International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 20-08-2022, Accepted: 05-09-2022, Published: 21-09-2022
Volume 7, Issue 3, 2022, Page No. 74-80

A comparative review of materiovigilance in India, US and UK

Ajay Kumar*, Minakshi Garg
Department of Regulatory Affairs, School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, New Delhi, India

Abstract
A wide range of medical devices are being used to diagnose, monitor, prevent and treat a variety of diseases. In order to ensure the safety of users/patients using medical devices, robust, sustainable and scaled monitoring of adverse events associated with the medical devices is of utmost importance. Therefore, post-market surveillance is necessary to ensure the safety and performance of medical devices and to evaluate their quality too.
For medical devices to be safe and of high quality, a well-structured regulatory system is essential. In 1992, five nations: The European Union, USA, Australia, Japan, and Canada formed the Global Harmonization Task Force (GHTF) with the goal of uniformizing national regulated medical devices and increasing access to safe, effective, and clinically beneficial medical technologies. Furthermore, regulated countries classify medical devices according to their associated risks. For a country like India, this is a new concept as its materiovigilance program was launched on July 6, 2015.
During the review process, our aim is to provide an overview of medical device related adverse events reporting in major countries like US, EU and India. The thorough understanding of current status of materiovigilance programme of these countries along with the classification, reporting criteria, what, where, how, who and why, timeframe and tools used for reporting.

Keywords: comparative, materiovigilance, Indias

Introduction
A medical device is crucial for diagnosing, prevention and treatment of many diseases. Currently, there are more than a million medical devices available, ranging from small bandages to complex MRI machines and medical software applications. The World Health Organization has defined medical device as any "instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose (s) of diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices providing information by means of *in vitro* examination of specimens derived from the human body; and 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."
However, medical devices also carry significant potential risks despite their immense benefits for patients. The risks associated with the use of medical devices include harmful effects, particularly on the patients/users/healthcare professionals, interactions with other substances, certain contraindications and malfunctions which may lead to serious injury or death. As a result, it is imperative to have a regulatory program to monitor the associated adverse effects.
During the 1970 Food and Drug Administration Modernization Act in the United States, Section 522 of the Act was enacted for class II and class III medical devices. European Union on June 1993, published Council Directive 90/385/EEC and 93/42/EEC outlining vigilance requirements for medical devices for member states and manufacturers, followed by incorporation of amendments of revision 5 of MEDDEV guidance 2.12–1 in 2007 [1].
Drug and Cosmetic Acts, 1940, and Rules, 1945, govern the safety, quality, and performance of medical devices in India. The Government of India in consultation with the Drugs technical advisory board has recently adopted Medical Devices Rules, 2017 to regulate import, manufacture, sales, and distribution of medical devices. It came into force on January 1, 2018 after being notified on January 31, 2017.

The classification of medical devices:

Medical devices are classified differently by each regulatory authority. Classification of medical devices generally follows these principles:

1. The risk associated with the medical device
2. Manufacturers' intended purpose for the device
3. The device's indications for use

The US Food and Drug Administration categorizes medical devices as Class I, Class II and Class III, according to Section 360c(a) of the FDA. There is a lot of difficulty in classifying products for applicants. The FDA provides a classification database to help people with this process.

Table 1: Medical Device Classification USFDA

Class	Risk	Regulation	Example
Class 1	▪ Low Risk ▪ 55% of Devices	▪ General controls for medical devices ▪ Exempt from premarket notification (510[k]) ▪ Exempt from medical device good manufacturing practices (GMPs) ▪ No approval needed	▪ Adhesive bandages ▪ Tongue depressors ▪ Crutches ▪ Ankle braces
Class 2	▪ Medium Risk ▪ 40% of Devices	▪ General controls for medical devices ▪ Premarket notification (510[k]) ▪ De novo pathway ▪ FDA clearance	▪ Syringes ▪ Pregnancy test kits ▪ Platelet-rich plasma preparation kits ▪ Lipoaspirate tissue processing system
Class 3	▪ High Risk ▪ 5% of Devices	▪ General controls for medical devices ▪ Investigational device exemption (IDE) (if clinical studies are required) ▪ Premarket approval (PMA) ▪ FDA approval	▪ Heart valves ▪ Pacemakers ▪ Hyaluronic acid ▪ Implanted prosthetics

