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A b s t r a c t
This research article, titled "Post Marketing Surveillance Requirements of Drug and Medical Devices Stents" provides a comprehensive overview of the post marketing surveillance of drug eluting stents in India and European Union (EU). The drug eluting stents are used for the treatment of coronary angioplasty Drug eluting stents can significantly reduce the rate of restenosis by 60-75% as compare to bare metal stents. New technologies are often introduced into the market without proper safety and effectiveness data. To know about the safety and effectiveness of the drug eluting stents after marketing, Post marketing surveillance plays a vital role it includes Periodic Safety Update Report (PSUR) and Post Marketing Clinical Follow Up Studies (PMCF) for the identification of residual risk during the process and also explained about the functions of manufacturer and notified bodies, regulatory requirements of drug eluting stents in India and European market.

Keywords: Drug eluting stent; Post market surveillance; Periodic safety update report; India; European Union (EU); Residual risk

A r t i c l e I n f o

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C o n t e n t s

1. Introduction

Drug eluting stents are used for the treatment of arteriosclerosis, which is used to remove the cholesterol deposited on the artery wall, and prevent the carcinogenicity by releasing anti proliferative drugs. To address this problem, drug-eluting stents are place in the artery, preventing it from narrowing or clogging. Thus, drug-eluting stents eliminate the need for repeated revascularization procedures that are used to treat restenosis (narrowing of blood vessels). Restenosis caused by various reasons at the same time solution for the restenosis is also complex method. Traditional bare-metal stents have restenosis rates of up to 25%; current 2nd and 3rd generation drug-eluting stents have reduced that rate to single digits. The Smithers apex reports details the product technology characteristics and description of product used for the atherosclerosis, the products including coronary catheters and various types of stents.

Post marketing surveillance is the part of the Phase IV clinical trials It refers to the monitoring the safety of devices once they reach the market after clinical trials. It evaluates devices taken by individuals under a wide range of circumstances over a longer period of time. Such surveillance is much more likely to detect previously unrecognized positive or negative effects that may be associated with a device. The majority of Post marketing

surveillance concern adverse reactions of device monitoring and evaluation. Other important Post marketing surveillance components include unapproved or off-label use of device. The documentations of adverse events associated with the medical devices are possible through post marketing surveillance plan [3]. Hence in the post marketing surveillance plan there is no inclusion and exclusion criteria involved it can be worked on unanswered questions during clinical trials. Post marketing surveillance studies are very well adapted to answer questions about quality safety benefits and treatments cost and tolerance of patients can be explained. Current information from the nationwide data obtained from the Eudravigilance programme of medical device in European Union and Metriovigillance programme of medical device from India clime-made data base and databases/registries. Each of these approaches has their own advantages and loopholes for providing in depth knowledge into different aspects of real world performance and usage of device. When these systems are evaluated, it is useful to consider the number of patients included and the details of data include adverse events and incidents associated with device and user errors are collected.

2. Methodology

The works in this category are very rare and on current topic nobody has published any content or any books so literature regarding this work is absent, regarding the plan of work the material and the information is gathered from the web, regulatory bodies, research clinics. And the following theory made from the collected data with the help of institutional guides and friends.

Regulatory Requirements of Post Marketing Surveillance. All regulatory systems recognize that adverse event reporting alone cannot capture all risks related to the use of medical devices. Medical devices long-term implantable devices and devices for home use are examples of cases where the evaluation of the performance from adverse event reports alone is difficult or even impossible. For this reason, the world global regulatory authorities conduct various programmes for the reporting of adverse events and incidents associated with the devices. In India Surveillance means practice of monitoring the safety of medical devices [5].

The word Market Surveillance is tasks performed by the regulatory authorities. While Post market Surveillance Refer to the activities carried out by the manufacturers. Corrective actions and preventive actions are carried out by the manufacturer to reduce the risk associated with the medical devices European Union New Medical Device regulations which are released on 26 may 2017, Meddev2.12-1 Rev8 Guidelines On A Medical Devices Vigilance System MEDDEV 2.12-2 Rev2 Post-Market Clinical Follow-Up (PMCF) studies and in India the Central Licensing Approval Authority (CLAA) monitors.

The Post marketing surveillance of medical devices and National Collaborating centre-MateroVigilance Programme of India, collaborates with Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST) for adverse event reports monitoring, National coordination center-MateroVigilance programme of India includes Indian pharmacopeia commission, technical support and resource center-Materio vigilance programme of India includes National Health System Resource Centre (NHSRC)are carried out the post marketing surveillance of medical devices (Table 1).

