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AN OVERVIEW OF THE POST MARKETING SURVEILLANCE OF MEDICAL DEVICES

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ABSTRACT
Medical Devices are evolving at a rapid rate to meet growing healthcare demands. The success, safety and efficacy of these health tools are critical and uncompromising. In today`s regulatory set-up, approval of medical devices stands on equivalence. Proof of clinical efficacy and long term safety is not a regulatory requirement. This article highlights the regulatory challenges faced by medical device manufacturers. Furthermore, particular emphasis is given to safety monitoring through post-marketing surveillance.

KEYWORDS: Medical Devices, Safety, Post-marketing surveillance, Regulatory, Monitoring.

INTRODUCTION

Medical device' relates to any instrument, apparatus, implant, machine, appliance, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, solely or together, for human beings, for one or more of the specific medical purpose(s) of a) diagnosis, prevention, monitoring, treatment or alleviation of disease, b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury, c)investigation, replacement, modification, or support of the anatomy or a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices, providing information utilizing in vitro examination of specimens derived from the human body; and d)does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.[1]

Medical devices have started gaining importance in the health care sector. Thus standardized regulatory framework is necessary to ensure that products entering the market are safe and efficient. To be updated on the regulatory requirements and their implementation in the process is one of the major issues for companies developing medical devices.

Classification of medical devices

As per European Regulations mentioned below in Table 1.

Table 1: Classification of medical devices according to European regulatory agencies.[2]

Classification	Risk Level	Example
Class I	Low risk	Stethoscope, Conductive Gels
Class II a	Medium risk	Antistatic Tubing for Anaesthesia
Class II b	Elevated risk	Ventilators, Infusion Pumps, Anaesthetic vaporizers
Class III	High risk	Implants and dressings made from collagen, Biological Heart valves

In India, medical devices are any apparatus, instrument, implant or other similar or related article, which are intended for use in diagnosis of disease, cure, mitigation, prevention or treatment of disease or intended to alter the structure or any function of the body and which does not achieve its primary intended objective through its chemical action within or on the body.[2]

As per Indian Regulations mentioned in Table 2.

Table 2: Classification of medical device as per Indian regulations.[2]

Classification	Risk level	Example
Class A	Low risk	Tongue Depressors, Thermometers
Class B	Low-Moderate risk	Suction Equipment, Hypodermic Needles
Class C	Moderate-High risk	Lung ventilator, Bone Fixation Plate
Class D	High risk	Pacemaker, Heart valves, Implantable Defibrillator

Challenges associated with Medical Devices

The regulatory scenario is, that most devices (in the EU and USA) have been approved for marketing by solely proving 'equivalence' to a prior legally marketed device – without having to necessarily illustrate long-term clinical efficacy or safety.[3] This has been the standard procedure for market approval for a long time. However, the term 'equivalence', can be somewhat misleading. Evidence of this can be observed when you look at the number of devices approved via this process and how far back the original approval goes.

In principle, by proving 'equivalence', manufacturers are not necessarily demonstrating the clinical efficacy or safety of the new device directly. They are rather demonstrating that the new device in question is 'equivalent' to the predicate device. Thus a new device that might not follow the same design, look, or be composed of the same materials, could be marketed to provide the same clinical efficacy and safety as the predicate device. The challenge is that medical technology is not this simple. The process of demonstrating 'equivalence' might have been acceptable when medical technology was less advanced. With access to the latest developments in engineering, mechanics, biomaterials, etc. devices gain more complexity and are designed more towards the individual rather than the general public.

Even though equivalence can be demonstrated somehow, it doesn't prove that a device will behave in the same way for all patients, or be able to provide the same benefits or safety. Especially if no scientifically-based evidence is available to support its efficacy and use.

But the European Union acknowledged that something must change, for minimal risks of new safety issues. Bearing in mind that Indian regulators use USFDA and EU as index countries to grant approval for new devices in India, the problem can be highlighted with the fact that, several recall and withdrawals have happened in India with serious consequences for Indian patients.

Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, blood products, herbals, vaccines, medical device, traditional and complementary medicines to identify new information about hazards associated with products and preventing harm to patients. The challenge of maximizing drug/device safety and maintaining public confidence has become increasingly complex.[4]

In 1989, three cases of sudden death were reported of patients who were administered barium through barium enema kits.[5] Consequently to these serious adverse events (SAEs), investigations were intensified to probe the potential cause of allergic reactions and death. Literature reviews indicate a potential problem with adverse reactions to latex-containing devices. Subsequently, the manufacturer of the enema tips voluntarily agreed to send out an urgent Medical Alert to approximately 10,000 radiologists notifying them of adverse reactions possibly related to latex allergy that could occur during barium enema procedures. An FDA Medical Alert that explained the occurrence of several severe allergic reactions to medical devices containing latex and proposed suggestions to screen and protect allergic patients, was also sent to physicians. This event set the pace for the development of regulations for medical devices since it was realized that this too could be responsible for serious adverse events.[5]

Another challenge associated with medical devices is the failure of these devices. A case in point was the failure of implants resulting in errors of implantation procedure led to the occurrence of pregnancy in 77% of women.[6]

Another area of concern was regarding the introduction of non-chlorofluorocarbon (CFC) propellants in metered-dose inhalers (MDIs) that may cause fresh attacks of asthma or failure to control asthma. This made it mandatory to institute effective measures to monitor the safety and efficacy of the new propellants.[7] This can be achieved through a stringent Pharmacovigilance (PV) system which contributes to the assessment of the risk-benefit profile of medical devices encouraging safe, rational and more effective use.[8]

In 1992, to bring about uniformity among the national medical device regulatory systems and increase the access to safe & effective clinically beneficial medical technologies, five-member countries conceived the Global Harmonization Task Force (GHTF). The five members were: European Union, United States, Australia, Japan, and Canada. The GHTF guides device manufacturers and users regarding mandatory reporting and voluntary reporting of adverse events respectively.[8] The CDSCO requires medical device manufacturers to report all adverse events associated with devices. The adverse event reporting requirements are depicted below in Table 3.

Table 3: Reporting regulations for medical devices of different countries.[5]

Pharmacovigilance aspects	India	US	UK
Post Marketing Surveillance activities	AE reporting for importers: complaint handling, adverse event reporting procedure	Medical device tracking, MDR, MDR event files, records, and written procedures. Complaint handling, Recall procedure and seizures	AE reporting, FSCA and field safety notices, Investigations, Enforcement, Post-market clinical follow-up records
Requires AE reporting by	Manufacturers only	Manufacturers, importers, user facilities, users, distributors and health professionals	Manufacturers, users, health professionals, authorized representatives and MHRA
Criteria for reporting	Event has occurred Medical device`s association with the event. The event led/might lead to death/serious injury	Death or serious injury, device malfunctions, user error, injury/illness requiring medical intervention	Event has occurred Medical device`s association with the event. The event led/might lead to death/serious injury
Reporting time frame	Unanticipated death or serious injury within 10 days. All other reportable events not later than 30 elapsed calendar days	Manufacturer: death. Serious injury, and malfunctions – 30 calendar days, and events requiring immediate remedial action – 5 working days. User facility: death and serious injury – 10 working days. Distributors and importers: death, serious injury and malfunction to the manufacturer – 10 working days.	Serious public threat – 2 calendar days Death / serious deterioration – 10 elapsed calendar days Other incidents – 30 elapsed calendar days After receiving user reports from MHRA, reporting 3 working days
Recall communication	-	Telephone calls, telegrams and mailgrams. First-class letters approved by FDA. General public warning Public warning through specialized news media.	FSN approved by MHRA as per specified format within 48 hours of FSCA. In case of urgency, through telephone, fax or by a visit.

POST-MARKETING SURVEILLANCE

Post marketing surveillance (PMS) is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market.[3]

Purpose: The ultimate goal of Post-Marketing surveillance is to continually ensure the safety, effectiveness, and quality of marketed medical devices with reasonable risk/benefit profiles.

Stakeholders: 1. Health Authority 2. Healthcare Facilities and 3. Manufacturers

1. *Health Authorities* have a role in the pre-market assurance of product safety and effectiveness, re-evaluate of AE report and safety monitoring take part in vigilance/surveillance activities and help in regulatory controls
2. *Healthcare Facilities* provide user training to the medical device users, ensure safety information disclosure to the patient, and provide medical device AE report.
3. *Manufacturers:* Undertake training programs, make safety information disclosure in information for users and labelling, handle and process AE reports regarding medical devices received by them, put up field safety notice and take preventive actions regarding safety and quality issues.

Benefits

- Patients and healthcare facilities are offered safety.
- Health and Regulatory Authorities are ensured the protection of public health.
- Manufacturers are offered the chance of bringing about improvements in their products based on the feedback received regarding real-world experience.

POST-MARKETING RISK CONTROL MECHANISM FOR MEDICAL DEVICES

The steps involved Post -Marketing Risk Control Mechanisms for Medical Devices are.

a) Monitoring of Medical Devices in the Post-Marketing Scenario

Monitoring may be undertaken for Safety purposes and Quality issues. Both types of monitoring may be Reactive or Proactive.

