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GLOBAL REGULATORY REQUIREMENTS MANUFACTURER RESPONSIBILITY FOR MEDICAL DEVICE VIGILANCE REPORTING.

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Abstract: Globally, every country has its mandatory regulatory requirements that need to be fulfilled for legally marketing medical device in the region. To sustain medical devices in the regulated and semi-regulated markets, manufacturers need to ensure that post-market surveillance machinery is an integral component of the manufacturer's quality management system. It is critically important that the safety and performance of medical devices are continually assessed by the manufacturers to ensure patient/user safety. Manufacturers track and investigate the reported incidents, and ensure dissemination of information to relevant stakeholders. Hence, it is important for the businesses to be aware and understand the vigilance reporting requirements of all the authorities that they operate under. The purpose of this paper is to understand the global regulatory requirements and manufacturers' responsibility towards the medical device vigilance system.

Keywords: Medical device,vigilance,GHFT

INTRODUCTION:

Global Regulatory Requirements and Manufacturers Responsibilities for Medical Device Vigilance Reporting for Medical devices are regulated differently across the globe and each country have its regulated or semi regulated market,and it provides statutory guidelines for the classification of medical devices,the introduction of new products,and device post-market monitoring. To date, the majority of medical devices have not undergone pre-market pre-clinical and clinical studies. Additionally,the design revisions and alterations throughout time are not tested on people. Therefore, there is a need for strong post-market surveillance data to ensure safety and performance of medical devices in the field and also ensure reduced probability of re occurrence of incidents associated with the use of a medical device. Robust, well-documented complaint/incident reporting processes need to be in place not only to meet the regulatory requirements, but also to provide evidence to manufacturers that their medical device continues to perform as expected,to run as intended and to maintain its state of the art.
Manufacturers are required to develop a tool/database to register the complaint, perform the product complaint investigation, and assess re portability to the regulatory agency. Some of the regulatory agencies such as The United States Food and Drug Administration (US FDA) require incident reporting through electronic format while some allow both paper & electronic formats. Most of the authorities make this information publicly available through databases such as Manufacturer and User Facility Device Experience or MAUDE, Database of Adverse Event Notifications or DAEN, and others. In addition, trend report is required to be submitted to the

regulatory agency if any statistically significant increase in the frequency or severity of incidents is expected. For example, all medical devices carry a certain level of risk in their clinical use and may suffer from mechanical, electrical, or biological failures. Other incidents such as physical damage, incorrect use, or malfunction may also result in death or serious deterioration in the health of patients/users. Outcomes of these incidents could range from undesirable side-effects, non-serious incidents that could impact the benefit-risk to serious incidents.

Hence, manufacturer/importer must track and report such incidents to the national regulatory agency in the region, where the incident occurred, and critical information must be shared in other regions where the same device is marketed. Furthermore, medical device safety communications such as field safety corrective actions or FSCAs are required to be circulated to the affected users with a copy to national regulatory agency in the terms of Field Safety Notice or FSN.

The purpose of this white paper is to understand the global regulatory requirements and manufacturers' responsibility towards the medical device vigilance system. This vigilance system helps to improve the protection of health and safety of patients, healthcare professionals, and other users by reducing the likelihood of re occurrence of incidents related to the use of a medical device. HISTORY Global Regulatory Requirements and Manufacturers Responsibilities for Medical Device Vigilance Reporting Since 1965, the Canada Vigilance Program has gathered and evaluated the reports of suspected harmful reactions to pharmaceuticals health product, including medical devices, which can be accessed through the Canada Vigilance Adverse Reaction Online Database. The post-market surveillance of medical devices was initiated in the United States of America with the passing of the Food and Drug Administration Modernization Act 1970. The Section 522 of the Food and Drug Modernization Act (FDAMA) made necessary for the manufacturers to conduct PMS of any device which is a class II or class III device. In 1989, the Therapeutic Goods Act in Australia provided standardized national controls over goods used in the prevention, diagnosis, treatment, or mitigation of a disease, disorder, defect, or injury. The National Health Surveillance Agency (ANVISA), Brazil's national regulatory agency, conducts vigilance and market surveillance activities in several areas such as drugs, food, cosmetics, and medical devices. To accomplish uniformity and harmonization across the national medical device regulatory systems and to boost the access to safe, effective, and clinically beneficial medical technologies, the Global Harmonization Task Force (GHTF) was formed in 1992 by five members: European Union, United States, Australia, Japan, and Canada wherein the device vigilance was among the study groups. In June 1993, the vigilance requirement for medical devices was published as Council Directive 90/385/EEC and 93/42/EEC, followed by incorporation of amendments of MEDDEV guidance 2.12–1 revision 8 in January 2013 by the European Union. The recent high- profile incidents such as the hip replacements and the breast implant crisis highlighted the urgent need for regulatory reform, and improvement in standards, processes, and procedures. In May 2017, the EU parliament approved and released the new regulations Medical Device Regulation (EU MDR 2017/745) and the In-Vitro Diagnostic Device Regulation (IVDR 2017/746) that laid out structured requirements for post-market surveillance. The China medical device adverse event monitoring network and reporting system began in 2010. The National Medical Products Administration (formerly known as China Food and Drug Administration or CFDA) is the body responsible for the medical devices' legislation and its implementation, including post market surveillance and vigilance.[1],[4]

