Alceon

MONTHLY NEWSLETTER

Aug 2020

Dear Readers,

Welcome to another issue of our newsletter. In this edition, our team has come up with information on two critical and interesting subjects.

In the first one, we are discussing the changes brought about by the new biological evaluation standard ISO10993-1:2018 and how the EU MDR will impact your biocompatibility evaluations. The new version of the standard is very much aligned with the EU MDR and an understanding of the same will be of help while you start planning to transit to the MDR.
In the second part, we are comparing the vigilance requirements from various major regulations. Vigilance usually covers activities such as adverse event reporting, recalls and field safety actions. We often see manufacturers focusing on just one or two of the regulations, mainly the US FDA and EU, while they export to a great many other countries. We have compiled the requirements from 14 countries. We are constrained by the size of the table and hence could not provide for more. If you want to get your vigilance procedure prepared to cover all countries you are exporting to, do contact us. We would be happy to help.

Hope you enjoy reading this month's edition and we look forward to getting your questions and feedbacks. Questions which are of interest to all readers will be published in future editions of our newsletter.

IN THIS ISSUE

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NEW REGULATORY REQUIREMENTS FOR BIOLOGICAL EVALUATION

01

The ISO10993-1 standard was first published in 1992 with the title "Biological Evaluation of Medical Devices - Evaluation & Testing". The standard was revised in 2003 and again in 2009. In 2009 they amended it to "Biological Evaluation of Medical Devices - Evaluation & Testing within a Risk Management process". This was a significant change from simply testing to evaluating the safety of the device. The content of the standard was still not so much about risk management and it was more about conducting tests.

The new ISO10993-1 was earlier used as a document which a manufacturer could use to refer to the table given in the Annex A and select the tests that need to be done.
With the publication of the 2018 edition, the focus is now to risk based evaluation, both in the title and content. The standard now requires the manufacturers to look more deeply into the chemistry and physics of materials that make a medical device and how they impact the safety of the device.

Increase in Scope

Biological evaluation now includes not just devices which come in contact with the patient, but also devices that come in contact with the user for the purpose of providing protection. For example, gloves and masks. Risks due to breakage or mechanical failure now are under the scope of the standard. So, such situations also need an evaluation for biological risks.

New Principles

The most noticeable change is in Annex A, where instead of tests to be conducted, the standard now provides 'end-points' instead of 'test-points'. The manufacturer is expected to collect data on the materials and if the data is not sufficient, only then conduct tests. The goal is to reduce animal testing whenever possible.
The standard now requires manufacturers to consider the effect of the packaging materials which come in direct or indirect contact with the device.
The principle that biological evaluation needs to be done for the whole lifecycle of the medical device is new. This may need a biological evaluation at the end of shelf-life.
For reusable devices, the manufacturer must evaluate the biological safety of the medical device for the maximum validated cycles of reuse.

Increased Endpoints

Additional endpoints such as material mediated pyrogenicity and sub-acute toxicity have been added to the Annex A table. Carcinogenicity, reproductive toxicity and degradation, which were there in the 2003 version of the standard, but missing from the 2009 standard, have made a comeback.
Some types of devices need additional endpoints in comparison to the earlier standard.

New Categories

A new category called 'transient' devices has been introduced. This is applicable for devices like needles and surgical blades, which are in contact for less than a minute. For such devices there is no more a need to do testing, unless coatings or lubricants are used.
The contact duration of 'permanent' has been changed to 'long term', which includes both implants and other long-term devices.
Categorization of gas pathway device components with only indirect contact, shall be based on ISO 18562.

Physical and Chemical Information

The standard has now added physical and chemical information as a prerequisite. This is a not a new requirement. It was there in the earlier version of the standard as well. However, now the standard requires one to gather this information before doing the biological safety assessment. So gathering this information is an essential first step.
One way of getting this information is by doing a material characterization, for which the standard refers to the ISO10993-18 standard.

