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RESEARCH ARTICLE

Regulation of Medical Device with Special Emphasis on its Registration Procedure and Adverse Event Reporting System in US and Australia

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ABSTRACT

A medical device is an instrument, apparatus, implant, in vitro reagent, or similar or related article that is used to diagnose, prevent, or treat disease or other conditions, and does not achieve its purposes through chemical action within or on the body. Regulation of device has also evolved due to an increasing awareness of the need for more consistent approach to regulatory documentation. The Global Cardiovascular Device industry is growing rapidly and exhibits signs that it will continue to evolve and expand to reach $97 billion by 2015. Over 80 million people suffer from cardiovascular diseases globally with more than 17 million deaths every year. Cardiovascular devices are life threatening devices and it is directly affecting the patient's life so strict and specific regulation is requiring for high-risk medical devices. In US, Food and Drug Administration evaluates high-risk medical device such as cardiac implantable, pacemaker, and implantable cardioverter-defibrillators via the Pre-Market Approval process. In Australia, Therapeutic Goods Administration regulates the medical device under the Australian Register of Therapeutic Goods. This article discuss about the general introduction about medical device, its classification, registration procedure, documentation required for registration and adverse event reporting system of medical device in US and Australia.

KEYWORDS

FDA, 510(k), PMA, CDRH, TGA, DEAL

INTRODUCTION

As per the Global Harmonization Task Force (GHTF) "Medical Device" means any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material, or other similar or related article, intended by manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose 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 for medical purposes by means of in vitro examination of specimens derived from the human body and which does not achieve its primary intended action in or on the human body by

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pharmacological, immunological or metabolic means but which may be assisted in its function by such means[1].

The GHTF regulatory body is now called as International Medical Device Regulatory Forum (IMDRF).

Significance of Medical Device

The new development of technology has decreased the morbidity and mortality of life. The medical development in terms of drugs and device has brought the robust change in the life span of humans. Medical device have increase the ability of physicians to diagnose and treat diseases, making great contribution to health and quality of life[1].

Active Implantable Medical Device

Active Implantable Medical Device means any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure[2].

Examples of AIMD

- Implantable cardiac pacemakers
- Implantable defibrillators
- Implantable nerve stimulators
- Bladder stimulators
- Diaphragm stimulators
- Cochlear implants
- Implantable active drug administration device
- Implantable active monitoring devices

Cardiovascular Implants

Cardiovascular implants have strong potential to reduce the overall treatment cost for heart disease and at the same time improve quality of life. A focus on developing new generations of pacing devices that reduce mortality and improve patient outcomes has resulted in greater pricing flexibility in an increasingly cost-conscious health-care environment. The fastest growth will be in structural implants, as technological advances in heart valves, ventricular assist devices and implantable monitors will encourage greater use. Cardiovascular disease broadly covers a range of conditions affecting both the heart and the blood vessels. Cardiovascular devices are high-risk medical device and they are life threatening to the patients so its strict regulations are requires[2].

Cardiovascular Medical Device Regulation in US:

- An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related articles, including any component, part, or accessory, which is:
  - ✓ Recognized by the official National Formulary, or the United States Pharmacopoeia (USP), or any supplement to them.
  - ✓ Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation treatment, or prevention of disease, in a man or other animals.
  - ✓ Intended to affect the structure or any function of the body of a man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of a man or other animals and which is not dependent upon being metabolized for the achievement of its principal intended uses.
- FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, re-package, re-label, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, and microwave ovens[3].
- In US medical devices are regulated by CDRH (Center for Device and Radiological Health).

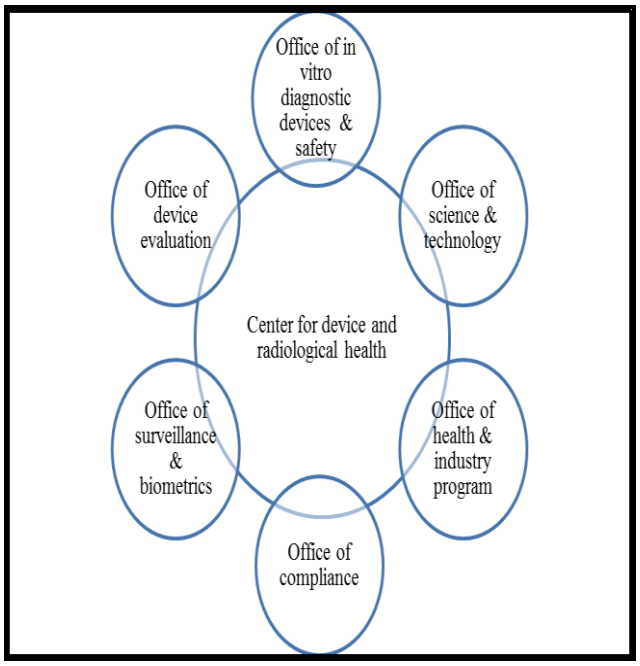

Figure 1: CDRH Regulatory Body

Classification of Medical Device as per US[5]