Post Marketing Surveillance Requirements of Drug Eluting Stents: Manufacturer of class IIa IIb, III medical devices should prepare the periodic safety update report and submit to the competent authority for notifying about the adverse events associated with the above classes of medical devices, implemented risk management plans, and the post marketing clinical follow up data for the class III medical devices is essential element of the conformity assessment to demonstrate the essential requirements of the drug eluting stents. Manufacturer of class III devices and implantable devices reports shall be submitted by means of electronic system to the NB'S involved in the conformity assessment. The Notified bodies shall review the report and shall add its evaluation to the database with details of any action taken such reports and the notified body evaluation shall be available to competent authorities through the electronic system (**Table 2**).

Post Marketing Clinical Follow Up Studies of Drug Eluting Stents in European Union

While clinical evidence is an essential element of the premarket conformity assessment process to demonstrate the conformity to essential requirements. Post marketing clinical follow up is mainly useful for the pre-market clinical data reveal any unanswered questions about safety or effectiveness, adverse events that warrant further investigation, if premarket clinical data improperly generalized and the lifespan of the device extended beyond the time frame that premarket clinical data, new information emerged that affects premarket data, extended population that were not included in clinical trials. It is important to recognise that there may be limitations to the clinical data available in the pre-market phase. Such limitations may be due to the number of subjects and investigators involved in an investigation, the number of subjects and investigators or the controlled setting of the clinical investigation versus the full range of clinical conditions encountered in general medical practice.

The favourable benefit risk ratio can be demonstrated by post marketing clinical follow up studies. As part of the manufacturer quality management system the identification of residual risk need appropriate post marketing surveillance plan the ISO 14971 is the international standard for the identification of residual risk associated with the medical devices. The residual risk should be investigated and assessed in the post market phase through systematic post market clinical follow-up studies post marketing clinical follow up is part of the clinical investigation, clinical investigation is the part of post

marketing surveillance for the critical examination of the risk associated with the devices. Clinical data obtained from the post marketing surveillance that include post marketing clinical follow up studies by the manufacturer are not intended to replace the data obtained from the premarket clinical trials necessary to demonstrate conformity with the provision of the regulations. However After placing the medical device on the market there is a difficulty to gather information. Post marketing clinical investigation is the study other than surveillance performed after marketing approval has been given to the device required by the Central Licensing Authority for optimizing the intended use of the medical device. Post Marketing Clinical investigation includes, The quality of the medical devices which was monitor under ISO 13485, Additional drug device interaction, Safety studies, Investigation designed to support use under the approved indication for the identification of mortality and morbidity of the medical devices especially drug eluting stents. It required when residual risk of a medical device that is used properly according to labeling. Long-term performance and impact of the medical device affected by new materials or technologies are used. Events that is specific to defined population groups. The medical device Performance is a more representative of the populations like pregnant and nursing women, paediatrics. New indication for use or claim has been approved. Significantly, changes have been made to the medical device (or) labeling.

Periodic Safety Update Reports of Drug Eluting Stents

Manufacturer of the class IIb and III and class C and D devices should submit the periodic safety update report throughout the lifetime of the device to PSUR respiratory in European Union and CLAA in India. Manufacturer of class IIa, IIb, and class III and Class C and D devices submit the periodic safety update report at least annually and for two years and later two years from the next submission. The regulatory authorities some time may increases the submission period more than five years based on the public health interest.

Format and Contents of Periodic Safety Update Report Includes as Follows in EU

The PSUR shall be based on all available data and shall focus on new information, which has emerged since the data lock point of the last Periodic safety update report, cumulative performance of device taken into consideration for the assessment of safety and benefit risk ration. The safety efficacy and effectiveness data used for the preparation of Periodic safety update report obtained from the non-clinical intervention, spontaneous reports, active surveillance, investigational product quality, observational studies and data usage and utilization of product, patients observation and clinical trials. The Periodic safety update report contains title page including signature of the manufacturer and contact information. Executive summary brief description about the device, followed by the table of content of the document.

Introduction of the device, therapeutic action and duration of effect and risk class of the device and intended use should be mentioned and worldwide market authorisation statues if there is any withdraw or recall of product from the market, and actions taken in the reporting intervals regarding safety and performance of the device, estimated exposure of the population for the clinical trials cumulative interval of clinical trials should mention clearly and data tabulation should be maintained. reference information which was obtained from the literature survey and serious adverse events from the clinical trials and interval summary tabulation from post marketing data sources, demonstrates about the adverse events should be maintained and summarizes the significant data obtained from the clinical trials (i.e., completed, ongoing, long term follow up and other the therapeutic used of medical device) and new safety data related to the drug-device or device-device, device-polymer combinations. summarizes the data regarding signal and risk evaluation and benefit risk evaluation, integrated benefit risk evaluation for the authorized indication should clear mentioned about the conclusions drawn from the post marketing data and appendices of Periodic safety update report if any.