The following definitions are worthy of note:

Physical and Chemical Information

Knowledge regarding formulation, manufacturing processes, geometric and physical properties and type of body contact and clinical use that is used to determine whether any additional biological or material characterization testing is needed.

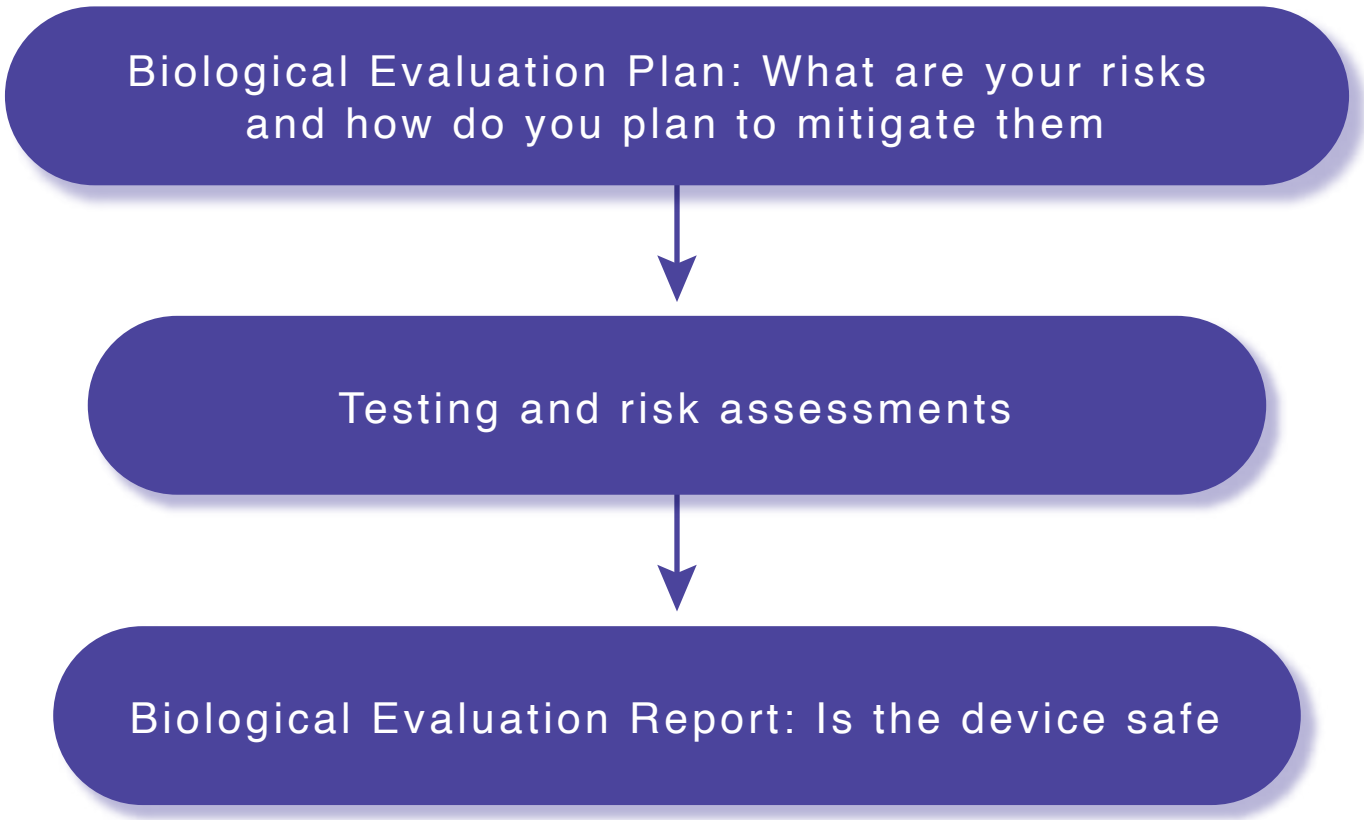
Material Characterization

Broad and general process of collecting existing information about a material's chemistry, structure and other properties, and if appropriate, new data, to facilitate the evaluation of these properties.