PURPOSE OF THE VIGILANCE SYSTEM:

Global Regulatory Requirements and Manufacturers Responsibilities for Medical Device Vigilance Reporting a vigilance system is required to improve the patient/user safety, by reducing the repetition of similar types of incidents or by decreasing the consequences of such incidents. This can be achieved by the tracking and investigation of reported incidents, and the dissemination of information.

Following are key objectives of a streamlined and compliant vigilance system:

- To help regulatory authorities in monitoring manufacturers' follow-up towards reportedincidents.
- To facilitate early and direct implementation of field safety corrective action, by easy correlation of data between regulatory authorities and manufacturers.
- To regulate the incidents/experience with same devices produced by different manufacturers.
- To provide vigilance aids in identifying new or escalating risks with a device, as well as feasible improvements to the usability or functionality of the device.

- To report device failures to manufacturers or regulators and help in identifying risks at the earliest possible time point.

Medical Device incident reporting is one of the post-market monitoring tools the regulatory body uses to track device safety and performance, identify potential device-related safety issues, and ultimatelty contribute to safety-risk assessments of the products. Mandatory reporters (i.e., manufacturers, importers, and device user facilities) are required to submit the adverse events and device-related incidences to the regulatory agencies within a specified time. Besides, the regulatory authorities also encourage health care professionals, patients, caregivers, and users to voluntarily submit serious adverse events associated with a medical device, use errors, product quality issues, and therapeutic failures. These safety reports, along with data from other sources, can provide critical information to manufacturers/regulatory agency which help to improve patient safety. The GHTF established the requirements for post-market surveillance that cover after-sale obligations, device performance monitoring, problem identification, adverse events reporting, safety alert, recall, and corrective actions.
[4]

Table no.01:Country wise database

Country	**Europe**	**USA**	**Japan**	**Canada**	**Australia**	**Brazil**
Regulatory agency/Authority	The Competent Authority of Member State in which that incident occurred	The Food and Administration (FDA)	Ministry of Health,Labor and Pharmaceuticals and Medical Devices Agency	Health Canada	Therapeutic Goods Association (TCA)	Agencia Nacional de VigilianciaSanitaria(ANVISA)
What to Report and when	Serious Public Health Threats no later than 2 days of becoming aware	Serious Public Health Threats should be submitted within 5 days of becoming aware of an event	MAH should report the matters specified in the items of Article 228-20,Paragraph 2 the Enforcement Regulations	Serious deterioration in health also includes a serious public health threat	Serious Threat to Public Health no later than 2 days after becoming aware	Death,Serious Public Health Threats and Counterfeit Devices no later than 3 days[72 hours]after becoming aware