Table 1: Classification of Medical Device in US

Class	Risk Level	Device Examples
Class-I	Low Risk	Elastic bandages, Examination gloves, Hand-held surgical instruments
Class-II	Moderate Risk	Acupuncture needles, Powered wheel chairs, Infusion pumps, Surgical drapes
Class-III	High Risk	Implantable Pacemaker, Pulse generator, HIV diagnostic tests, Automated external defibrillators, Endosseous implants

- In US there are mainly 2 procedures for the registration of the medical devices.
  - ✓ 510k
  - ✓ PMA (Pre-Market Approval)
- Any manufacturer, re-packer, re-labelers, foreign manufacturer or exporter require to submit the 510(k) for medical device registration.
- For the high-risk medical device the PMA procedure is used and for the registration of high-risk medical device the clinical data must be required.

New Device Registration and Listing

- Establishments that are involved in the production and distribution of medical devices intended for commercial distribution in the United States are required to register annually with the FDA.
- Registration information must be submitted each year between October 1 and December 31, even if no changes have occurred.
- Listing information must be reviewed each year between October 1 and December 31, at the same time you review your registration information. Submit any updates at that time.
- Submit registration and /or listing information within 30 days of an establishment beginning an activity or putting a device into commercial distribution[3].

510(k) Submission Process

- To demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device.
- The 510(k) process is relatively rapid, flexible, and adaptable to many different device types and risk levels.
- Devices that have successfully gone through the 510(k) process are described as 510(k) cleared.
- For the Class-I & Class-II device registration process the 510(k) procedure is used and this process does not require any clinical data [(3)].

510(k) Procedure for Registration of Medical Device[5]