In practice there are three ways in which data can be obtained:

- Supplier Information
- Predicate Testing
- Material Characterization

In conclusion, the ISO10993-1 requires the manufacturer to take the following 3 steps:



New Requirements of the EU MDR

The EU MDR has set new requirements regarding biocompatibility of the devices, which are now more aligned to the requirements of the ISO10993-1:2018.

1. The MDR has added a requirement to focus on 'substances' in a medical device rather than on 'materials'. So a tubing can be made of a material like polyvinyl chloride (pvc) but there can be several substances that may be a part of the tubing besides pvc alone.
2. Specific need to evaluate how substances are absorbed, distributed, metabolized and excreted.
3. Evaluate the impact of processes on material properties. Such as, how the manufacturing processes can impact the material properties.
4. Reduce risks as far as possible from substances and particles emerging from wear debris, degradation products and processing residues.
5. Evaluate the risks due to the size and properties of particles which can be released into the patient or user's body.
6. The MDR Annex I section 10.4 requires not more than 0.1% w/w of carcinogens, reproductive toxins and mutagens (CMR) of category 1A and 1B as well as endocrine disrupting (ED) substances, 1 and 2, unless the manufacturer can show that the use of the substance is justified from a benefit-risk analysis. The MDD was concerned with only phthalates, which is a CMR substance. So this requirement is a major change in the MDR.

The requirement is for the following types of devices:

Invasive device in direct contact

Devices to administer or remove medicines, fluids or gases

Transport or store medicines, fluids or gases to administer

The Technical File in its pre-clinical data section now also needs to have information on the physical, chemical and microbiological characterization of the materials used. This requires a much more detailed evaluation of materials similar to what the ISO10993-1:2018 requires.
To conclude, both the ISO10993-1:2018 and the EU MDR now require that manufacturers spend a considerable amount of time and effort to prove that the materials they are using are safe, using sound scientific rationale. Needless to say, this requires manufacturers either to have more qualified technical experts (like chemists and toxicologists) in their team or look for outside help.
In future editions, we will cover aspects of material characterization as provided by ISO10993-18:2020 (chemical characterization of materials).