	Serious incidents no later than 10 days of becoming aware	Deaths,serious injuries and malfunctions should be submitted within 30 days of becoming aware	Death and other serious events (within 15 calendar days)	A mandatory serious incident should be submitted within 10 days of becoming aware	Adverse Events no later than 10 days after becoming aware	Adverse Events whose recurrence has the potential to cause a major adverse event no later than 10 days after becoming aware
	Incidents no later than 15 days of becoming aware		The same cases as described above that could be attributed to the malfunction of medical device within 30 calendar days	A mandatory non serious incident should be submitted within 30 days of becoming aware	Near Adverse Event no later than 30 days after becoming aware	Technical Complaints which may lead to a major adverse event no later than 30 days after becoming aware
Trend or Periodic Reporting required	Yes-Trend reporting(article 88)	Alternative summary report (ASR)	Periodic Reporting	No	Periodic Safety Reports and trend report	Annual Reports are submitted for the first 3 years of device approval
How to Report	Via EUDAMED	1.Electronically submit medical device reports. 2.Web interface using the e submitter application AS2 Gateway to Gateway using HL7 KSR XML	To consult by telephone with PMDA and upload to the undesignated website page of PMDA	Via email,fax(613-954-0941)or mail:Canada Vigilance-Medical Device Problem Reporting Program	Via IRIS	Via SNVS
Information publicly available	Via EUDAMED	Via Manufacturer and user facility device experience (MAUDE)	Available only in their local langauge		Via Database of Adverse Event Notification	Available only in their local language

Table no.02:Summary of Mandatory Reporting Requirements for Manufacturers and Importers.

REPORTER	WHAT TO REPORT	REPORT FORM #	TO WHOM	WHEN
Manufacturers	30 day reports of deaths, serious injuries and malfunctions	Form FDA 3500A *	FDA	Within 30 calendar days of becoming awareof an event
	5-day reports for an event designated by FDA or an event that requires remedial action to prevent an unreasonable risk of substantial harmto the public health	Form FDA 3500A *	FDA	Within 5 work days of becoming awareof an event
Importers	Reports of deaths and serious injuries	Form FDA 3500A *	FDA and the manufacturer	Within 30 calendar days of becoming awareof an event
	Reports of malfunctions	Form FDA 3500A *		Within 30 calendar days of becoming awareof an event

1. European Union:

The EU MDR and EU IVDR will fully apply in the EU Member States from May 26, 2021, and May 2022 respectively. The new regulations strengthen vigilance, post-market surveillance, and other requirements for manufacturers. The European Commission's Guidelines document on a medical device's vigilance system (MEDDEV 2.12 -1 rev. 8 January 2013) illustrates that manufacturers are required to notify the relevant national competent authority about incidents and field safety corrective actions (section 5.1 and 5.4 of MEDDEV 2.12 -1 rev. 8). The manufacturer is also required to investigate/evaluate the incidents and take necessary corrective action (section 5.2 and 5.3 of MEDDEV 2.12 -1 rev. 8). Global Regulatory Requirements and Manufacturers Responsibilities for Medical Device Vigilance Reporting United States The Medical Device Reporting regulation (21 CFR Part 803) contains mandatory requirements for manufacturers, importers, and device user facilities to report specific device-related adverse events and product issues to the FDA. On Feb. 14, 2014, the FDA published a rule, stating manufacturers and importers are required to submit initial and supplemental adverse event reports in electronic format through FDA's Electronic Submission Gateway (ESG). The MAUDE database holds medical device reports submitted to the FDA by mandatory/voluntary reporters and available online to the public.[4]

2. Australia:

The Therapeutic Goods Administration or TGA's official webpage has a "safety information" section, which provides information on current and historic recalls of medicines and medical devices, advice issued by TGA about products, monitoring communications, information on reporting problems, and how the safety of the therapeutic product is monitored. In 2012, the DAEN was launched to support better health outcomes by providing access to the information that the TGA gathers while monitoring medical devices' safety in Australia. TGA's Incident Reporting and Investigation Scheme (IRIS) emphasize adverse events/incidents related to the use of medical devices. The investigations of incidents or potential adverse events reported from devices' users can lead to actions such as product recalls, safety alerts, product improvement, user education, and compliance testing.[4]

3. China:

The National Medical Products Administration or NMPA (formerly known as China Food and Drug Administration or CFDA) established in 1998 and structured around two main departments dealing with medical devices