Table 2: A similar classification system has been established by the Medical Regulation Agency (MHRA) for medical devices

Class	Risk Level	Requirements	Examples
Class 1	Low Risk	Premarket Notification	Dressings
Class 2a	Low-medium risk	Certification by notified body	X-ray film
Class 2b	Medium-high risk	Certification by notified body	Blood bags, contact lens care
Class 3	High risk	Certification by notified body	Bone cement, cardiac stents

Table 3: The CDSCO is responsible for classifying medical devices into four categories (A, B, C, and D) under the authorisation of Drug Controller General of India (DCGI).

Class	Risk Level	Examples
Class A	Low Risk	Absorbent Cotton wools, Surgical Dressings, Alcohol swabs etc.
Class B	Low-Moderate Risk	Thermometer, BP monitoring device, Disinfectants etc.
Class C	High-Moderate Risk	Implants, Haemodialysis catheter etc.
Class D	High Risk	Angiographic guide wire, Heart valve

Adverse event reporting

Reporting adverse events associated with medical devices can be made easy with the help of the adverse event reporting system. In order to protect and improve the health and safety of patients or users, it is imperative that the adverse events be reported. As a result, we can prevent the adverse event from recurring in the future.

According to FDA regulations i.e. Medical Device Reporting (MDR), manufacturers and importers are required to report serious injuries, deaths, and malfunctions, and users are required to report fatalities and serious injuries at their facilities.