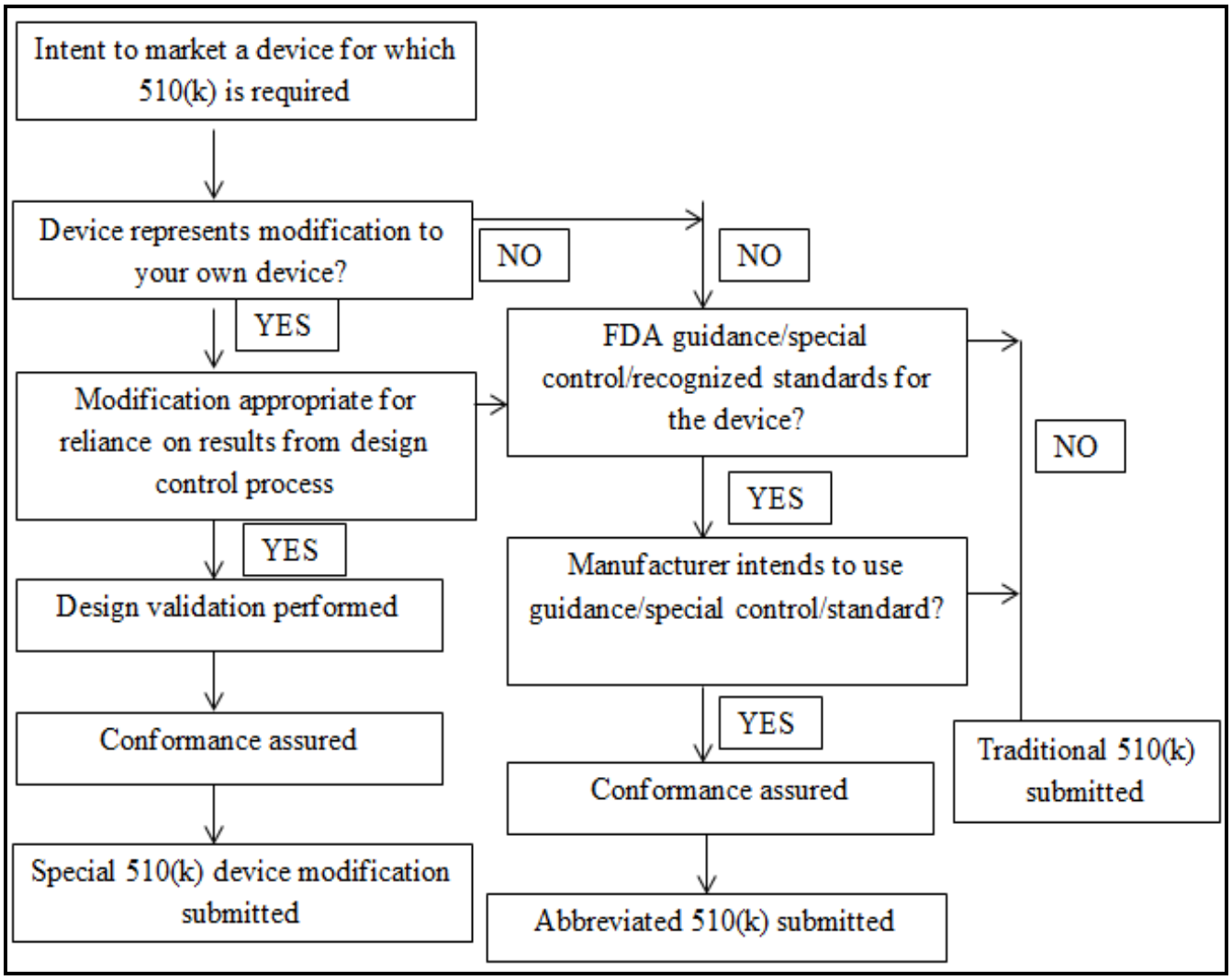

Figure 2: 510(k) Process

510(k) Review Fees[5]

- Medical Device User Fee and Modernization Act of 2002 authorize FDA to charge a fee for medical device Premarket Notification 510(k) reviews.

Table 2: 510(k) Registration Fees

FY 2012 device review user fees (U.S. dollars)		
Submission	**Standard fees**	**Small business fees**
510[k]	$4,049	$2,024
513[g]	$2,971	$1,485

FDA will adjust these fees each year to account for inflation, changes in workloads, and other factors. The small business fee is 50% of the standard fee.

Submit a 510(k) for a Change to an Existing Device

The purpose of this guidance is to provide direction to manufacturers on deciding when to submit a 510(k) for a change to an existing device.

Procedure

- The type of modifications addressed in the draft guidance includes labeling changes,

technology or performance specifications changes, and materials changes.

- When making the decision on whether to submit a 510(k), the manufacturer's basis for comparison of any changed device should be the device described by the cleared 510(k) or to their legally marketed preamendments device.
- That is, manufacturers may make a number of changes without having to submit a 510(k), but each time they make a change, the device they should compare it to is their most recently cleared device.
- When contemplating changes to a device, manufacturers should use the flowchart for each individual type of proposed change, e.g., performance specification change, material change.
- If a manufacturer's consideration of all proposed changes results in a decision merely to document the decision-making, they should document the application of the model along with the necessary records of the validation of changes to the device.
- In those circumstances where the proposed change is not addressed in the flowchart or in a device-specific guidance document, manufacturers are encouraged to contact the Office of Device Evaluation in CDRH to find out whether other, specific guidance exists or if additional help is available[3].

Components of 510(k)[3]

1. The cover sheet (FDA form 3514)
2. The cover letter
3. Table of contents
4. User fee information
5. Statement of substantial equivalence
6. Labeling
7. Advertising or promotional material
8. Comparative information
9. Biocompatibility assessment
10. Truthful and accurate statement
11. Clinical data
12. Shelf life indication for use form
13. Indication for use form
14. 510(k) summary

PMA Procedure for Registration of Medical Device[5]

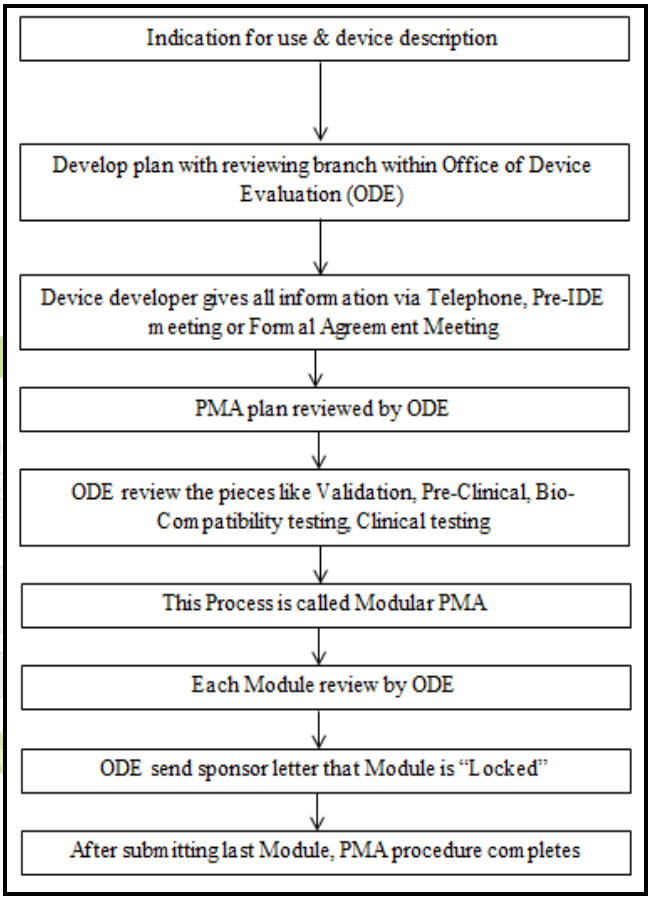

Figure 3: PMA Process

PMA Review Process[5]