Format and Content of Periodic Safety Update Reporting India: Subsequent to approval of an Investigational medical device, it shall be closely monitored for their clinical safety once they are marketed. The applicants shall furnish Periodic safety update report in order to the report all the relevant new information from the appropriate sources related to safety and indicates whether changes will be made to product information in order to optimize the use of the product. One medical device should be covered under the one Periodic safety update report. Both clinical and non-clinical data are published under single Periodic safety update report. The Periodic safety update report should submit for six months for first two years and annually for next two years. The duration Periodic safety update report may extend based on the public interest and severity of adverse events associated with devices.

The Title Page of Periodic safety update report contains the signature and address of the manufacturer, and followed by the introduction about the device, risk based classification, intended use and therapeutic effect, Current worldwide marketing authorization status of medical device should be mentioned and withdrawal of the device from the any world market or recall of device from the world market should be mentioned, estimated patients exposure under clinical trials and the reference information obtained from the literature survey and customer feedback should Cleary mentioned in the document, overall safety information and adverse events associated with the device can be mentioned. Conclusions drawn from the studies are mentioned followed by the appendix of the document (**Table 3**).

3. Results and Discussion

Combination Products: Combination products were first recognized in the Federal Food, Drug and Cosmetic Act of 1990 (Shea, 2011). According to 21 CFR 3.2(e), combination products can be defined as:

(1) A product comprised of two or more regulated compounds, 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 labeling, 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, whereupon approval of the proposed product, the labeling 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;
(4) Any investigational drug, device, or biological product packaged separately that, according to its proposed labeling, 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 (Combination Products, 2009). In order to handle a number of unmet healthcare needs, many life science companies have collaborated to develop a wide range of combination products (Medical Device and Diagnostic Industry, 2007). Along with drugs, devices and biologics, combination products are a different category of medical products (Michael, 2009). Development of these combination products leads to a number of regulatory and scientific challenges (Medical Device and Diagnostic Industry, 2007).

Drug-Eluting Stents

Drug-eluting stents are the coronary artery stents that prevent fibrosis and thrombus, which would otherwise result in blockage of stented arteries, called restenosis (Scribendi, 2013). A stent is a metal mesh tube which houses a balloon that is blown up in order to widen the clogged artery. After angioplasty, stents are used to keep the arteries open. Drug-eluting stents that are coated with a drug (immunosuppressive class) release the medication slowly. This released medication helps in preventing the growth of tissue around the artery lining that would otherwise increase the risk of blocking the artery again (Mayo Clinic, 2011). As the stent portion of the product is used to widen the blocked artery and the drug portion helps in preventing the blockage of the widened artery, drug-eluting stents are good examples of combination parts. Therefore, I have chosen to use this product type of a sophisticated combination of device and drug when evaluating the success of the regulatory review of this class as well as when evaluating the similarity in regulatory review across the major markets of the world. The first drug-eluting stent, Cypher-Sirolimus, was released into the market in 2003 after a large pivotal study (Scribendi, 2013).

The success of combination products is estimated by comparing the number of approvals with that of the number of recalls from the market during the time period of 2003 to 2012 as the first drug eluting stent is approved in 2003. The drug eluting stent is taken as an example to represent the combination products as these contribute about ninety percent of the combination products market value. The number of drug-eluting stent systems approved by the FDA is calculated and the number of drug eluting stent systems recalled from the market is estimated. By comparing these two, the percentage of recalls from the total number of approvals is calculated. This percentage is then compared with the percentage of recalls from total number of approvals of drugs and devices.

In order to check whether there is similarity in regulating the combination products, the drug eluting stent is taken as an example, and the regulations followed by different countries are observed. The various aspects that each country takes into consideration in order to regulate drug-eluting stents are also observed. Finally, analysis is performed by checking whether a given combination product is classified, reviewed and regulated similarly and on a similar basis in major pharmaceutical markets (US, Europe, Japan, Australia and Canada) to determine whether there is any similarity between countries in regulating combination products.