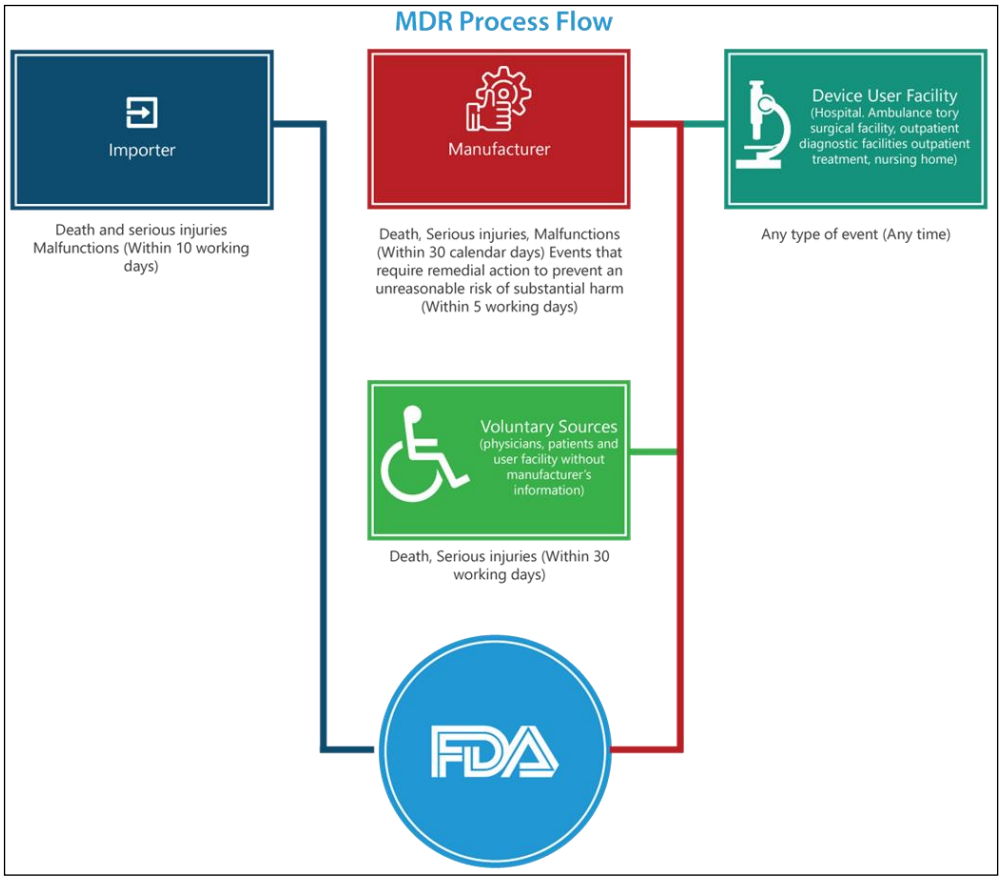

Fig 1: MDR Process Flow

In the EEC Directives, manufacturers of medical devices or their authorized representatives are required to notify MHRA and other competent authorities, as well as the EEC, of certain types of incidents.
An initiative called Materiovigilance Programme of India (MvPI) was launched on July 6, 2015 by the Drug Controller General of India (DCGI) in the Indian Pharmacopoeia Commission in Ghaziabad. This program aims to raise awareness among healthcare professionals about medical device adverse events (MDAE). There is a two-page reporting format, which MvPI has developed to capture all information regarding the device, the patient, the adverse event, the regulator, and the reporter in detail.

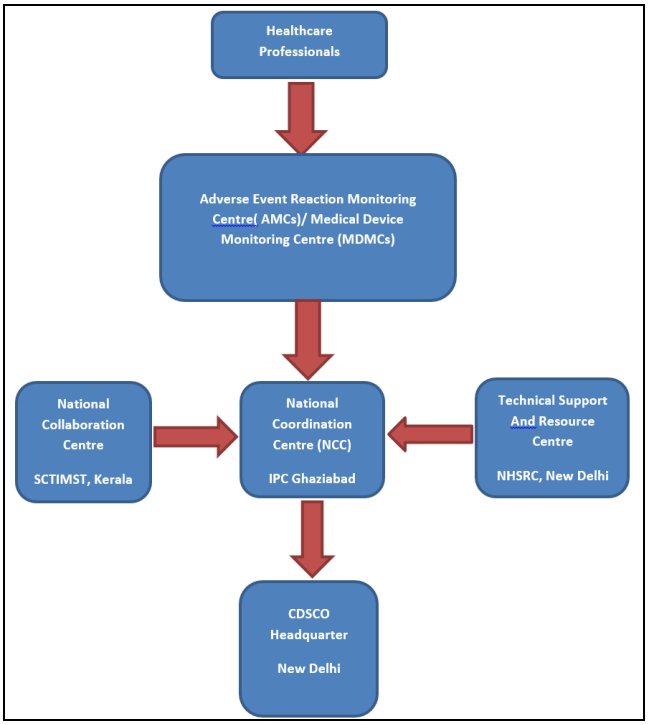

Fig 2: MvPI process chart.

Type of Reports

Currently, the FDA requires the manufacturer to submit five MDR reports, namely:

1. 30-Day Report: The report must include information on death, serious injury, malfunctions, and complaints.
2. 5-Day Report: This report must be submitted for serious unexpected event which require immediate action.
3. Baseline Report: To be reported for the first time. It can be of two types i.e. model type or device family type.
4. Supplemental Report: It is considered as a follow-up report. It is to be submitted within 1 month after receipt of additional information.
5. Annual certification: The certification is required to minimize the unintentional reporting errors that have been submitted during the 12-month period. The annual certification has to be submitted during the firm's annual registration date.

In the United Kingdom, the adverse event can be reported by submitting the reports in different forms such as:

1. Initial report: Initial reporting of adverse event to MHRA for record and evaluation.
2. Periodic summary report: These reports are submitted in an agreed format and frequency for the device and incident between the manufacturer and MHRA after submission of one or more initial reports.
3. Trend reports: These reports must be submitted when there is a significant increase in the rate of already reportable events, incidents that are usually exempted from reporting, and events that are usually not reportable.
4. Final reports

In addition to providing periodic reports or trend reports to the MHRA, the manufacturer must conduct an investigation after the initial report in consultation with the user. In the event of an initial assessment involving alterations to the device that could affect subsequent analysis, the MHRA must be informed of such changes before they are made.