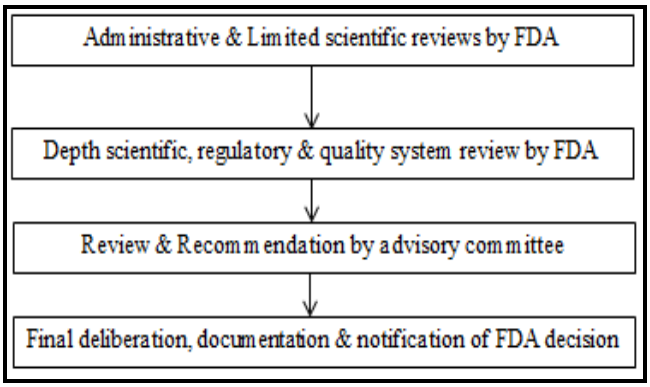

Figure 4: PMA Review Process

PMA Components (21CFR814)[5]

1. Cover page
2. Table of contents
3. Summary of safety and effectiveness
4. Device description and manufacturing data
5. Performance standards referenced
6. Technical data (nonclinical and clinical)
7. Justification for a single investigator
8. Bibliography
9. Device sample (If requested)
10. Labeling
11. Environmental assessment
12. Device Review Fees

Device Review Fees[5]

Table: 3 Device Review Fees

FY 2012 Device Review User Fees (U.S. Dollars)		
Submission	**Standard Fee**	**Small Business**
Premarket Application	$220,050	$55,013
First premarket approval submission (PMA) from firms with gross receipts or sales ≤ $30 million	Not Applicable	Fee is Waived
Panel-track Supplement	$165,038	$41,259
Efficacy Supplement	$220,050	$55,013
180-day Supplement	$33,008	$8,252
Real-time Supplement	$15,404	$3,851
Annual Report	$7,702	$1,925
30-day Notice	$3,521	$1,760

Payment Process[5]

1. Electronic payment
2. Mailing in a Paper Check
3. Payments by Wire Transfer

Medical Device Regulation in Australia

Definition

- A medical device is any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:

  I. Diagnosis, prevention, monitoring, treatment or alleviation of disease;

  II. Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;

  III. Investigation, replacement or modification of the anatomy or of a physiological process;

  IV. Control of conception;

  V. And that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means; or

- Any instrument, apparatus, appliance, material or other article specified under subsection (2A); or
- Any instrument, apparatus, appliance, material or other article that is included in a class of instruments, apparatus, appliances, materials or other articles specified under subsection (2B)[7].

Medical Device Regulation in Australia

- The Therapeutic Goods Administration (TGA) a division of the Australian Government Department of Health and Ageing is responsible for administering the Act and associated legislation.

Adverse Device Effect Reporting[5]