- Department of Registration
- Department of Supervision Medical device manufacturers, importers, distributors, and medical institutions are responsible for filing a report on suspicious medical device adverse event (AE) with their local medical device monitoring institution and the legal agent. According to the decree, NMPA adverse events reporting timelines are:
- Within 7 days,suspected medical device-related deaths must be notified.
- Serious Adverse Events (SAEs) occuring in less than 20 days;
- Overseas Adverse Events 30 days
- Public Health Hazard shall be reported in 12 hours Serious AEs outside of China must be reported to the NMPA within 15 working days. Within 20 working days of the initial report, the medical device manufacturer must also file a "Supplementary Report on Medical Device Adverse Event," providing more details about the adverse event. Additionally, manufacturers of Class II and III medical devices must file an "Annual Report on Medical Device Adverse Events" with their local monitoring institution each year by the end of January, summarizing and analyzing the AEs over the past year.[4]

4. Eurasian Economic Union (EEU) :

The Eurasian Economic Union entered into force on 1 January 2012 and includes the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, and the Russian Federation. In March 2017, the Belorussian Ministry of Health clarified its requirements for reporting adverse events for manufacturers of medical devices. All the serious or unexpected adverse events during its usage/exploitation, peculiarities of interaction with other medical devices must be reported to the regulatory agency. The Government of the Russian Federation's Order No. 323 dated 30 June 2004 "On the approval of the statement on the Federal Service for Surveillance in Healthcare", state functions related to the safety monitoring of medical devices are tasked to the Federal Service for Surveillance in Healthcare (Roszdravnadzor). Any information related to adverse events in Russia shall be submitted to Roszdravnadzor. Any adverse event that poses a serious threat to the public is to be submitted immediately after the causality assessment, but no later than 2 days after being made aware. Death or other serious incidents to be submitted immediately after causality assessment, but no later than 10 days. All other adverse events, for which there is no need for immediate reporting, is to be submitted soon after causality assessment, but no later than 20 days.[4]

5. Singapore:

National regulatory authority of Singapore i.e., Health Sciences Authority or HSA, as part of its vigilance post-market surveillance activity, runs a system for the collection and distribution of FSCA, to ensure the safety of medical devices suspected of being potentially harmful to users, due to nonconformity to quality, safety, and performance requirements. The adverse event reporting timelines are: • Within 48 hours for events that represent a serious threat to public health; • Within 10 days for events that have led to the death, or a serious deterioration in the state of health, of a patient, a user of the medical device, or any other person; • Within 30 days for events where a recurrence/repetition of which might lead to the death, or serious deterioration in the state of health, of a patient, a user of the medical device or any other person All information regarding medical devices registered in Singapore are made publicly available online through the Singapore Medical Device Register (SMDR) database.
[4]

6. Argentina:

National Administration of Drugs, Foods, and Medical Devices (ANMAT) is the medical device regulatory authority of Argentina and is responsible for the authorization, registration, standardization, and vigilance and monitoring of devices with the specific purpose of ensuring their compliance with efficacy, safety, and quality requirements. Techno-vigilance program was developed by ANMAT to collect, access, and manage medical devices' adverse events and this program helps the early detection of adverse and performance failure in the stage of widespread use[4]

7. Mexico:

In Mexico, the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) is responsible for ensuring high quality, effectiveness, and safety of the medical devices. In early 2013, the techno vigilance system was introduced to support post-market device monitoring and management of adverse event reporting and corrective actions. The COFEPRIS website provides information only inSpanish.[4]

MANUFACTURERS RESPONSIBILITY

Manufacturers are responsible for reporting all serious incidents immediately after analyzing the causal relationship between the incident and device, and circulate FSNs to the relevant competent authorities. After serious incident notification, the manufacturers are necessary to implement a systematic procedure for incident investigations, to ensure that any risks or issues associated with the use of their device are identified at an early stage. If needed, an FSCA will be implemented to reduce the risk associated with the use of the device. To ensure timely reporting of serious incidents, the manufacturer may submit an initial report that is incomplete and then follow up with the patients, doctors, or users to create a complete report. The well-defined process to perform the incident investigation, within a specified time frame allows the final/follow-up conclusion to be submitted to the regulatory agency within the timeline. The final report will set out conclusions and, where relevant, indicate correctiveactions to be taken. Systematic approach to ensure timely submission:

- Establish complaints receiving system, includes local telephone numbers, email addresses, fax, postal address, and other appropriate contact details of competent staff who can collate the required information.