In India, the CDSCO has classified reports as initial, final, and/or trend reports with regard to time and date. It is recommended to choose the type of report based on the availability of appropriate data within the time frame specified for the report.

Reporting time frame

FDA requires reporting of events to be done not only by the manufacturer but also by the user facility and distributor as well. The manufacturer must submit four reports depending on the event reported: first, 30 d reports for death, serious injury, or malfunctions; second, 5 d reports for events requiring immediate remedial action (FDA form 3500A); third, baseline report (FDA form 3417) to provide basic data on the device, subject to MDR report (30 or 5 d); and finally, annual certification (FDA form 3381).

In United Kingdom, the manufacturer is required to report within the time frame relating to the type of incident upon becoming aware that an event has occurred and one of its devices has caused or contributed to the incident, i.e.,

1. Serious public threat within two calendar days after the date of awareness
2. Death or serious deterioration in state of health within 10 elapsed calendar days after the date of awareness
3. Other incidents, immediately after assessing the link between the device and the event within 30 elapsed calendar days
4. Manufacturer's written acknowledgment of user reports from MHRA to manufacturer within three working days of receiving user report
5. Voluntary reports may be submitted at any time, and may be on the events other than death, serious injury, or malfunction as defined.

The manufacturer's incident report form should be used for initial, follow-up, and final incident reports. A written report should be provided immediately following an oral report and should state that the manufacturers make it without prejudice and does not implied any acknowledgement of liability for the incident or its applicability. It is the manufacturer's or authorized representative's responsibility to submit an initial incident report to MHRA for record keeping and evaluation, and then follow up with a final report, which should not be delayed for lack of information.

Materiovigilance programme of India

According to the Drug and Cosmetic Act, 1940 and Rules, 1945, medical devices in India are regulated for their safety, quality, and performance. Medical devices were not monitored properly in India for a long time due to lack of proper systems. In consultation with the Drugs technical advisory board, the Government of India has recently enacted the Medical Devices Rules, 2017 to regulate the import, manufacture, sales, and distribution of medical devices. It was notified on January 31, 2017 and came into force from January 1, 2018. On July 6, 2015, the Indian Pharmacopeia Commission (IPC), Ghaziabad introduced the materiovigilance program of India (MvPI). This program aims to monitor medical device-associated adverse events (MDAEs), raise awareness among health care professionals about MDAE reporting, and provide independent, credible evidence-based

safety data on medical devices. MvPI is regulated by the Central Drug Standard Control Organization (CDSCO) and the IPC functions as the National Coordination Center (NCC).

Table 4: Reporting timeframe of an event or incident in India is shown in the table below:

'Reporter'	'What to report'	'To whom Report'	Timeline
Manufacturer	Initial report of an event on 'MDAE' reporting form with remedial action to prevent public from irrational risk. Initial report on Death or serious public threat due to adverse event or incident.	MvPI	Within 5 working days of becoming aware of an event
Manufacturer	'MDAE' reporting form with causality assessment report and future corrective or preventive actions taken in a define timeframe	MvPI	Within 30 calendar days of becoming aware of an event
Healthcare service provider /clinical establishment	'MDAE' reporting form with causality assessment report	MvPI	'MDAE' reporting should be submitted within 5 working days of becoming aware and root cause analysis in next „30 calendar days"

Conclusion

The use of medical devices has increased over the past few years. However, there are insufficient measures to protect patients from the untoward consequences of medical devices use. This article provides a comparative analysis between Indian Materiovigilance programme, US-FDA Medical devices and UK-MHRA Medical Device Regulations. The Materiovigilance Program is one of the best initiatives by different countries to ensure the safety of medical devices around the world. A comprehensive implementation of this program is required to ensure the safety of device users or patients who use it. Additionally, these programmes reduce the risk associated with using medical devices by preventing redundancy of adverse effects.

