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Research Article

GLOBAL REGULATORY ASPECTS OF WOUND CARE AND BURN DRESSINGS

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ABSTRACT

Objective: The objective of the study was to present an overview of regulatory requirements for wound and burn care dressings.

Methods: A total of 80 research and review articles including regulatory guidelines to control the marketing of wound and burn care dressings recommended by international regulatory agencies were reviewed.

Results: A wide range of dressings, as a new target of the healing process, have been developed due to continued growth and innovations in the field. Ideal dressings should be safe and achieve healing at a reasonable cost with minimum inconvenience to patients. It is mandatory that manufacture and sale of such dressings are approved by the relevant health authority of each country. This article provides manufacturers with an overview regarding regulatory approval procedures for marketing such dressings in different countries and addresses the gaps and challenges in the existing guidelines aimed at maintaining product quality. It provides a comparative analysis of the differences in regulatory requirements and highlights that ongoing discussions and appropriate actions are required to support the continuous development of these dressings. Most countries have their own regulatory guidelines, and the approval processes differ according to the country. Quality parameters concerning the type of material, pore size, sterilization methods, shape and size, and labeling are not discussed in guidelines; therefore, innovators and manufacturers are facing tough challenges to showcase their products in the market, and this further leads to either lack of market availability or high cost of such dressings.

Conclusion: Development of common quality guidelines is essential for market availability of low-cost, high-quality dressings.

Key words: Surgical dressings, Wound dressings, Regulated market, Semi-regulated markets, Approval process, Burn dressings.

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INTRODUCTION

Burn and wound injury is a prevalent and burdensome critical care issue. Furthermore, burn wounds are complex and present unique challenges that require specialized care to protect from microbial infection [1]. According to the World Health Organization (WHO), more than 300,000 deaths occur each year as a consequence of fire-induced burns [2]. Approximately 3.5 million burn patients globally enter the outpatient health service system and receive some level of medical attention. The burden of such injuries generally falls on poor patients as they cannot afford costly treatments, and a primary contributing factor that leads to infection and finally to death in this population is poor hygiene. Burn injury management is challenging, due to significant fluid loss, tissue damage, and deep wounds, thus contributing to death [2,3]. At present, various novel dressings are being developed worldwide; however, due to lack of clear understanding of approval procedures, they are not accessible to patients.

This study provides details regarding the regulatory status, including approval procedures, and regulatory hurdles for new innovations that are not yet available for patient use. Decisions that are made regarding regulatory approval for a specific product lie within the regulatory authority of the country in which the product is to be marketed. A comparative study detailing regulatory requirements, approval timelines, and required approval fees in different countries has been conducted [2,3]. It has been identified that there is an utmost requirement for common regulatory guidelines; especially quality guidelines that may help attract more innovators and manufacturers to produce such dressings.

Globally, over 100 million surgical incisions occurring per year require wound management, indicating a 3.1% compound annual growth rate (CAGR) [4]. The prevalence of various wound types is shown in Table 1 [4].

A wound is generally defined as a disruption in the continuity of the epithelial lining of the skin or mucosa [5]. There are many types of wounds with multiple causes for their occurrence. The healing process is very complex; to prevent from microbial infection and to facilitate the body's natural healing mechanisms, an optimal healing environment and an appropriate wound dressing are often required [6].

There is a wide range of advanced and traditional wound care and burn dressings available, and the global wound dressing market is expected to expand at a CAGR of 4.5% during the forecast period from 2014 to 2020. In 2013, the global wound dressing market was estimated to be greater than US$7.5 billion, and by 2020 it is projected to be more than US$10.1 billion [7]. Standard wound dressings include wound closure products (gauze tapes, sponges, surgical cotton swabs, and others), basic wound care products, and antiseptic dressings. More advanced wound dressings include emerging and existing products such as films, foam dressings, Hydrofiber dressings, hydrocolloids, hydrogels, collagen dressings, and alginates [8,9]. Various types of advanced wound care dressings currently available are shown in Table 2, and research and development are ongoing.

Simple wound care or surgical dressings currently available cannot be used to cover the entire burned skin surface area of patients. Therefore, to overcome the challenges associated with the management of wound care and burn injuries, clinical trials are underway to evaluate novel products, such as Beta foam and Allevyn Silver dressing for burn wounds and acute burns, Inerpan for the treatment of partial-thickness burns, and honey for wound management [22,23].

Table 1: Estimated prevalence and growth rate of various wound types, 2011–2020 [4]

Wound type	Worldwide prevalence (thousands)	CAGR (2012–2020) (%)
Surgical wounds	114271	3.6
Traumatic wounds	1627	1.7
Lacerations	20645	1.2
Burn wounds	10221	1.2
Chronic wounds	40400	7.6
Carcinoma	618	3.0
Melanoma	103	3.2
Skin cancer	103	3.1

CAGR: Compound annual growth rate

In general, wound care and burn dressings are classified on the basis of the risk associated with the wound and are categorized as medical devices [24]. They are classified as Class I–IV and, in some countries, they are classified as Class A–D. Class A or Class I wound dressings are generally associated with low-risk wounds, and a low regulatory standard is required for their approval [24]. General classification is shown in Table 3.

In regulated markets (the USA, the European Union [EU], and Japan), wound dressings are classified as ClassA medical devices, for which no separate dossier submission is required, and maintenance of the safety and quality of the product is mainly the manufacturer's responsibility [25]. In emerging markets, they are classified as medical devices, although in some countries, proper classification and guidelines have not been established yet. These countries seek for