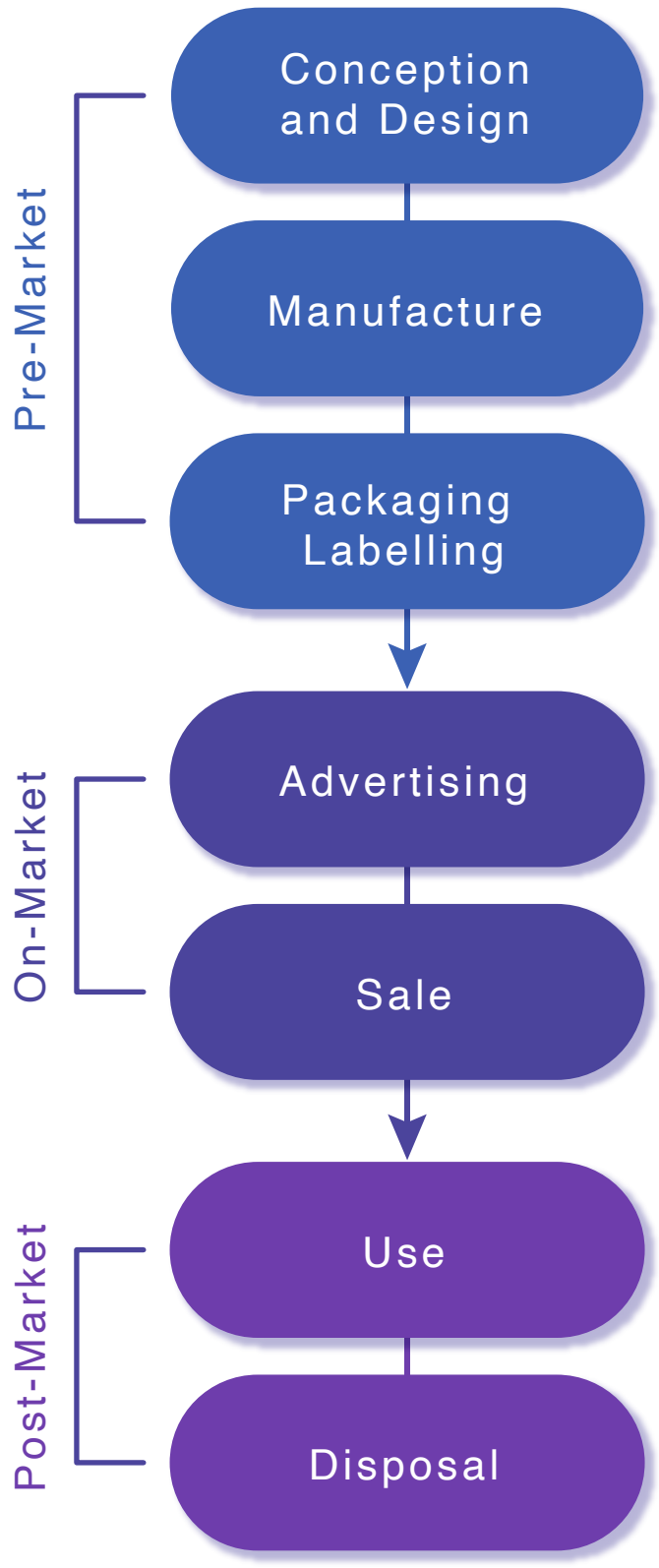
Alceon can support you in terms of conducting a biological risk assessment and prepare your biological evaluation plans and reports through our in-house toxicological expert.

MEDICAL DEVICE VIGILANCE SYSTEM

02

Medical device regulators in the past have focused quality regulations on the device design and development process, but more recently, updates to medical device standards such as ISO 13485:2016 have seen the inclusion of additional post-market requirements, reflecting an added emphasis on full-lifecycle management of medical devices. The life cycle of a medical device is divided into Pre-Market, On-Market and Post-Market phase as shown in the figure below.

The post-market stage of a device's life cycle includes post-market surveillance activities conducted to ensure that adverse events involving the medical device are reported, clinical follow-up studies may be conducted and the manufacturer can address complaints or adverse events and make improvements to the product.