Table 5: Differences in medical device vigilance of India, US and UK:

Parameters of countries	FDA (US)	CDSCO (INDIA)	MHRA (UK)
Definition of medical devices	This category includes all instruments, appliances, materials, machines, implants, software, accessories, and disinfectants used in diagnostics or *in vitro* testing.	Include devices that are intended for "internal* or "external* use in the diagnosis, "treatment", "mitigation" or "prevention" of disease or disorder in humans or animals, mechanical contraceptives, disinfectants, insecticides, *in vitro* diagnostic materials, "surgical dressings" and "surgical bandages".	Excludes materials used for disinfection of medical devices
Medical device Classification	Three Classes: I, II and III	4 Classes: Class I, Class II, Class III and Class IV	4 classes: class I, class IIa, class IIb, and class III
Basis of Classification	Level of control and marketing requirements	Risk based	Risk based
Post marketing surveillance of medical device	Started in 1990 under Safe Medical Device Act	Started in 2015 under Materiovigilance Programme of India	PSURs apply to class IIa, IIb and III medical devices under the MDR
Who can report adverse events	Manufacturer, importer, device user facility, patient, healthcare professionals, consumers	Manufacturers, Healthcare professionals, pharmacists, nurses, hospital technology managers, biomedical engineers	Manufacturers, users, health professionals, authorized representatives, and MHRA
Criteria for reporting	Death, serious injury, device malfunction,	Device malfunction, serious injury, death	Event has occurred Medical device's association with

			the event Event led/might lead to death/serious injury
Non- reportable events	Manufacturer can request remedial action exemption (RAE) if information received is erroneous When device is manufactured by other manufacture	Side effects related to medical device are expected by manufacturer's labelling, exceeded shelf- life of device, root cause of event is patient's pre-existing condition, protection mechanism inbuilt in medical device functioned correctly, and deficiency found in medical device before using it.	User-detected deficiencies Root cause of the adverse event is due to the patient's pre-existing condition Exceeded service life of device Likelihood of adverse event is acceptable after risk assessment Side effects clearly identified in the manufacturer's labelling and documented in device master record
Reporting timeline	30 calendar days- Death, severe injury and malfunction 5 working days- events requiring remedial action are reported by manufacturers. 30 calendar days- Importers need to report death, serious injuries and malfunctions. 10 working days- User facility report, device related death and device related serious injury and annual summary of death & serious injuries by January 1 of preceding year.	Death or serious public threat reported by manufacturer within 5 working days, MDAE reporting form, causality assessment report, corrective, preventive action within 30 calendar days by manufacturer and health care professional.	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.
Types of Reports	30-day report 5-days report Individual adverse event reports Baseline report Supplemental report Semi-annual reports Annual report	Initial Reporting; Trend Reporting; Final Reporting	Initial reporting of adverse events Final reports Periodic summary reporting Trend reporting
Applicable forms	FDA 3500 FDA 3500A FDA 3419 FDA 3381 FDA 3417	Medical Device Adverse Event Reporting (MDAER) Form Field Safety Corrective Action(FSCA) Form	Manufacturer's incident report form Online reporting for manufacturers by MORE

Acknowledgements
I would like to express my gratitude to Delhi Pharmaceutical Sciences and Research University for inspiring me to publish this article.

Financial Disclosure statement:
The author received no specific funding for this work.

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

References
1. Gupta SK. Medical Device Regulations: A Current Perspective. J Young Pharm,2016:8(1):6-11.
2. CDSCO. Medical Device Rule [Internet]. Ministry of Health & Family Welfare Government of India; 2017 [cited 2019 Sept 2]. https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_i d=MzMzNg==
3. CDSCO. Classification of Newly Notified Medical Devices to be updated with Classification list of Medical Devices and IVDs, Drug Controller General (India) [Internet] India: CDSCO; 2019 [cited 2019 Jul 12].