Table 2: Types of advanced wound care and burn dressings

Type of dressing	Examples/product brand names	Components	Intended use	References
Advanced wound dressings				
Foam dressings	Biatain, tegaderm, restore, optifoam, mepilex, PolyMem, Cura form (3M)	Polymers, often polyurethane	For use beneath compression stockings, for patients with venous leg ulcers	[9-11]
Hydrocolloid dressings	Biopad, tegasorb, comfeel, hydrocoll, varihesive E, medihoney tube (Coloplast/ Sween)	Adhesive, absorbent, and elastomeric components, carboxymethyl cellulose	Intended for use on light-to-moderate exuding, acute or chronic partial- or full-thickness wounds	[9-11]
Film dressings	3M Tegaderm, Pro-claude, Polyskin II, ProCyte film (proCyte)	Single thin transparent sheet of polyurethane coated on one side with an adhesive	Superficial wounds with little exudate, secondary dressing to attach a primary absorbent dressing	[9-11]
Hydrogel	Aquasite, ReliaMed, Anasept, Flex derm, Nu-Gel (Dow Hickam, Johnson &Johnson)	Three-dimensional networks of cross-linked hydrophilic polymers	Used to retain the gel in shallow wounds	[9-11]
Alginate dressings	Bioguard Roll gauze, Kerlix AMD, Algicel, Melgisorb (Kendall)	Calcium or calcium-sodium salts of natural polysaccharides	For moist, moderate-to-heavy exuding wounds	[9,10,12]
Collagen	Prisma, Promogran, Stimulen (Systagenix)	Collagen	Wounds with minimal, moderate, or heavy drainage	[9,10,12]
Therapy device				
NPWT				
Conventional NPWT	VAC therapy, vista versatile (Boehringer wound systems LLC), Engenex®	Consist of three components: Porous non adhesive packing material, occlusive seal, airtight container system	Potential to accelerate healing process	[9-13,15,16]
Oxygen and hyperbaric oxygen equipment	OxyHeal (OxyHeal Health Group)	Hydrogel sheet containing glucose and an enzyme oxidase	Stimulates wound healing	[9,12,14]
Electrical stimulation devices	POSIFECT (Biofisica LLC)	Derived from two 3-V nominal lithium coin cell batteries that deliver electric current to the wound bed	Stimulates the wound healing process	[9,14,17-19]
Active wound care device				
Artificial skin and skin substitutes	Biobrane, TransCyte (Smith and Nephew)	Biosynthetic skin substitute	Provides protection from bacterial influx and mechanical coverage	[12-14]
Surgical wound care				
Fibrin-based sealants	Fibrin-coated wound dressing (3M)	A fibrin-coated dressing with a flexible film layer, a pressure-sensitive adhesive layer, and a fibrin powder layer	Used as a scaffold in tissue regeneration strategies	[9,16-18]
Collagen-based sealants	Regranex, Autogel, Multidex gel (Smith and Nephew)	Comprised collagen or hyaluronic acid	Stimulates wound healing	[9,12,14]
Anti-infective dressings	Silver dressing, Algidex, Aquacel Ag (DeRoyal)	Hybrid dressings that provide healing advantage	Broad-spectrum activity	[9,12,19-21]

NPWT: Negative pressure wound therapy, VAC: Vacuum-assisted closure

US and EU approval marks and do not ask for additional approval, if products have been previously approved in these countries [26-28].

USA

In the USA, surgical and wound care dressings are regulated by the Food and Drug Administration (USFDA) under the Medical Device Regulation Act and are classified as Class I and II [29]. In general, classification depends on the complexity and invasiveness of the dressings. Examples of dressings are detailed in Table 4.

For Class I dressings, separate regulatory approval is not required, unlike Class II dressings that require 510 (k) approval. This approval process requires demonstration of "substantial equivalence" to a similar device marketed before 1976 and does not require any clinical research, for example, Oasis Wound Matrix, Prisma, and Medihoney [30,31].

Class III wound care dressings are considered to have the highest risk, for example, derma graft, designed to restore the dermal bed in diabetic foot ulcers, thereby improving the wound healing process and allowing patients' own epithelial cells to migrate to the wound and close it. Apligraf is a living cell-based product for chronic venous leg ulcers and diabetic foot ulcers. Apligraf is supplied as a living, bi-layered skin substitute. These are the only two wound care products approved by the FDA under Class III [32].

The well-defined approval procedure for wound care dressings in the US motivates researchers to present new and innovative products designed for clinical access and application.

Approval procedure

- Step 1 (identification of classification): According to USFDA medical device guidelines, surgical dressings are categorized as Class II medical devices.
- Step 2 (identification of predicate): Before registration, a check of predicate devices in the USFDA-provided database is required. Predicate devices are listed as similar medical devices prior approved by the USFDA through the 510(k)-approval process. An exact classification of a product and all its requirements can be easily identified through this database.
- Step 3 (identification of pre-requisites and regulatory requirements): According to the USFDA guidelines, wound care dressings are categorized as Class II, for which no separate dossier submission is required. The product classification codes are used to determine whether any standards and/or guidance documents apply to the device. Before submitting the application, applicants are required to complete the following:
  - Quality management system (QMS)
  - Literature supporting substantial equivalence to the predicate
  - Clinical data, if available (the USFDA may raise safety efficacy questions)
  - 510 (k) application form for USFDA notification.
- Step4 (Submission request to FDA): Following classification identification and before final submission, a request is made to the USFDA.
- Step 5 (FDA feedback): The FDA will review the classification of products and the similarity of claimed predicate devices.
- Step 6 (submission and review): Applicants then submit the application to the FDA and pay for the stated fee to have the submission reviewed. FDA will review the submission within 90 days and may request additional information, as appropriate. Successful applicants will be issued with a 510 (k)-clearance letter, along with a 510(k) number by FDA.
- Step 7 (issuance of a clearance letter): A clearance letter is required to market the product in the USA. A clearance letter is an FDA declaration that a product is substantially equivalent to a predicate device selected through the 510 (k) process, which has previously been cleared by FDA for sale. The clearance letter should be uploaded onto the FDA website under "device listing and establishment registration system" using the FDA's unified registration listing system.
- Step 8 (renewal and validity): Once FDA issues a 510 (k) approval, a number is assigned with an unlimited period of validity. However, it is mandatory to remain in compliance with the quality system and within all FDA regulations to continue the sale of the product in the USA. FDA may conduct random inspections of the manufacturing facility to ensure compliance with the quality systems regulation (21 code for federal regulations part 820.70). The full approval procedure is outlined in Fig. 1 [31].