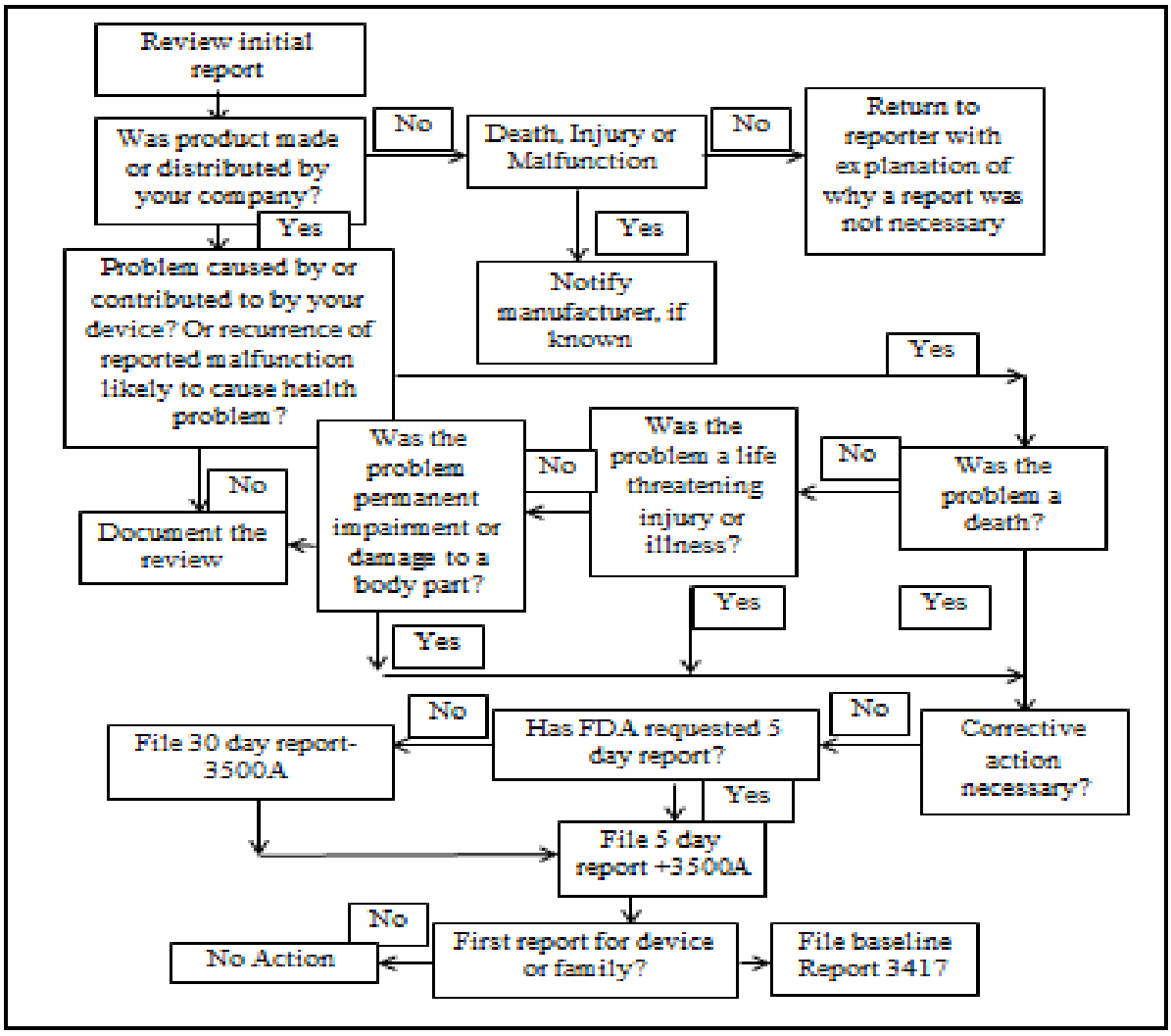

Figure 5: Adverse Event Reporting

Classification of Medical Device in Australia[7]

Table 4: Classification of Medical Device in Australia

Class	Risk Level	Device Examples
Class-I	Low Risk	Reusable surgical instruments, Scalpel
Class-IIa	Low-Medium Risk	Hypodermic needle, Suction equipment
Class-IIb	Medium-High Risk	Ventilators, Orthopedic implants
Class-III	High Risk	Drug eluting cardiac stents
AIMD	High Risk	Implantable pacemaker

- The Office of Device Authorization (ODA) is the office of TGA where pre-market regulation of medical device has been done.
- For the post-market regulation the Office of Product Review (OPR) is responsible.
- Medical device regulation is needed for the high level protection of public health and safety [(7)].

Medical Device Registration Using DEAL System

- For the registration of medical device we need to create the e-business account for the DEAL (Device Electronic Application Lodgment) system.
- New user need to complete a client details form and e-business access.
- After getting the user name and password we can directly it on TGA online website on DEAL home page.
- Following information of Manufacturer's evidence added in system:
  - ✓ Client reference and details
  - ✓ Conformity assessment certification including the certificates details and if there are any restrictions on the scope
  - ✓ Class of the device
  - ✓ Conformity assessment procedure
  - ✓ Conformity assessment body
  - ✓ Manufacturer's details including name and address
  - ✓ GMDN code
- Manufacturer's evidence currently takes between 5-10 days to accept by TGA[6].

Documents to Submit for Medical Device Application[7]

- ✓ Client reference and details
- ✓ Conformity assessment certificate including the certificate details
- ✓ Class of device
- ✓ Conformity assessment procedure
- ✓ Manufacturer's details including name and address
- ✓ GMDN code

Manufacturer's detail accepted by TGA then enters the detail in DEAL system:

- ✓ Sponsor's reference and detail
- ✓ Class of device
- ✓ Purpose of the device
- ✓ Manufacturer's name and address
- ✓ GMDN code
- ✓ Ingredient detail for medicated or formulated device
- ✓ Payment method of fees
- ✓ Indicate to cancel current Registered/Listed ARTG numbers that the device inclusion will be replaced.
- ✓ Device application form will take 6-10 weeks to be approved by TGA.

Re-Certification

TGA conformity Assessment Certificates are issued for 5 Years. After expiration of the certificate if manufacturer wants to continue to supply devices covered by certificate in Australia, they need to apply for re-certification. Application for the re-certificate need to submit to the TGA. Re-certification process is same as new certification process[7].