- Manufacturers/importers are required to maintain complaint files and establish and maintain procedures for receiving, reviewing, and evaluating complaints.

- Manufacturers are required to develop a tool or database to resister and process compliance.

- Every complaint (written, electronic, or oral communication) must be evaluated /investigated to determine if it is a re portable adverse event.

- Its manufactures/importers responsibility to assess the causal relationship between the device and the incident of:The healthcare professional's opinion based on available evidence of The results of the manufacturer's respective preliminary assessment of the incident o Evidence of previous, similar Incidents of Other evidence held by the manufacturer o It's difficult to make a judgment when there are multiple devices and drugs involved.

- Criteria to assess the seriousness of the event: The event which led, or might have led, to one of the following outcomes:

- Death of a patient, user, or another people of serious deterioration in state of health of a patient, user, or other person.
- Life-threatening illness.
- Permanent impairment of a bodily function or the long term damage to a bodily component.

- A condition necessitating medical or surgical intervention to prevent life-threatening illness or permanent impairment.
- A condition that requires hospitalization or significant prolongation of existing hospitalization.
- Any indirect harm (see definitions) as a consequence of an incorrect diagnostic or IVD test results when used within the manufacturer´s instructions for use.
- Fetal distress, fetal death, or any congenital abnormality or birth defects.
- To establish complaint handling procedure i.e. receiving, processing, and regulatory submissions (via paper or electronic submission).[4]

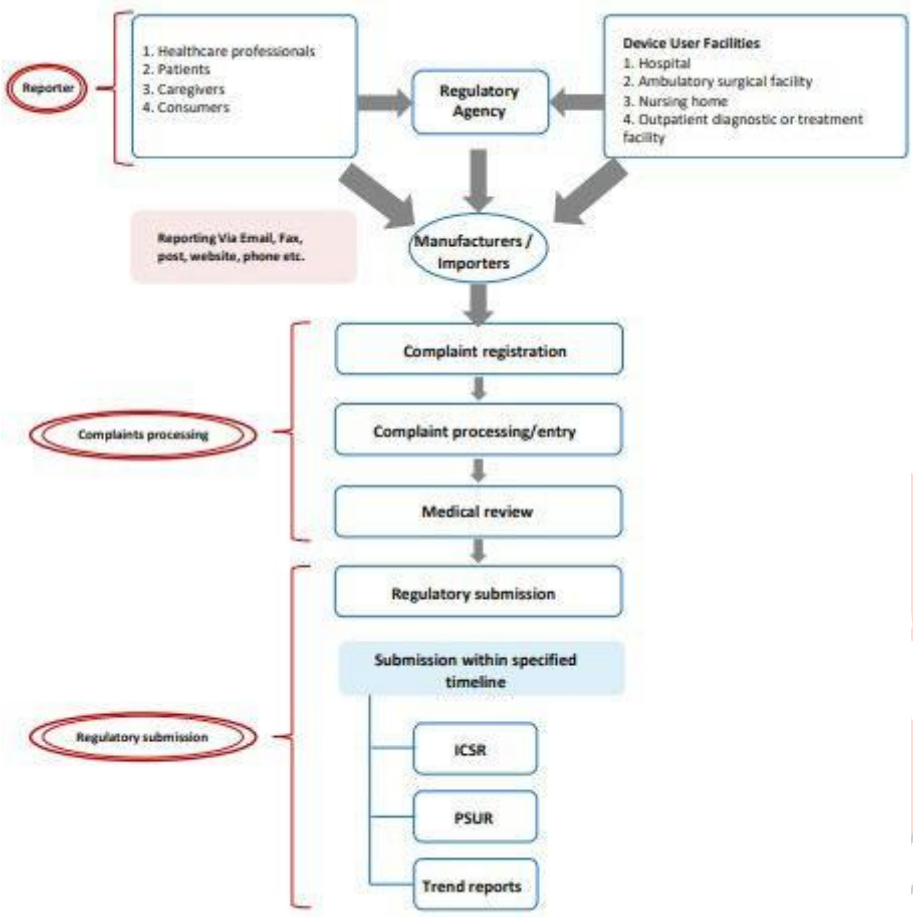

Figure no.01:Vigilance Workplace/Process Flow

COMPLAINT HANDLING PROCEDURE

A Complaint handling procedure should be designed to support the reporting of concerns and to streamline the process.This may include:

- Definition of a complaint that requires to be broad enough to ensure compliance with vigilance requirements in all regions anywhere the device is placed on the market.