Table 3: General classification of wound dressings [24]

Class	Risk level	Type of dressings
A	Low	Wound dressing
B	Low-moderate	Hydrogel dressings
C	Moderate-high	Deep wound dressing
D	High	Medicated dressings, sterile dressings, products containing biomaterials of human origin

EU

The European Medicines Agency is the regulatory body for wound care and burn dressings within the Medical Devices Directive (MDD) 93/42/EEC [29]. To commercialize wound care and burn dressings in the EU, a European Conformity (CE) Mark certificate is needed [33].

Approval procedure

- Step 1 (classification and applicable MDD directive)
  In accordance with the EU Directive93/42/EEC, wound dressings are categorized as Class I (non-sterile and non-measuring), or Class I (sterile and measuring).
- Step 2 (identification of regulatory requirements)
  Before submitting the application, compliance with the following regulatory requirements is needed:
- QMS in accordance with the 92/43/EEC
- Technical file in compliance with 92/43/EEC
- Safety tests in accordance with EU standards
- International Organization for Standardization (ISO) 13485
- Declaration of conformity.
- Step 3 (preparation of technical documents)
  Detailed information concerning the product is provided in this section, in accordance with the 94/42/EEC directive. Implementation of a QMS is required in accordance with Annexure-II of the Medical Device Directive and ISO 13485 standards. Manufacturers are

Table 4: List of dressings and associated level of risk [30]

Type	Examples	Level of risk	FDA classification	Regulatory requirements
Fabric dressings	Hydrophilic wound dressings, occlusive wound dressings, hydrogel wound dressings	Low risk	Class I	Approval not required; the FDA only needs to be informed before marketing. It is the responsibility of the manufacturer to maintain the safety and quality of the product
Advanced wound care dressings	Medihoney, Prisma, Oasis wound matrix	Intermediate risk	Class II	510 (k) approval is required

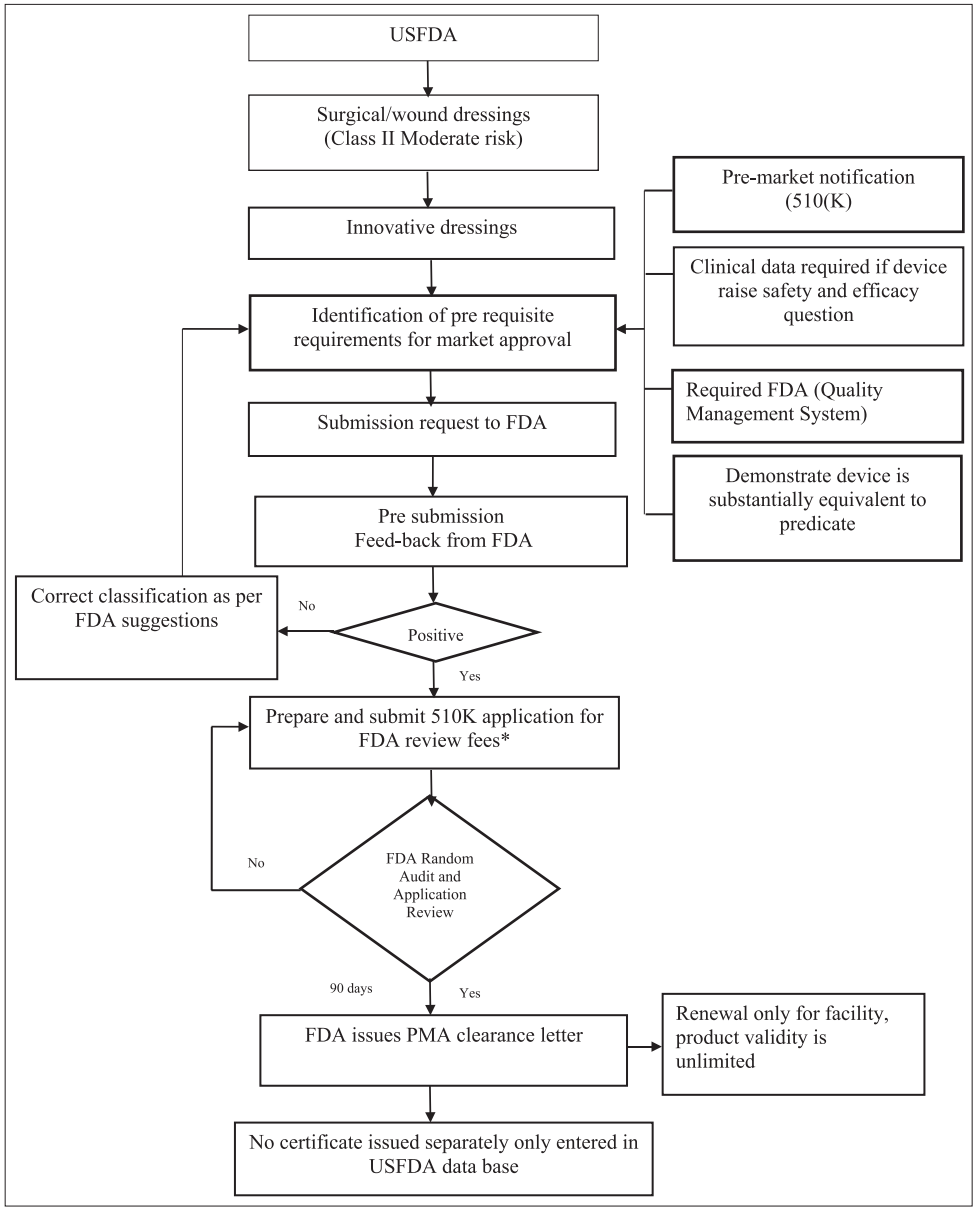

Fig. 1: Decision tree for the approval process in the United States [29-32]. *Application fees ($5018) are revised annually. Updated information concerning fees can be obtained at: Support@fdaagents.com. PMA: Pre-market approval application, FDA: Food and Drug Administration

required to submit a declaration of conformity, which is a legally binding document stating that the device complies with the applicable directive.