Monitoring for Safety Issues: Reactive forms of monitoring safety issues may be accomplished through timely reporting of adverse events to medical devices to the regulatory authorities who had approved the medical devices and submission of Periodic Safety Update Reports (PSURs) for the marketed medical devices at stipulated times to the concerned regulatory authorities.

Concerning proactive monitoring of safety issues, this may be undertaken by monitoring domestic and global

safety alerts regarding the medical devices at applicable regulatory intelligence sites.

Awareness of AE reporting system by device users and healthcare providers can be promoted to improve the collection of post-market data which are meaningful and useful for evaluation.

Monitoring for Quality Issues: Timely reporting complaints received about the marketed medical devices to the Defective product reporting system is a reactive form of monitoring medical devices for quality issues.

On the other hand, the manufacturer may proactively monitor the quality of the marketed medical devices through tracking domestic and global quality alerts about the medical devices at the applicable regulatory intelligence sites. Other methods of proactive monitoring include regular sampling/testing through post-market quality surveillance programs and conducting manufacturer inspections as well as joint post-market audits by the teams that include the members of the marketing authorization holder and the quality assurance team members of the manufacturing site.

b). Risk Analysis/Re-evaluation: Based on the outcomes of the monitoring reports the Marketing Authorization Holder/Manufacturer needs to analyse the risk factors and re-evaluate options for improving safety or quality issues. The problems may be of the following types: a) Device defect or use error, b) The single-case or systematic problem, c) Device-specific or device type-specific problem and d) Relation to the manufacturing process.

c). Risk Control: Once risks have been identified, corrective actions need to be undertaken and in the case of safety issues the labelling may be amended appropriately, advocate restricted use of the concerned medical device if necessary and have an extended duration of the post-marketing surveillance monitoring. Specific actions include a) notify manufacturer to take appropriate action, such as product correction (e.g., labelling change); b) Sales restriction (till correction is verified); or c) Market withdrawal.

In case of quality issues, the marketing authorization holder may undertake recalls of the defective medical devices, recommend product withdrawals, perform audit inspection or sample testing, issue a public announcement (safety alert or recall notice), inform targeted healthcare providers, and escalate safety monitoring of the reported product or same type of product.

d). Risk communication: Once the risks have been identified, it is binding on the manufacturer or the marketing authorization holder to retrain the stakeholders through educational materials and dissemination of new information that would be useful in alleviating the risks.

PMS is a major regulatory demand in Europe and the United States. Robust, predictive post-market surveillance systems that take care of medical device safety after launch, decrease costs and demands on resources and increase product safety and its performance.

However, PMS is required to be implemented as a proactive activity carried out by manufacturers to establish, implement and keep up to date a systematic procedure to collect and review experiences of their devices on the market. The purpose is to identify any need to apply corrective or preventive actions.

PMS of medical devices is more than just a regulatory requirement, it is good business ethics. It helps the manufacturer understand the performance of the device once placed on the market and provides continuous feedback that enables manufacturers to maintain a high standard of product quality and consumer satisfaction. It also minimizes exposure arising from incidents through effective warning and product recall processes and procedures.[3]

Companies may use existing processes, or implement new ones, to achieve the above. These could be.

- Complaints procedures
- Vigilance procedures
- To Check authority websites for information on AE/SAEs or recalls of similar devices
- Post-market clinical follow-up (PMCF) studies
- To set-up keyword alerts on search engines
- Social media monitoring
- Feedback from users (via email/website/surveys)

The data gathered should be used for ensuring the quality, performance and safety of the device. This is achieved through analysis of the information to assess for any significant increase in the frequency or severity of incidents that are not serious incidents or expected undesirable side effects. By performing an assessment we could determine if the new information would have a significant impact on the benefit-risk analysis conducted in the original risk analysis. This is done by updating and improving the risk-management documents. For example, post-market data collected may indicate a risk has a higher probability of occurrence than first estimated. Updating the risk analysis will initiate an update in different domains such as update in the design, manufacturing process, labelling and/or instructions for use of the device.

Under section 522 of the Federal Food, D & C Act in the Safe Medical Devices Act of 1990 (SMDA), the FDA is authorized to require manufacturers to conduct PMS for a few class II and class III medical devices. These are:

1. Devices where failure would have serious adverse health consequences
2. Devices that are implanted within the body for more than one year

3. Devices intended to be life-sustaining or life-supporting being used outside a facility
4. Devices expected to have significant use in paediatric populations

The design of the post marketing study is based on type of medical device as mentioned in table 4.[9]

Table 4: Types of post marketing studies of medical devices.