- Confirmation/clarification on how the first time awareness date of the complaint is established to allow a deadline for vigilance reporting.

1. Healthcare professionals
2. Patients
3. Caregivers
4. Consumers Regulatory Agency Device User Facilities like Hospital , Ambulatory surgical facility ,Nursing home , Outpatient diagnostic or treatment facility Reporter Manufacturers / Importers

Complaint registration Complaint processing/entry Medical review Regulatory submission Submission within specified timeline ICSR PSUR Trend reports Reporting Via Email, Fax, post, website, phone etc. Complaints processing Regulatory submission.

- A requirement to notify complaints within a predetermined time frame to enable timely vigilance reporting.

- Manufacturer Incident Report (MIR) form to capture all the required information to the database and investigate the incident.

- Process for obtaining the complaint product(s) back, or images from a procedure to allow for a thorough investigation to be completed and a root cause established wherever possible.

- Trending process to understand the escalation of any product issues, which further helps in planning the action where required (e.g. a recall, FSCA). Global Regulatory Requirements and Manufacturers Responsibilities for Medical Device Vigilance Reporting Manufacturers will submit a trend report to the regulatory agency if any statistically significant increase in the frequency or severity of incidents is expected, for example, undesirable side-effects or non-serious incidents that could have an impact on the benefit-risk analysis. Such incidents may lead to risks to the health or safety of patients, users, or other persons that are unacceptable when weighed against the intended benefits. Dissemination of Information A key part of the medical device vigilance system is the dissemination of information, which helps to prevent the recurrence of incidents or to alleviate the consequences of such incidents. When the competent authority notifies a manufacturer to communicate the suspected serious incident reported by a healthcare professional, patient, or user, the manufacturer is required to-

- Submit a serious incident report to the respective competent authority within the time frame.

- Submit an explanatory statement, to the competent authority, if the manufacturer believes the suspected serious incident does not fulfill the reporting criteria. Medical device safety communications need to be circulated to healthcare professionals and medical device ‘users‘. Those are:

1. Communications circulated by the manufacturer or their local agent - field safety notice (FSN).
2. Communications circulated by a regulatory agency. Manufacturers will ensure that the FSCA related information is brought to the attention of users of the device under question utilizing an FSN without having any delay.

Examples of some actions that can be communicated via an FSN include:

- Medical device recall
- Device modification or design change
- Device exchange • Device destruction

Some guidelines specify the format and distrubution of FSN.The manufacturer can send the FSN by email, post, fax, or in some instances, hand-deliver the notice. The FSN includes the correct identification of the manufacturer (by including, if issued, SRN), the device or devices affected (by including the relevant UDIs), and clear explanation, without understating the level of risk and reasonsfor the FSCA.[1]

CONCLUSION

Manufacturers/importers need to be aware and understand the vigilance reporting requirements of all the authorities that they are operating under. Robust, well-documented complaint/incident reporting processes need to be in place not only to meet the regulatory requirements, but also to provide evidence to manufacturers that their medical device continues to function as intended is to deliver what is promised and to maintain the state of the art. Manufacturers are required to develop a tool/database to resister the complaint, perform the product complaint investigation, and assess re portability to the regulatory agency. Some of the regulatory agencies require incident reporting through electronic format (for example, US FDA) and some allow both paper &electronic format. Most of the authorities make this information publicly available through the database (for example, MAUDE, DAEN, etc.). The medical device vigilance system is required to improve the protection of the health and safety of patients and users by reducing the probability of reoccurrence of incidents associated with the use of a medical device. The trend report needs to be submitted to the regulatory agency if any statistically significant increase in the frequency or severity of incidents. Medical device safety communications, for example, FSCAs are required to be circulated to healthcare professionals and users without delay bythe means of FSNs.[4]

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