- Step 4 (submission of application to the Ministry of Health [MOH])
  The application is submitted to the MOH along with the specified fee.
- Step 5 (application review)
  The QMS/technical dossier is reviewed by the regulatory body, and an audit is scheduled.
- Step 6 (audit by the notified body)
  If a wound care dressing is categorized as Class I (sterile and non-measuring), the QMS and technical file or the design dossier should be audited by the notified body. After a successful audit, the European CE marking certificate for the device and an ISO 13485 certificate for the facility are issued.
- Step 7 (certification/validity and renewal)
  CE marking certificates are typically valid for 3 years. ISO 13485 certification must be renewed every year. Every year, the EU notified body will check compliance with 92/43/EEC. The full approval procedure is outlined in Fig. 2 [33-38].

Japan

The MOH, Labor, and Welfare (MHLW) in Japan regulates wound care dressings under the medical devices category [29,39]. The Japanese Pharmaceutical Affairs Law (PAL) defines wound care dressings as medical devices that are intended for use in the diagnosis, treatment, or prevention of disease in humans or animals, or intended to affect the structure or functions of the bodies of humans or animals. To engage in marketing, wound care and burn dressings manufacturers should obtain marketing business licenses (Marketing Authorization Holder [MAH]). The approval process is overseen by the Pharmaceuticals and Medical Devices Agency (PMDA), a division of the MHLW. To market surgical or wound dressings in Japan, manufacturers/marketing holders must register the device through the following procedures:

- Step 1 (classification determination): According to the Japanese PAL and the Japanese Medical Device Nomenclature codes, wound care dressings and surgical dressings are categorized as Class I and as general medicine Class I medical devices.
- Step 2 (identification of regulatory requirements): Before submitting an application for marketing approval, manufacturers should prepare

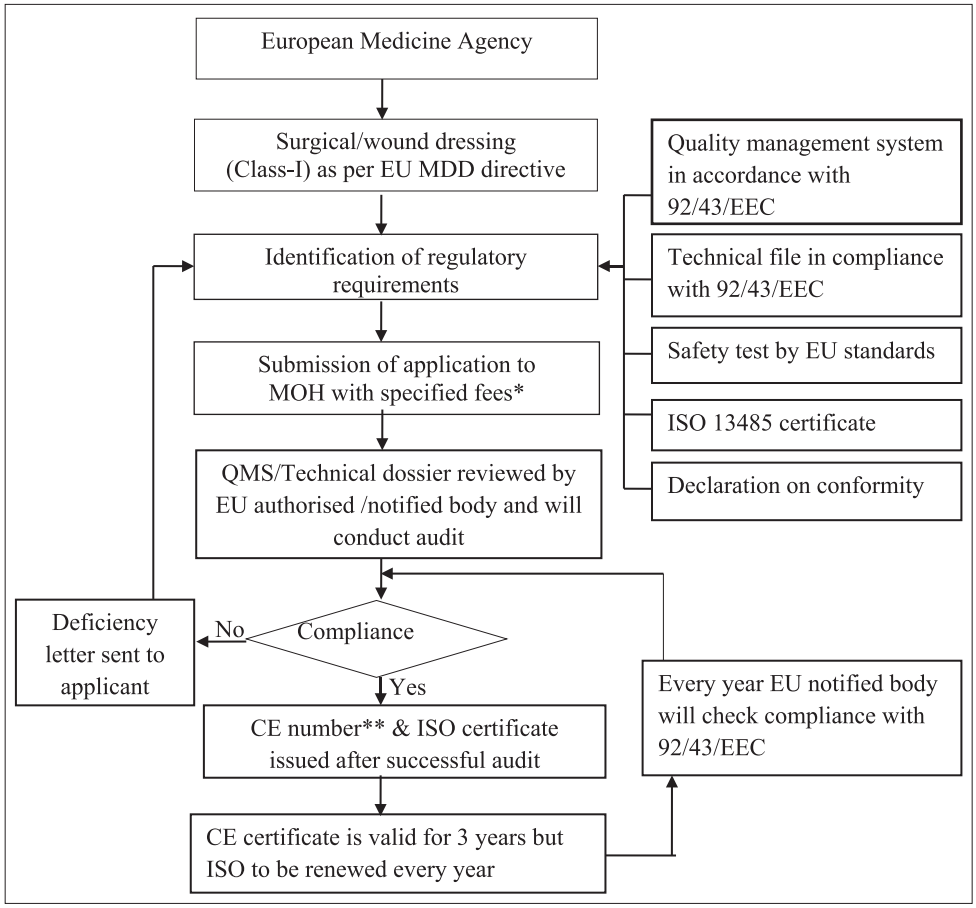

Fig. 2: Decision tree for the European Union approval procedure. *Fees vary in 30 member states. More details available on: http://www.mhra.com/cost-and-fees-for-the-registration-with-MHRA.html **No separate regulatory approval required. Manufacturers can use the CE mark if their product fully complies with the EU directive. QMS: Quality management system, MDD; Medical device directive

the following documents and product information. All documents must be written in Japanese.

Information required for surgical dressings as Class I medical devices in Japan:

- QMS in compliance with Japanese Ordinance 169
- Self-declaration
- Completed pre-market application form
- Category or classification of the product
- Generic name, if any
- Proprietary name
- Intended use
- Shape and structure including the following items, where applicable: Color photo, size and weight, components and accessories, electrical rating, and block diagram.
- Raw materials: Quantity (weight and percentage), materials specification (chemical and/or physical characteristics).
- Product specifications (defined according to each product), for example, appearance and/or physical characteristics.
- Directions for use
- Manufacturer(s) and manufacturing method
- Storage conditions and shelf life
- Notes on the following items, where applicable: Single-use or not, and usage of components of other medical devices
- Package inserts (directions for use) draft
- Color photo (digital image).
- Step 3 (submit pre-market application): Submission of the application for foreign manufacturer accreditation (Form No. 18) and implementation of the QMS.
- Step 4 (conformity assessment): After submission of all documents and required information, a conformity assessment is undertaken by the regulatory body.
- Step 5 (certification or renewal and validity): After 1 month, a decision regarding approval/rejection is reached by the PMDA. No separate certificate is issued for Class I devices, and approval is valid until there is any change in the QMS. The full approval procedure is outlined in Fig. 3 [39].