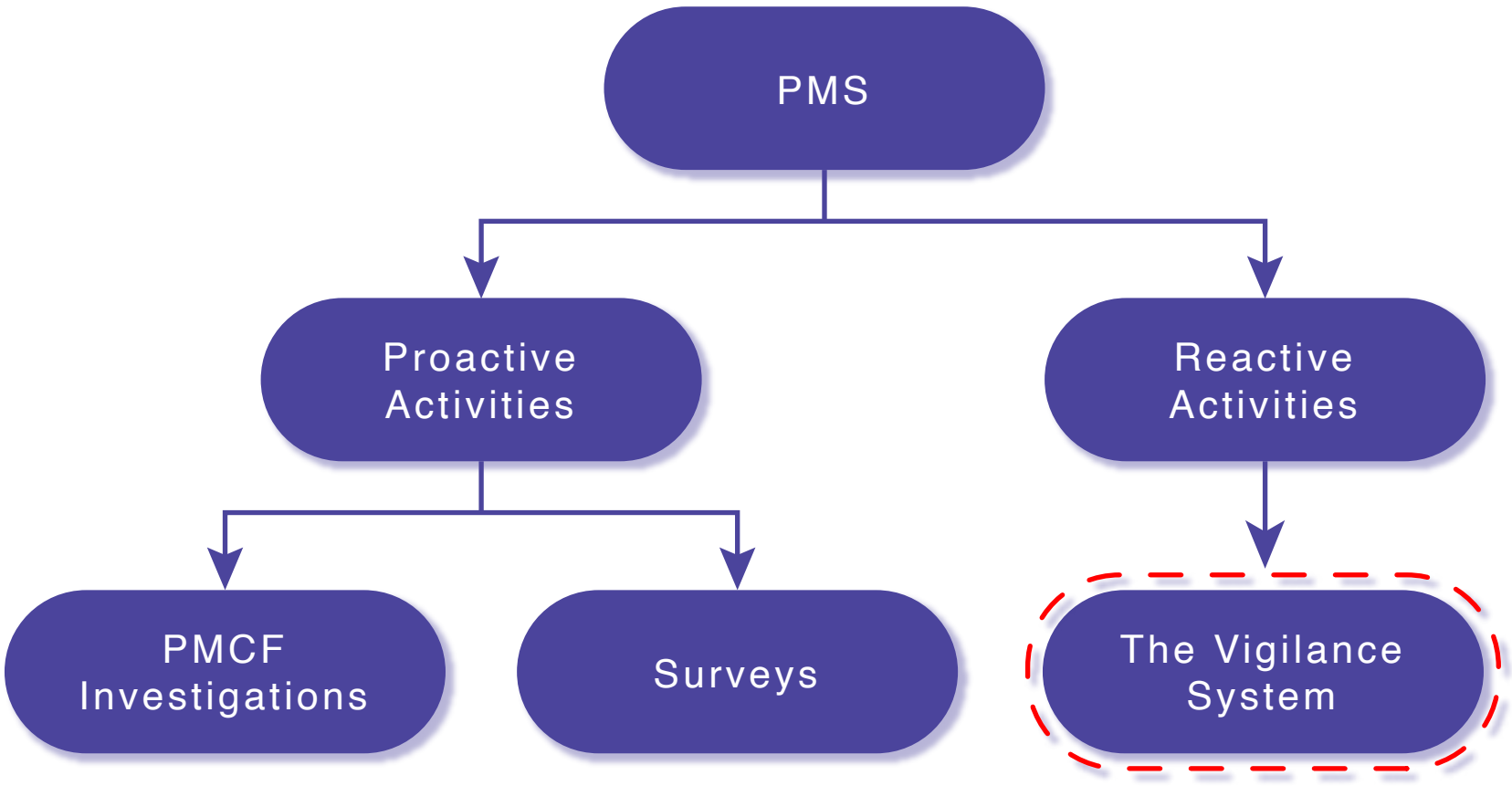


Product Life Cycle

Vigilance System

It is critically important that the safety and performance of medical devices are continually assessed when they are in use i.e. post-marketing, as the information collected during the pre-marketing phase is incomplete about adverse incidents and this is mainly because:

- No amount of rigour in the pre-marketing review process can predict all possible device failures or incidents arising from device misuse.
- It is through actual use that unforeseen problems related to safety and performance can occur.



Post-Market Surveillance (PMS)

*The above are only examples of proactive PMS activities and not an exhaustive list

Post-market surveillance is a broad term that covers all monitoring activities of medical devices in use. The two principal activities within surveillance are “post-market surveillance studies” and “adverse incident reporting”.