Discussion

The combination products that are discussed here are the drug-eluting stents. The first drug eluting stent was approved by the FDA in 2003 and was a Johnson & Johnson Cordis Corporation product. In the span of 10 years from 2003 to 2012, 16 drug eluting combination products were approved and released into the market. Six leading medical device manufacturing companies are producing these combination products. Of these 16 stents, Cook's product Zilver PTX drug-eluting peripheral stent was withdrawn from the market. Cook identified the reason for this as the nonconformance of the design criteria for the inner component of the delivery system. On the whole, only one product has been recalled from the market out of the 16 products, or withdrawal rate is 6.25% in 10 years. Except for the recall of Zilver PTX, all of the other issues are minor and can be rectified with the proper marketing of the companies and better postmarket surveillance of the FDA.

Sixty Class III medical devices have been approved by the FDA between 2010 and 2012 and 15 devices were withdrawn from the market due to various reasons, during the same period for a withdrawal rate is 25%. Of the 209 New Chemical Entities that were approved by the FDA between 2010 and 2012 are 209 two were removed from the market as of June 2013. The withdrawal rate is currently ~1%.

The frequency of the market withdrawal of combination products, devices and drugs is approximately 6%, 25% and 1%, respectively. While the numbers are very small with limited time on the market, it appears that the withdrawal

rate for the combination product used as an example falls between that for devices and drugs. It appears that the FDA has not found the review of combination products appreciably more difficult than that of the other classes as judged by market success. Further data will be required to make a more definitive statement as further marketing history is generated for this new product type.

Worldwide Regulations and Similarity in Regulating

The combination products are well defined in FDA regulations. There are distinct regulations for classifying, reviewing and regulating a combination product. The FDA has drafted clear guidelines on which manufacturing regulations have to be followed while manufacturing a combination product. The device component must comply with 21 CFR 820 regulations; drug components must comply with 21 CFR 210 & 211 regulations; and biologic components must comply with 21 CFR 600-680. Even if a combination product is approved under drug regulation/device regulation/biologic regulation, all of the components must comply with their respective manufacturing regulations. The adverse events are reported based on the regulations under which a product is approved. The number of marketing applications and marketing approvals are determined based on the classification of the product.

There is no particular definition for combination products in Europe, Japan or Australia. There isn't an agency or office like the Office of Combination Products to regulate the combination products. The combination products are classified based on the primary mode of action, which is effective and has an intended purpose of use. The device component must follow device regulations; the drug component must follow drug regulations and the biologic component must follow biologic regulations while manufacturing a combination product. The adverse events are reported based on the classification under which the combination product is approved. There isn't any clear demarcation of how many applications have to be filed for marketing approvals. The combination product regulations followed in Canada are much more similar to those of the USA. The combination products are clearly defined and regulated. A new policy has been drafted which accommodates the regulations that have to be followed for combination products. The combination products are classified based on the primary mode of action.

In the case of drug-eluting stents, all the major pharmaceutical markets (US, Europe, Japan, Australia and Canada) have identified it as a device, and all the markets have classified and assigned it as a device based on the primary mode of action. Quality system regulations for manufacturing the device component and GMP regulations for manufacturing the drug component are followed in all of the countries. As the product is approved as a device, all of the adverse events are reported based on the adverse events reporting regulations of the device by all of the countries. A single marketing application is filed for premarket approval of the drug eluting stent in the USA. A single SHONIN application for a device is filed in order to get marketing approval in Japan. In Australia, conformity assessment is made by device programs, which then grants the approval for marketing. The drug eluting stent is classified, reviewed and regulated in the same manner in all of the countries. The basis for classification of combination products is also similar in all of the countries. All of the countries have classified and assigned the combination products based on their primary mode of action and are following device manufacturing regulations for device components and, drug manufacturing regulations for drug components during the manufacture of the drug eluting stent. All of the countries reported the adverse events based on the device regulations. A single marketing application is filed under device by all of the countries. Hence, we can say that there is similarity in regulating the combination products by different countries. However, each country has to draft particular guidelines for better regulation of combination products. The guidelines may be summarized as:

- Particular guidelines on filing the marketing applications
- How many marketing applications have to be filed for different combination products?
- Distinct adverse event reporting regulations
- On what regulations have to be followed if there is any adverse event because of the ancillary action providing component
- Distinct post-market regulations
- To what extent the assigned regulatory body must seek help or information from other regulatory bodies
- Defining the combination products
- It is also advisable to set up a committee like the Office of Combination Products in the USA and the Therapeutic Products Classification Committee in Canada in order to classify the combination products and assign them to the particular agency or board and also to make sure that there is a timely and effective premarket review and consistent and appropriate post-market regulation.