Canada

Wound care and surgical dressings are classified as medical devices and are defined in the *Food and drugs act,* which "covers a wide range of health or medical instruments used in the treatment, mitigation, diagnosis, or prevention of a disease or abnormal physical condition." The approval process is regulated by the *medical devices regulations (MDR) and* wound care dressing classifications depend on their intended use or the risk associated with the use of dressings. If a product is classified as a Class I device, a medical device license is not required. The rules governing the classification of medical devices are outlined in schedule 1 (parts 1 and 2) of the MDR. The approval procedure is detailed in Fig. 4 [40,41].

- Step 1 (determining classification): In accordance with the Canadian MDR schedule 1, wound care and surgical dressings are categorized as Class I medical devices.
- Step 2 (identification of regulatory requirements): Before application for market approval, manufacturers should make available the documents listed below:
  - Medical device establishment license with a list of manufacturers (MDEL)

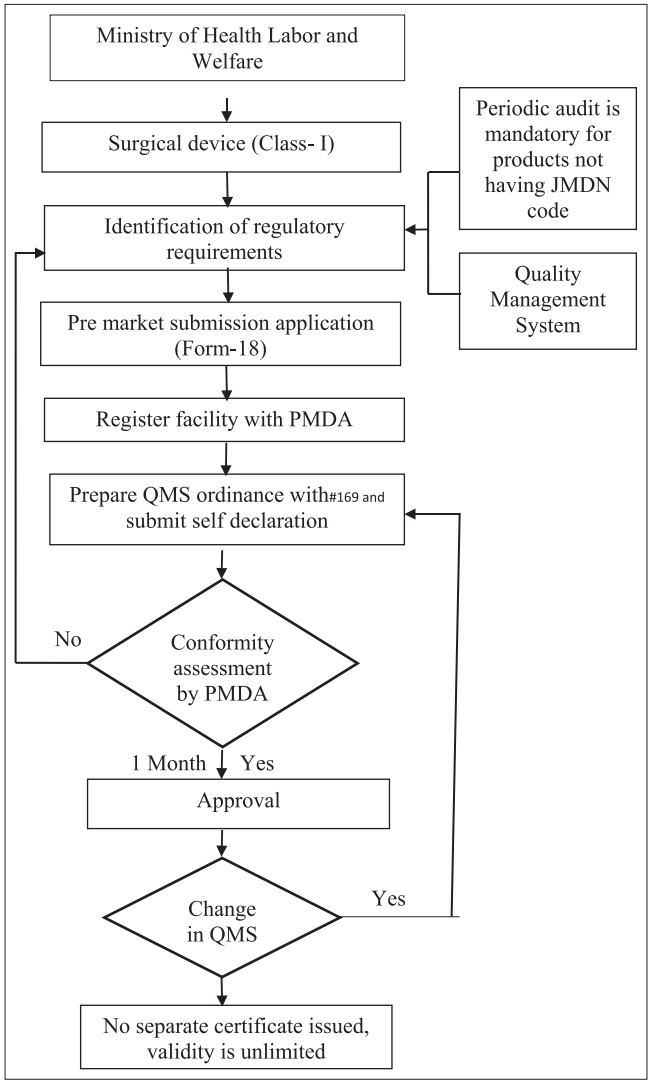

Fig. 3: Decision tree for the approval procedure in Japan [38]. PMDA; Pharmaceutical and Medical Device Agency, JMDN; Japanese Medical Device Number, MAH; Marketing Authorization Holder

- ISO 13485:2003 quality system management
- Safety and effectiveness data.

- Step 3 (submission of MDEL): Application for an MDEL, that is, a permit for the distributor/importer, or a manufacturer of Class I devices. Submission of the MDEL application for Class I devices.
- Step 4 (fee submission): After submitting an MDEL application, payment of CAD$7344 should be submitted within 30 days to the appropriate authority.
- Step 5 (review of MDEL application): The MDEL application is reviewed by the Canadian Registrar, and the approved application is posted on the Health Canada website.
- Step 6 (renewal and validity): Following approval, no separate certificate is issued, and under section 48 of the regulations, license holders are required to notify the health authority within 15 days in case of a change in the name or address of the license holder, or a change in the name, title, or telephone number of the contact person identified on the application.

Renewal is not required as licenses have an unlimited period of validity, but the MAH is required to pay an annual fee to Health Canada, and failure to do so may result in the license being revoked. The full procedure is outlined in Fig. 4 [40-42].

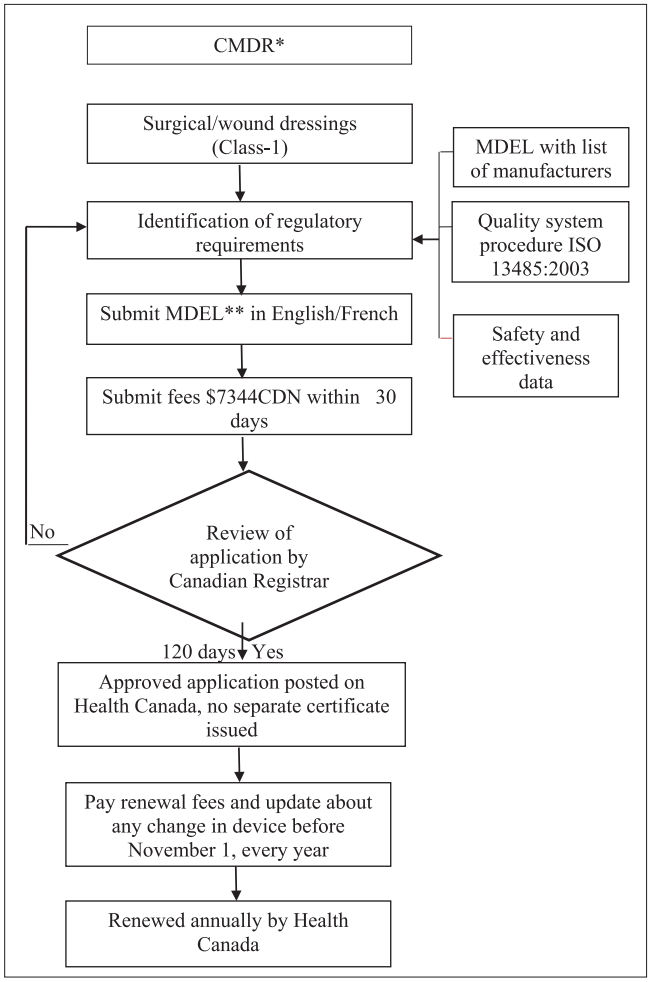

Fig. 4: Decision tree for the approval procedure in Canada*Canadian Medical Device Regulation;Medical Device Establishment License; No fees for Class 1 devices**