In post-market surveillance studies, specific and structured data collections are required of the manufacturer in one of two situations:

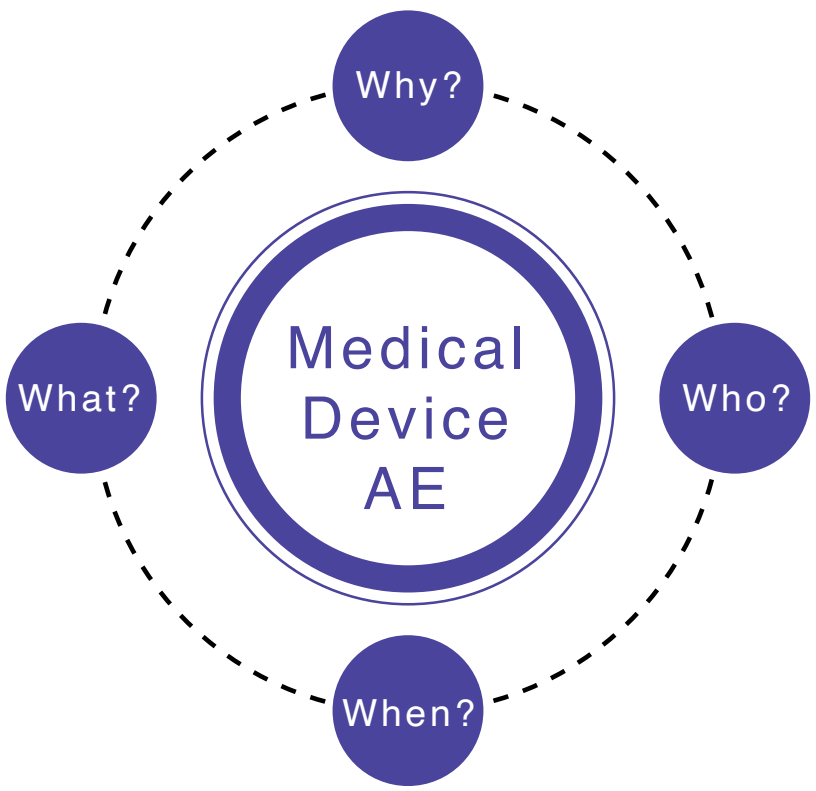
1. As a condition of product approval, or
2. To re-affirm product safety when post-market adverse incident reports suggest that pre-market safety claims are inconsistent with actual use and result in an unacceptable risk.

Purpose of the Vigilance System

- To improve the protection of health and safety of patients, users and others by reducing the repetition of the same type of adverse incident. This is to be achieved by the evaluation of reported incidents and, where appropriate, dissemination of information which could be used to prevent such repetitions or to alleviate the consequences of such incidents.
- To enable the Regulatory Authorities to monitor the effectiveness of the manufacturers' follow-up on reported incidents. The Regulatory Authority should take any further action that may be necessary to supplement the actions of the manufacturer.
- To facilitate a direct and early implementation of **Field Safety Corrective Action**, by allowing the data to be correlated between Regulatory Authorities and manufacturers.
- To enable the health-care professionals and user representatives who are responsible for the maintenance and the safety of medical devices to take the necessary steps once the corrective (or other) action is identified. Such steps should, where practicable, be taken in cooperation with the manufacturer.
- Regulatory Authorities may also monitor experience with devices of the same kind (for instance, all defibrillators or all syringes), but made by different manufacturers. They may then be able to take measures applicable to all devices of that kind. This could include, for example, initiating user education or suggesting re-classification.

Reporting Medical Devices Adverse Events

Adverse incident reporting requires the registration and investigation of an adverse incident relating to the use of a device, and the authority necessary to oblige the manufacturer to recall or modify a defective device.



The adverse event reporting system has been considered as a tool to improve and protect the health and safety of patients and users, thereby reducing the likelihood of adverse events, to prevent the repetition of adverse events, or to alleviate consequences of such repetition.

Reportable Adverse Events

The reportable adverse events include the following:

- If an event has occurred, and the manufacturer becomes aware of the information
- If it is assessed that the manufacturer's device is associated with the event based on the opinion from the available information
- If the event has led to or might have led to death or serious injury of a patient, user, or another person.