Following documents has to be submitted by manufacturer:

- ✓ All design, production and labeling changes implemented since the certificate was issued
- ✓ Clarification of the current critical suppliers
- ✓ Sterilization arrangements for sterile product
- ✓ Origin country, species, production arrangement for animal, original material

Classification Rules for Class-III and AIMD as per the TGA[8]

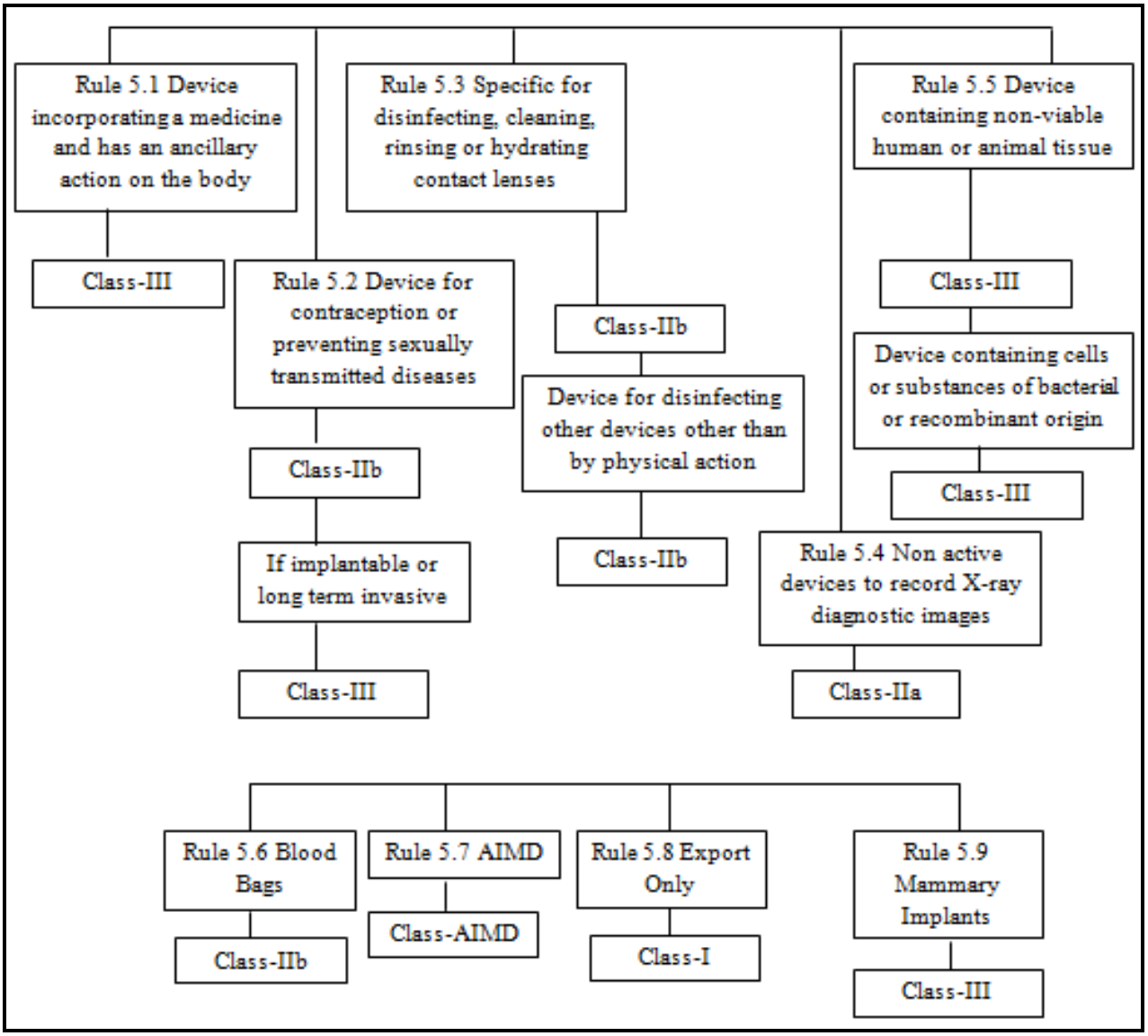

Figure 6: Classification Rules for Class-III & AIMD as per TGA

Standards Used for the Medical Device Manufacturer[7]

Table 5: Medical Device Standards

ISO Standard	USE
ISO 14971	Application of risk management to medical device
ISO 13485	Quality management system
ISO 10993	Biological evaluation of medical device
ISO 60601	Medical electrical equipment
ISO 10282	Single use rubber surgical gloves

Medical Device Regulatory Process in Australia[6]