Australia

In Australia, surgical and wound care dressings are regulated by the Therapeutic Goods Administration (TGA). To obtain access to the Australian market, manufacturers are required to register their product on the Australian Register of Therapeutic Goods (ARTG). Regulations and classification of wound care dressings are similar to those in Europe [29,43].

The full approval process, along with the necessary requirements for application, is outlined in Fig. 5.

- Step 1 (determination of classification): Correct classification of the product is required to register the product in Australia. Classification can be determined with TGA schedule 2 regarding Australian Therapeutic Goods (Medical Devices) Regulations, in which devices are categorized as either Class I (non-sterile and non-measuring) or Class I (sterile and measuring).
- Step 2 (identification of regulatory requirements): Before submitting the application for approval, applicants should make available the documents listed below:
  - Manufacturer evidence of EU approval/CE marking or Global Medical Device Nomenclature (GMDN) code. If the device has already obtained CE marking, the TGA approval process is simplified, as Australia recognizes CE marking.
  - Online application in the eBusiness Services system
  - Australian sponsor
  - Audit fees
  - Declaration of conformity.

- Step 3 (application submission): The Australian sponsor submits the medical device application online. The application should include an intended purpose statement, classification, and GMDN code.
- Step 4 (application review): The application is reviewed by the Australian regulatory body, and an assessment report is prepared. On the basis of the assessment report, a TGA audit of the facility is decided.
- Step 5 (approval/rejection): TGA will approve or reject the application and, if successful, issue a listing number for the ARTG.
- Step 6 (renewal and validity): The validity of the approval is unlimited as long as there are no changes to the product or its intended use, and the ARTG listing fee of AUD$ 60 is paid annually [43-46].

Brazil

In Brazil, approval is required to market any health, domestic, or imported products by the MOH. The National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA), a federal agency subsidiary to the MOH, is responsible for the regulation, control, and supervision of products and services that pose a risk to public health. ANVISA issued the Resolution of the Board of directors (RDC) No. 185, which regulates the registration of medical devices and classifies them into four classes according to the risks associated with their use [29,47].

Approval process for surgical dressings

Surgical device manufacturers are required to obtain ANVISA approval before selling their products in Brazil. The regulatory requirements for approval are similar to those identified in the European MDD 93/42/EEC 65.

- Step 1 (determining classification)
  According to Annexure II of the Brazilian Resolution RDC 185/2001, surgical and wound care dressings are categorized as Class 1 medical devices (low risk). There are two registration routes: Cadastro and Registro, and it is important to determine whether the device requires the Cadastro or the Registro approval process. The Cadastro process pertains to lower risk devices. As such, wound care dressings require approval through the Cadastro approval process. This review process has a simpler application pathway and typically requires less time than Registro approvals [47-50].
- Step 2 (identification of regulatory requirements)

The following are required:

- Manufacturing unit prepared in line with Brazilian Good Manufacturing Practices (BGMP)
- Labeling in Portuguese
- Proof of registration in other countries
- Technical file, if previously prepared for either the USA or the EU regulatory body.

Other possible ways to satisfy the requirements for all devices include obtaining a Certificate of Free Sale, or a device registration certificate proving home-country approval from MOH, or demonstrating a proof of registration in any two other markets with reasons why the device does not have home-country approval.

- Step 3 (appointment of a Brazilian registration holder [BRH])
  Company that holds a company working allowance permit from ANVISA should be appointed, as the BRH.
- Step 4 (application submission): Provide a letter of authorization to the BRH, who will submit the registration application and technical file to ANVISA.
- Step 5 (BRH audit): Class I device manufacturers (Cadastro) must comply with BGMP requirements (ANVISA will not conduct an audit).
- Step 6 (application review): ANVISA reviews the registration application for all classes. If approved, ANVISA will publish the registration number in the Diário Oficial da União. Registration is valid for 5 years. The full procedure is outlined in Fig. 6 [47-50].

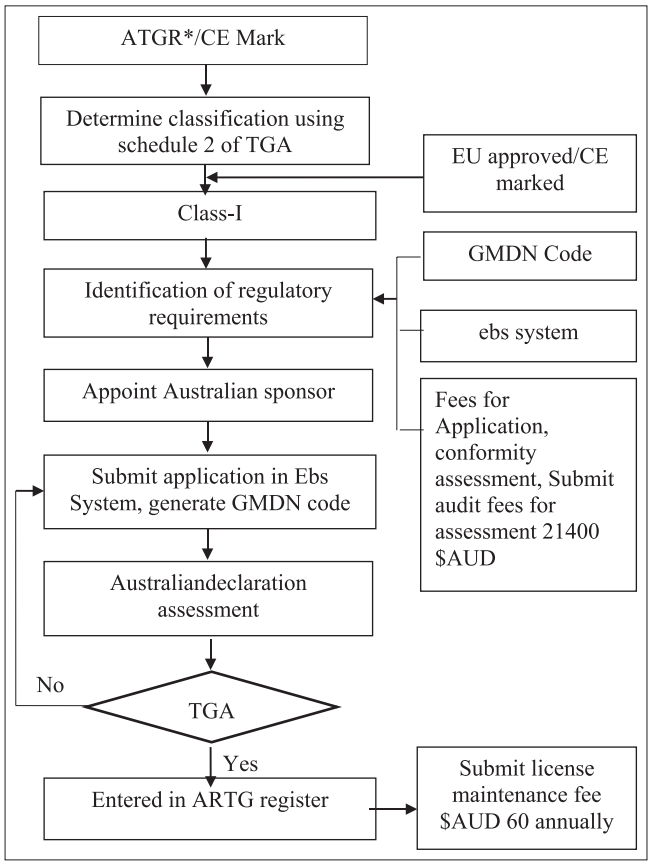

Fig. 5: Decision tree for the approval procedure in Australia. *Australian Therapeutic Goods Regulations, ARTG; Australian Register for Therapeutic Goods