Type Of Study/Conditions	Post Market Clinical Investigation	Post Marketing Surveillance	Observational /Non-Interventional Study	Registry	PSUR
Clinical Investigation Plan	✓ specific In / Ex	✓ As per IFU / Approved Indication	✓ As per IFU / Approved Indication	✓ As per IFU / Approved Indication	✓ As per IFU / Approved Indication
Study Design (Probable)	Prospective, Non Randomized Single Blind	Prospective, Non-Randomized	Prospective, Non-Randomized	Prospective, Non-Randomized	NAP
Number Of Sites/Patients	As Per CIP (sponsor defined)	All sites / All implants	As Per CIP (sponsor defined)	As Per CIP (sponsor defined)	All sites / All implants
DCG(I) Approval	✓	✓ (CoA)	-	-	CoA
Free Device	✓	X	X	X	X
Medical Device Rule	✓	X	X	X	X
Investigator Brochure	-	IFU	IFU	IFU	✓
Informed Consent	✓	✓	✓	✓	X
Investigator Undertaking	✓	✓	✓	✓	X
Ethics Approval	✓	✓	✓	✓	X
SAE Reporting	✓	ADE Reporting	ADE Reporting	ADE Reporting	Materiovigilance
Annual Safety Report	✓ (6 months)	✓	X (per requirement)	X (per requirement)	X (per requirement)
Insurance	✓	X	X	X	X

PSUR- periodic update safety report; IFU- instructions for use; CIP- clinical investigation plan; ADE- adverse device effect

DEVELOPING A GOOD POST-MARKET SURVEILLANCE SYSTEM

Manufacturers of medical devices may not have the experience or resources to create a centralized safety function and proactive PMS. They may only realize its importance when faced with findings from regulatory authorities and notified bodies. Given this, the pressure to improve the PMS program is on and an accelerated effort to comply may be prohibitively expensive.

Working ahead of time with an experienced team will help to establish a robust and predictive PMS approach by:

1. Identifying sources of relevant data and prioritizing the impact on product quality.
2. Proposing a central safety repository to assure data collection, aggregation and analysis, revealing signals of potential issues before they occur.
3. Breaking down silos between functional groups and assuring active participation of all constituents, including distributors.
4. Identifying the technology needs to support the PMS as designed

Easy Availability of information makes healthcare professionals and consumers make informed choices based on references, data, and reviews. Therefore, it is likely that healthcare professionals (and consumers) will be more prone to choosing medical devices that have the necessary evidence to support their claims which in turn could be affecting sales and the success of these devices.[3]

Collecting more data is therefore not just a benefit for consumers, but also for manufacturers – and as such, should be accepted by both sides.

THE WAY FORWARD

Legal obligation and actions in laws and regulations: Post-marketing surveillance should be made mandatory for serious AE reporting and safety monitoring of medical devices. There should be a re-evaluation of product safety and the effectiveness of the devices.

Guidance for healthcare facilities and manufacturers regarding the monitoring of medical devices should be provided.

Proactive actions: Vigilance activities of global information need to be initiated by manufacturers. Educational training should be provided to end-users. Seminars need to be conducted to improve the quantity and quality of AE reports. An experience sharing platform should be provided for clinical engineers. Discretionary studies with medical devices should be undertaken for long-term effects.

Other resources: There should be voluntary accreditation of biomedical engineers who could help in the management of medical devices in healthcare facilities.

CONCLUSION

In sum, a stringent medical device post-marketing surveillance protocol needs to be implemented as an essential part of safety monitoring in the real-life setting as well as in research settings of clinical practice. This will help to efficiently monitor the safety profile of the marketed medical devices. Thus, the goal of safe and effective use of medical devices can be achieved leading to drastic improvements in the overall standard of health care that would be beneficial to all the stakeholders.

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ABBREVIATIONS

EU	European Union
PV	Pharmacovigilance
AE	Adverse Event
USA	United States of America
SAEs	Serious Adverse Events
FDA	Food & Drug Administration
CFC	Chlorofluorocarbon
MDIs	Metered-Dose Inhalers
PMS	Post-Marketing Surveillance
PMCF	Post-Market Clinical Follow-up
GHTF	Global Harmonization Task Force
SMDA	Safe Medical Devices Act, 1990
PSURs	Periodic Safety Update Reports
USFDA	United States Food & Drug Administration
CDSCO	Central Drug Standard Control Organization