Non-Reportable Adverse Events

The regulated countries defined not-reportable events similarly with few exceptions.
The following events are exempted from reporting in all countries:

- If the deficiency of a device is found by the user before its use and no serious injury has occurred
- If the root cause of the adverse event is due to a patient's pre-existing condition
- If the shelf life or service life of the device was exceeded before its use by a patient
- If the design feature for protection against malfunction complied with the relevant standards and operated correctly
- If the deficiency had a negligible likelihood of causing death or serious injury and had been established and documented as acceptable after a risk assessment
- If the side effects are expected and foreseeable from the manufacturer's labelling, are clinically well known, and are documented in the device master record, with an appropriate risk assessment
- If the adverse event was caused by errors of use and abnormal use

Responsibility of Adverse Event Reporting

In most cases, the establishment i.e. manufacturer or its authorized representative, importer or distributors reports an adverse event.
In the following table, we have collated information from several countries/regulations to highlight the differences and similarities among them.

#	Country	Canada	USA	Europe MDR	Brazil	Australia	Japan	United Kingdom	India	Egypt	Saudi Arabia	China	New Zealand	Indonesia
1	Regulatory Agency	Health Canada (HC)	The Food and Drug Administration (FDA)	European Medical Device Regulations (EU-MDR)	Agência Nacional de Vigilância Sanitária (ANVISA)	Therapeutic Goods Association (TGA)	Ministry of Health, Labour and Welfare/ Pharmaceuticals and Medical Devices Agency (PMDA)	Medicines and Healthcare Project Agency (MHRA)	Central Drugs Standard Control Organization (CDCSO)	Medical Device Safety Department Egyptian Pharmaceutical Vigilance Center	Saudi Food and Drug Authority (SFDA)	National Medical Products Administration (NMPA)	Medicines and Medical Device Safety Authority (MEDSAFE)	Ministry of Health
2	Reporting Authority	Manufacturer, Canadian Importer	Manufacturer, Importer	Manufacturer	Manufacturer, Brazilian Registration Holder	Manufacturers Australian Sponsor	Manufacturer Market Authorization Holder	Manufacturer Authorized Representative	Manufacturer	Manufacturer Importer Healthcare Professional	Manufacturer Importer Healthcare Professional	Manufacturer Healthcare Professional	Manufacturer Healthcare Professional Patients	Manufacturer
3a	Method of Reporting Adverse Event	Serious deterioration in health also includes a serious public health threat which is any incident type, which results in imminent risk of death, serious deterioration in health, or serious illness that requires prompt remedial action	Form FDA 3500A should be submitted within 5 days of becoming aware of an event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health	'Serious Public Health Threats' no later than 2 days of becoming aware	Death', 'Serious Public Health Threats' and 'Counterfeit Devices' no later than 3 days (72 hours) after becoming aware	'Serious Threat to Public Health' no later than 2 days after becoming aware	Market Authorization Holder should report the matters specified in the items of Article 228-20, Paragraph 2 of the Enforcement Regulations concerning the products when the institutions and relevant registered manufacturing sites have cognizance of the matters concerned	Serious public threat shall be reported within two calendar days	Unanticipated death or serious injury shall be reported within 10 days	Serious public health threat should be reported immediately not later than 2 calendar days after awareness by the Manufacturer of this threat	Serious public threat shall be reported immediately	Adverse event has to be reported in 12 hours NMPA	Death and Serious Injury initial report of adverse event has to be submitted within 10 calendar days	Serious adverse event reporting will be submitted in 15 days