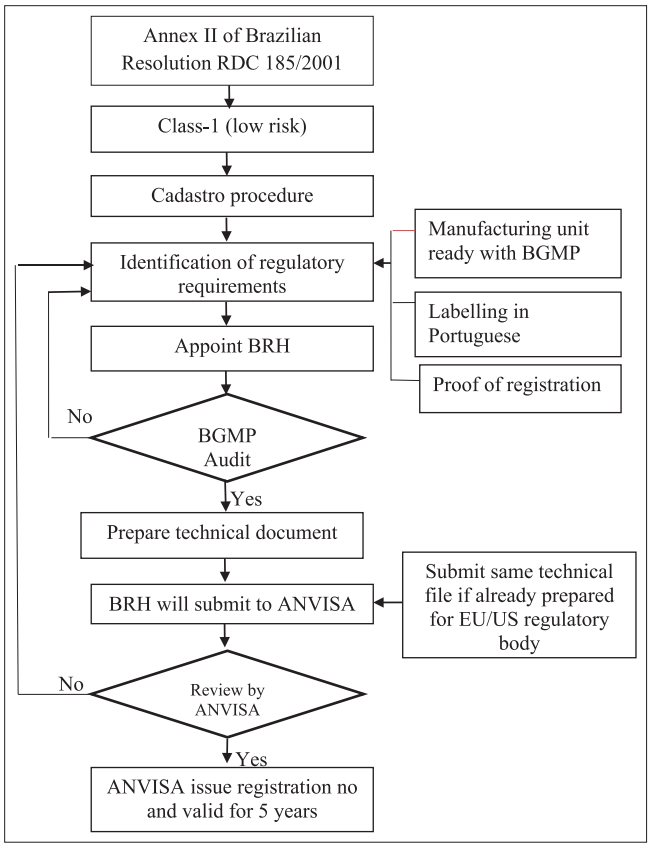

Fig. 6: Decision tree for the approval procedure in Brazil. BGMP: Brazilian good manufacturing practices, BRH: Brazilian registration holder, and ANVISA: National Health Surveillance Agency, Brazil

China

The China FDA (CFDA) is responsible for the registration of wound care and burn dressings. It is mandatory to obtain pre-market approval from the State FDA (SFDA). The Center for Medical Device Evaluation (CMDE) is responsible for the registration process**.** The general administration of quality supervision, inspection, and quarantine is responsible for mandatory safety registration, certification, and inspection of certain devices. The procedures for wound care dressing registration are governed by two main regulations. Both regulations describe the legal requirements for medical device registration in China [29,51].

The SFDA registration process is divided into five steps, and the complete application procedure takes 105 working days, excluding the time period for testing or conducting clinical trials. The full procedure is outlined in Fig. 7.

- Step 1 (classification of product): The Chinese classification system for medical devices is similar to the European system; however, there are differences and applicants are advised to carefully consult the classification list published by SFDA. With reference to the published SFDA list, surgical and burn dressings are categorized as Class III medical devices.
- Step2 (identification of regulatory requirements): Before application for market approval, applicants should make available the requirements listed below:
  - Completed application form for the device
  - Legal qualification certificate
  - Business license
  - Market approval in the country of origin
  - Product standard selection
  - Operational manual
  - Quality reports: Clinical trial reports, if available
  - Agent authorization letter
  - Company authorization letter
  - Self-declaration
- Required fee of US$50,000.
- Step 3 (appointment of an agent): A legal agent should be appointed to submit an application and issue a letter of application stipulating the relationship between the agent and manufacturer.
- Step 4 (dossier preparation and application submission): Once medical device specifications have been completed and the required documents have been compiled, as identified in Step 2, the application should be submitted to SFDA for CMDE review.
- Step 5 (testing review of application): After submission of applications to CMDE, sample testing is undertaken in China. As stated in the regulations, sample tests must be completed within 45 working days. When sample tests have been completed, and the applicable fees have been paid, the test laboratory will issue a report (valid for 6 months) to be submitted as part of the medical device registration.

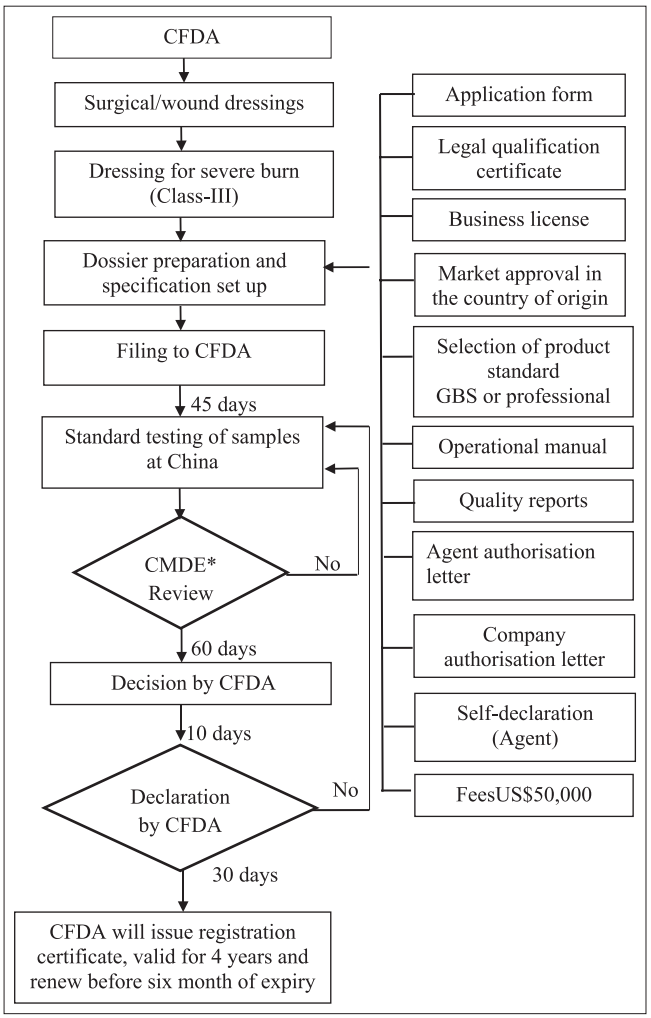

Fig. 7: Decision tree for the approval procedure in China. *CDME: Center for Medical Device and Evaluation, SFDA: State Food and Drug Administration, CFDA: China Federal Device Authority