Table 1: Regulatory bodies for post market surveillance in INDIA and EU

India	EU
The regulatory bodies like CLAA (Central licensing approval authority) the branch of CDSCO adopt the guidelines from BIS and ISO and monitor the post marketing surveillance data of medical devices	EU the post marketing surveillance data is monitored by EUDAMED, CMdh and EMA

India	EU
Sree Chitra Tirenal Institute for Medical Sciences and Technology (SCTIMST) for adverse event reports monitoring	MEDDEV2.12-1 Rev8 "guidelines on a medical devices vigilance system"
National coordination centre-Materiovigilance programme of India	MEDDEV2.12-2 Rev2 "post-market clinical follow-up (PMCF) studies"
	Periodic safety updates report respiratory is also one of regulatory body for the post marketing surveillance

Table 2: Post market surveillance requirements for DES in India and EU

S. No.	Parameters	India	EU
1	Definition	Practice of monitoring safety	Active collection of information on safety
2	Regulation	CLAA branch of CDSCO (BIS, ISO)	EMEA (CMdh. PSUR respiratory)
3	Requirements	PMCI, PSUR	PMCF, PSUR
4	What to report	Adverse events associated with device	Trend reports, incident report, user error, adverse events
5	Whom to report	DCGI, SCTIMST	PSUR Respiratory, CMdh, forwarded to EMEA
6	How to report	Through e-submission gate way	e-submission, web client
7	Format	-	Xml zip file (data should >10 Mb)
8	Who can report	Manufacturer physician, Pharmacist, Nurses, Common People	Manufacturer, Physician, Nurses, General Public
9	Time scale for reporting incidents	30 days from the first marketing approval, if suspected unexpected adverse events 15 days from incident occur date	Serious public health threat 2 days Death or Unanticipated serious deterioration in state of health 10 days, Others 30 days
10	PSUR submission intervals	Every 6 months for first two years and annually for next two years	Every 6 months for first two years and annually for next three years

Table 3: What should be reported in PSUR of drug eluting stents

<table>
<tr><th>Individual incident reporting</th><th colspan="2">Periodic summary reports</th><th>Report at the time the adverse trend is identifies</th></tr>
<tr><td rowspan="3">Clinical/Symptomatic Death that is probably or possibly device related MI or heart failure that is probably or possibly device related Acute coronary arterial perforation/dissection leading to haemopericardium/pericardial Cardiogenic shock</td><td>Clinical</td><td>Periodicity</td><td rowspan="3">All reportable adverse incidents Clinical/Symptomatic Side branch occlusion Distal emboli (tissue, thrombotic/thrombus, plaque)Acute peripheral artery injury/perforation/dissection Non-fatal bleeding complications (e.g. hemorrhage), which may require transfusion Infection-local and/or systemic Peripheral vascular or nerve injury</td></tr>
<tr><td>Adverse reaction associated with the stent material (including, drug or polymer carrier) and/or delivery system materials</td><td>12 Monthly</td></tr>
<tr><td>Stent/target vessel thrombosis (Thrombotic occlusion/embolism), In-stent re-stenosis, target vessel or lesion</td><td>3 Monthly</td></tr>
</table>

Individual incident reporting	Periodic summary reports		Report at the time the adverse trend is identifies
	revascularization		
	All CVA (Stroke and TIA) within 12 months of PCI procedure. Listing acute, sub-acute and late strokes separately. This should be separated out by ischemic stroke.	3 Monthly	

4. Conclusion

Understanding the Post marketing surveillance requirements of drug eluting stents in Indian and European market and also explained about duties of manufacturer and regulatory bodies during Drug Eluting Stents post marketing surveillance. Mainly highlighted the periodic safety update report of manufacturer in India and EU and residual risk identification by using post marketing clinical follow up studies in EU and their regulatory requirements. In the market, many products, such as drugs and devices, as well as drugs and biologics, have been combined to make new products. But this combination has the potential to offer unique regulatory challenges to the regulatory agencies. Following particular regulations for combination products is a very complex process, as they are made up of different constituent parts, each with its own respective regulations. The number of approvals and recalls of drug-eluting stent systems may estimate the regulatory review success of combination products in the past 10 years. Out of 16 approvals, there is only one recall of the entire product. Twenty-five percent of Class III devices have been withdrawn during the same period while just over 1% of NCEs have been withdrawn. These preliminary data indicate that the regulatory agencies are successfully reviewing these combination products. Further data will be need to be examined as additional marketing history is generated. Different countries follow the same process for classification and assigning the combination product. The way of regulating the combination products is similar in almost all the major pharmaceutical markets. Thus, there is similarity in regulating the combination products.

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