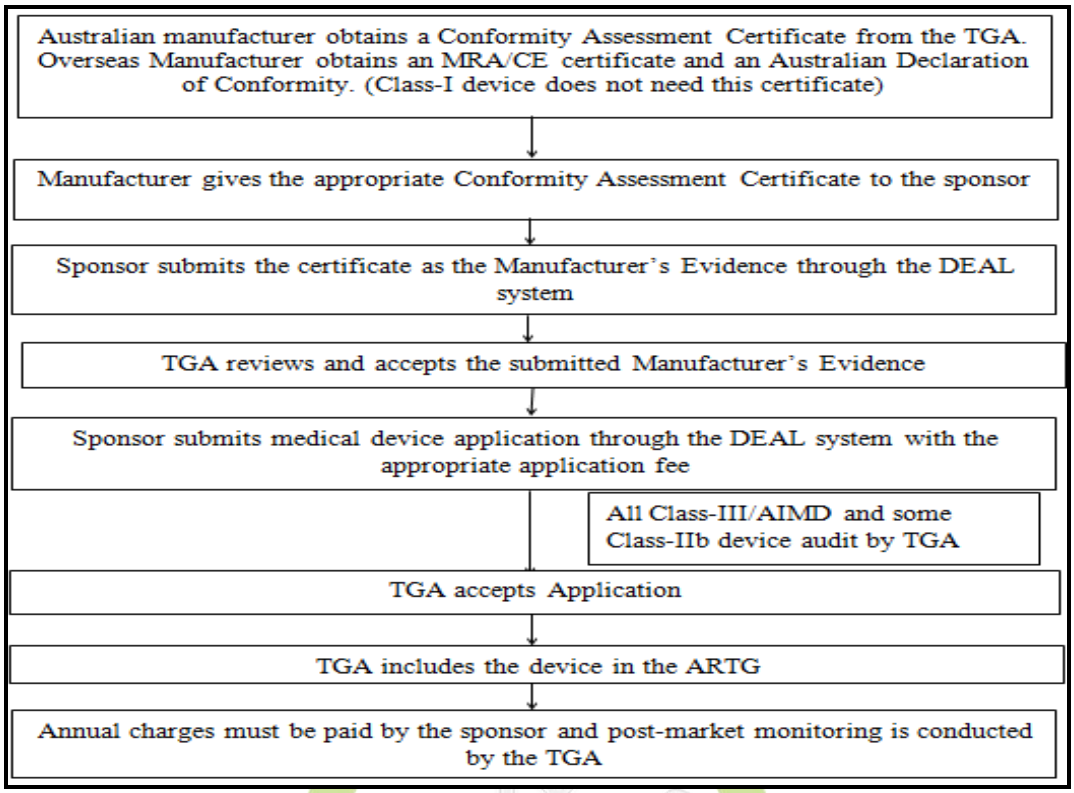

Figure 7: Medical Device Regulatory Process

Fees for Cardiovascular Medical Device[7]

Table 6: Fees for Medical Device in Australia

Class	Application Fees ($ AUD)	Annual Fees ($ AUD)
Class-III	960	960
AIMD	960	960

Conformity Assessment Fees[7]

Table 7: Conformity Assessment Fees

Conformity Assessment	Initial Assessment ($ AUD)	Changes ($ AUD)	Surveillance Audits ($ AUD)
Full Quality Management System Audit	21,400	12,900	6,250
Design Examination	42,400	25,500	
Type Examination	29,500	17,800	
Verification	20,700		
Product Quality Management System Audit	18,800	11,300	6,250
Product Quality Management System Audit	16,100	9,710	6,250

- ✓ Details of all medicinal substances and production arrangements
- ✓ Post-market performance data for each device including adverse events and recalls.

Adverse Events

Any events that meet three basic reporting criteria even if it does not involve a patient or user should be reported[9]:

1. Adverse event has occurred
2. Manufacturer's medical device is associated with adverse event
3. The event led to death or serious injury
4. Death
5. Serious injury or serious deterioration to a patient, user or other person

Table 8: Adverse Events

Adverse Events	Description
Malfunction or deterioration in the performance of device	Failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions
Inadequate design	Design or manufacturing of a device is found deficient
Inaccuracy in the labeling, Instructions for Use	Inaccuracies include omissions and deficiencies
Significant public health concern	Include the significant event that become a potential public health hazard

Reporting of Medical Device

Only adverse events that occur in Australia are required to be reported to the TGA. Adverse events that occur overseas for devices supplied in Australia do not need to be reported to the TGA. The reporting requirements for sponsors are conditions on the inclusion of medical devices in the ARTG. In complex situation it should be assumed that the device was associated with the events. Where possible the manufacturer should consult with the user and medical practitioners to retrieve the device[9].