Available from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_i d=NDM5Ng==
4. Guidance Document: Materiovigilance Programme of India (version 1.1) [Internet]. IPC; 2009 [cited 2019 Sept 9]. Available from: http://www.ipc.gov.in/news-highlights/574-guidancedocument-materiovigilance-programme-of-india-version1-1.html
5. Rani SD, Singh KD. Materiovigilance: An Emerging Discipline. Int J Sci Res.,2018:7(6):15-6.
6. Chauhan P, Zarreen A, Iqubal Mk. Current Status of Materiovigilance Globally-an Utter Overview with Clinical Case Perusal. Int J Pharm Pharm Sci.,2019:11(10):1-8.
7. Kumar P, Kalaiselvan V, Kaur I, Thota P, Singh GN. Materiovigilance Programme of India (MvPI): A Step Towards Patient Safety for Medical Devices. Eur J Biomed Pharm Sci.,2016;3(12):497-501.
8. Gupta P, Janodia MD, Jagadish PC, Udupa N. Medical device vigilance systems: India, US, UK, and Australia. Med Devices Evid Res.,2010:3(1):67-79.
9. Medical devices Imports: Single regulatory framework likely for all medical devices. The Economics Times [Internet], 2019. [cited 2019 Dec 23]. Available from: https://economictimes.indiatimes.com/industry/healthcare/ biotech/healthcare/single-regulatory-framework-likelyfor-all-medicaldevices/articleshow/71450245.cms?from=mdr.
10. India strengthens medical device regulation. ICIJ [Internet]. 2019 Oct 21 [cited 2019 Dec 20]. Available from: https://www.icij.org/investigations/implant-files/indiastrengthens-medical-device-regulation.
11. Nautiyal S. MvPI reports 1,213 medical devices adverse event reports from across country since 2014 [Internet]. Mumbai: Pharmabiz, 2019. [cited 2019 December 15]. Available from: http://www.pharmabiz.com/NewsDetails.aspx?aid=11747 6&sid=1.
12. Implant Files – First official red flags: over 500 adverse events. The Indian Express [Internet]. 2018 Nov 26 [cited 2019 Dec 23]. Available from: https://indianexpress.com/article/india/implant-files-firstofficial-red-flags-over-500-adverse-events-5463990/
13. Shukla S, Gupta M, Pandit S, Thomson M, Shivhare A, Nath G. Implementation of adverse event reporting for medical devices, India. Bull World Health Organ.,2020:98(3):206.
14. European Commission Enterprise and Industry: Medical Devices. Cited 2010 Apr 27. http://ec.europa.eu/enterprise/sectors/medical-devices/ index_en.htm. Accessed 2009 Sep 25.
15. Council Directive 93/42/EEC concerning medical devices. 1993 Jun. Cited 2009 Sep 5. http://ec.europa.eu/enterprise/sectors/ medical-devices/documents/revision/index_en.htm
16. Registration of medical devices. http://www.mhra.gov.uk/Howweregulate/Devices/Registrationofmedicaldevices/index.htm. Accessed 2010 Apr 29.
17. Council Directive on the approximation of laws of the member states relating to active implantable medical devices (90/385/EEC). 1990 Jun 20. Cited 2010 Mar 15. http://eur-lex.europa.eu/LexUriServ. do?uri = CONSLEG:1990L0385:20071011:en:PDF
18. Comparison of the device adverse reporting systems in USA, Europe, Canada, Australia and Japan. Global harmonization task force, 2002. Available from: http://www.imdrf.org/docs/ ghtf/final/sg2/technical-docs/ghtf-sg2-n6r3-2002- comparison-device-adverse-reporting-systems-020521.pdf [Last accessed on 22 Dec 2018]
19. The Medical Devices Regulations. UK Statutory Instruments, 2002, 618. Available from: http://www.legislation. gov.uk/uksi/2002/618/introduction/made [Last accessed on 23 Mar 2019]
20. Medical device manufacturers. Guide to inspections of medical device manufacturers, USFDA, 1997. Available from: https://www.fda.gov/ICECI/Inspections/InspectionGuides/uc m074899.htm [Last accessed on 26 Dec 2018]