3b	Method of Reporting Adverse Event	A mandatory problem report should be submitted within 10 days of becoming aware when a patient, user or other person died or experi-enced a serious deterioration of health as a result of the event	Form FDA 3500A should be submitted within 30 days of becoming aware of reports of deaths, serious injuries and malfunctions	'Serious Incidents' no later than 10 days of becoming aware	Major Adverse Events' and 'Minor Adverse Events, whose recurrence has the potential to cause a major adverse event' no later than 10 days after becoming aware	'Adverse Events' no later than 10 days after becoming aware	Impediment Cases with the possibility of death or impediment Hospital admission to alleviate impediment or cases that extend hospital admission Congenital diseases are to be reported within 15 calendar days	Death or serious deterioration within 10 elapsed calendar days	Other reportable events shall be reported not later than 30 calendar days	Death or serious incident should be immediately reported no later than 30 calendar days following the date of awareness of the event	-	-	Minor Injury which may lead to market action initial report in 10 days and final report to be submitted in 120 days	Severe /moderate adverse event will be reported in 30 days
3c	Method of Reporting Adverse Event	A mandatory problem report should be submitted within 10 days of becoming aware when a patient, user or other person died or experi-enced a serious deterioration of health as a result of the event	-	'Incidents' no later than 15 days of becoming aware	Technical Complaints, which may lead to a major adverse event, if at least one of the following conditions are met: • Possibility of technical complaint recurrence is not remote • A similar occurrence has already caused or contributed to death or major health damage [adverse event] in the last 2 years • The manu-facturer would need to carry out action to prevent a serious public health threat • It is likely the error of use • No later than 30 days after becoming aware	Near Adverse Event no later than 30 days after becoming aware	The same cases as described above that could be attributed to the mal-function of the medical device within 30 calendar days	Other incidents, immediately after assessing the link between the device and the event within 30 elapsed calendar days	All other reportable events not later than 30 elapsed calendar days	-	All other reportable events not later than 30 elapsed calendar days	-	-	-

4	How to Report	Via email, fax (613-954-0941) or mail: Canada Vigilance – Medical Device Problem Reporting Program Marketed Health Products Directorate Health Canada Address Locator 1908C 200 Eglantine Driveway Ottawa, Ontario K1A 0K9	The FDA has two options for manufacturers and importers to electronically submit Medical Device Reports: Web Interface using the eSubmitter application AS2 Gateway-to-Gateway	Via EudaMed	Via SNVS	Via IRIS	To consult by telephone with PMDA and upload to the designated website page of PMDA	-	Manufacturers or healthcare professional should contact by email or fax	Manufacturers or healthcare professional should contact by email or fax	Manufacturers or healthcare professional should contact by email or fax	Manufacturers or healthcare professional should contact by email or fax	Patients, caregivers, healthcare professionals and suppliers are all encouraged to lodge an adverse event report if an incident has occurred by email *devices @health.govt.nz*	Manufacturers or healthcare professional should contact by email or fax
5	Reporting Required for Events Outside	No- There is one exception to this that is outlined in Section 59(2) in the regulation: a foreign incident which resulted in the decision to undertake a field action should be reported to Health Canada provided it also meets the reporting requirements set forth in Section 59(1) of the regulations	Yes- US manufacturers of medical devices that are not cleared or approved in the USA, but are exported to foreign locations, are also subject to the Medical Device Reporting regulation using HL7 ICSR XML	Yes – any field safety corrective action in respect of devices made available on the Union market, including any field safety corrective action is undertaken in a third country concerning a device which is also legally made available on the Union market, if the reason for the field safety corrective action is not limited to the device made available in the third country	If the event is associated with a registered medical device outside of Brazil and the model/batch or serial number was imported into Brazil, the reporting criteria include 'Death', 'Serious Public Health Threats' and 'Counterfeit Devices' no later than 10 days after becoming aware	No	Yes- adverse events that occur worldwide that are associated with products approved for sale in Japan should be reported to Pharmaceuticals and Medical Devices Agency (PMDA); if the device involved in an adverse event is manufactured using similar manufacturing processes, even if it is not sold in Japan and depending on the issue, it is subject to reportability	Yes- adverse events that occur worldwide that are associated with products should be reported	Yes- adverse events that occur worldwide that are associated with products should be reported	-	Yes- adverse events that occur worldwide that are associated with products should be reported	-	-	-

*While we have taken care that the information provided in the above table is correct, the reader is advised to consult the regulatory source directly before implementation of vigilance procedures

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