Details to be Included in Adverse Event Report

There are two report forms available on the TGA website:

- Medical device adverse event reporting by medical device users for use by medical device users to report any suspected problems with a medical device that has or may present a health hazard. Typical problems include deficiencies in labeling, Instructions for Use or packaging, defective components, performance failures, poor construction or design
- Medical device adverse event reporting by medical device manufacturers and sponsors to be used by medical device sponsors, manufacturers or their authorized representatives for mandatory reporting of adverse events associated with a medical device[9].

If a person is not able to access the forms on the TGA website, they should ensure that the report includes the following details:

The Sponsor's:

- ✓ Name
- ✓ Address
- ✓ Contact number
- ✓ Fax number
- ✓ Date when the event came to know

Information of device:

- ✓ Name of the device
- ✓ Commercial name
- ✓ Catalogue number
- ✓ ARTG number

- ✓ Model number
- ✓ Serial number
- ✓ Batch number
- ✓ Lot number
- ✓ Software version
- ✓ If implantable, date of implant & date of explant
- ✓ Location of the device in the body

Adverse Event Reporting Flow Chart in Australia

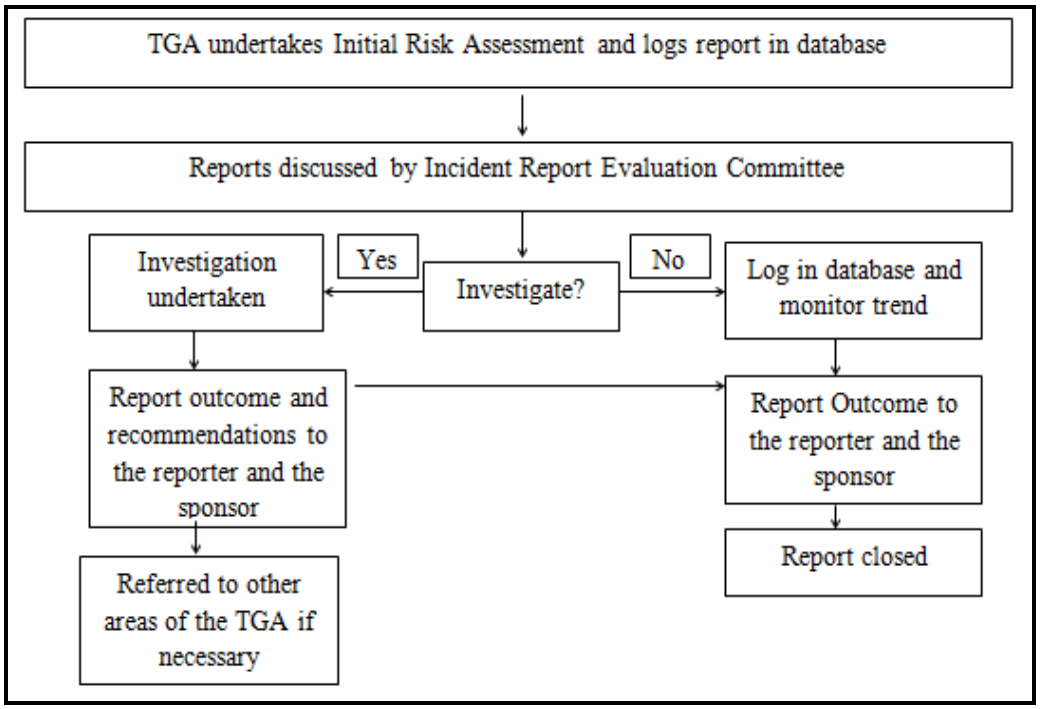

Figure 8: Adverse Event Report

RESULT

Comparison Table

Table 9: Comparison Table

PARAMETER	US	AUSTRALIA
Regulatory Authority	U.S. Food and Drug Administration (USFDA)	Therapeutic Goods Administration (TGA)
Guidance to Follow	CDRH	ARGMD
Classification	3 Class Class-I Low Risk Class-II Moderate Risk Class-III High Risk	5 Class Class-I Low Risk Class-IIa Low-Medium Risk Class-IIb Medium High Class-III High Risk AIMD high Risk
Registration Procedure	2 Procedure 510(k) PMA	Single Procedure DEAL System
Registration Period	5 Years	5 Years
Rules	Not Specified	22 Rules

CONCLUSION

Medical devices are approved in US mainly by 2 procedures 510(k) and PMA. For the high-risk medical device the PMA procedure should be followed. High-risk medical devices are the life threatening device which requires strict regulation to follow for the marketing of the devices. For the high-risk device approval the clinical data should be submitted. In Australia, for the registration of medical devices a common procedure should be followed for all type of the medical devices but for the high-risk medical devices which are considered in Class-III and AIMD requires the specific rules to follow for the registration of them in TGA. Medical devices should be safe and efficient for the use to the patients so it requires the strict and specific rules to be followed. Now a days use of medical device is increased a lot so the medical device regulation should be strict and specific as per the country guidelines provided by the each country.

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