Type testing may be avoided if the imported medical device meets the following criteria:

- The medical device has previously received market approval by the relevant authority in the country of origin
- The manufacturer holds a valid ISO 9000 (or equivalent) certificate
- No significant differences exist between the device for application and device registered in terms of structure, performance, and safety.
- Step 6 (evaluation)
  Technical evaluation involves systematic examination that focuses on the safety and effectiveness of the medical device. The evaluation is performed by internal CMDE reviewers and may involve external experts. On completion of the technical evaluation, CDME will issue an evaluation report indicating its judgment on the device. The evaluation report is submitted to SFDA for final approval. According to related regulations, SFDA may send an inspection/auditing group to manufacturers abroad to check for their quality assurance system based on Chinese National Standards GB/T 19001–ISO9001, 19002–ISO9002, and any other relevant medical device standards and registered product standards. CMDE will review the application and decide within 60 days. CFDA will respond within 10 days and provide a registration certificate within 30 days. A decision tree for the approval procedure in China is outlined in Fig. 7 [51].

Singapore

The Health Sciences Authority (HSA) is the regulatory authority responsible for the marketing of wound care and burn dressings in Singapore. According to the act and regulations, all sterile wound care dressings in Singapore must be registered for approval before placement in the Singapore market, unless it is stated that registration is not required. Product registration is not required for non-sterile dressings, although they must conform with the regulations before their placement in the Singapore market [52].

The full approval procedure is detailed below, and the flowchart for the procedure is shown in Fig. 8.

- Step 1 (classification of surgical dressings):
- Class A, non-sterile dressings: Class A, non-sterile dressings do not require registration with HSA, although they must conform with the essential principles of safety and performance of the products before entering the Singapore market.
- Class A, sterile dressings: Class A, sterile dressings require submission of an application dossier through the Medical Device Information and Communication System (MEDICS), and a payment of an application fee is immediately required on submission.
- Step 2 (identification of regulatory requirements)

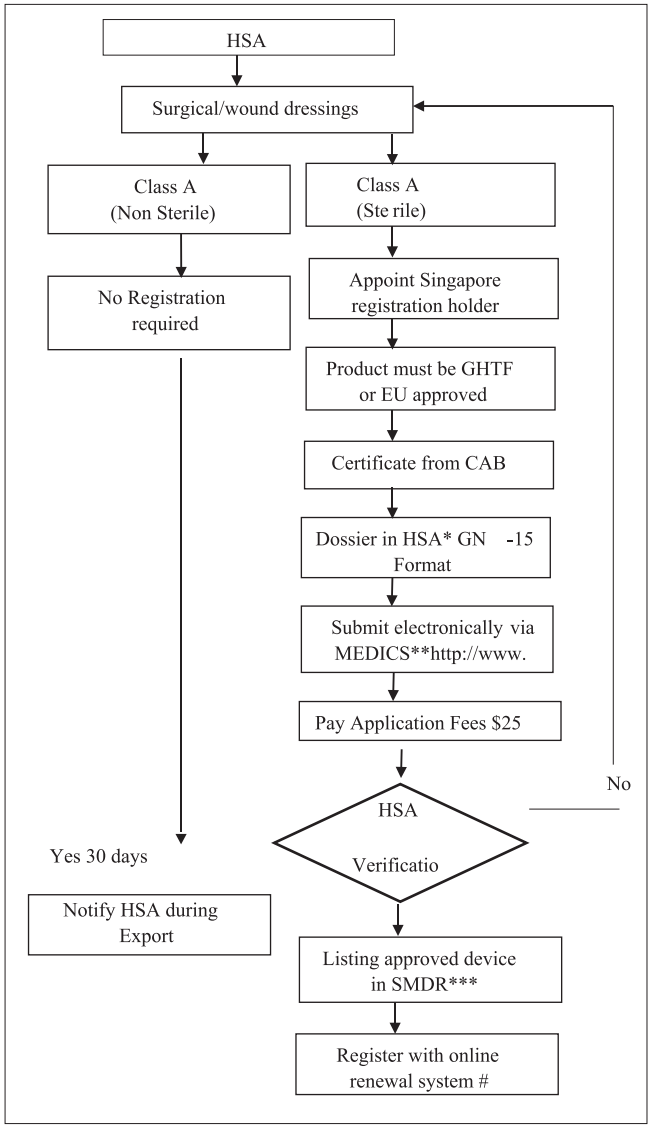

Fig. 8: Decision tree for the approval procedure in Singapore. *Health Science Authority, ** Medical Device Information and Communication System, ***Singapore Medical Device Register, and CAB: Confirmatory Assessment Board

General requirements

- The product must be approved by the Global Harmonization Task Force (GHTF) or must be EU-approved
- Certificate from the conformity assessment board
- Dossier in HSA, Guidance Notification (GN-15)format
- Submission through MEDICS
- Submission of fees.

Documents required for Class A (sterile) dressings

- Letter of authorization
- Proposed device labeling
- A list of all materials of animal, human, microbial, and/or recombinant origin used, and the manufacturing process, if applicable
- Sources of all materials of animal, human, microbial, and/or recombinant origin used, and the manufacturing process (if applicable)
- Information on sterilization method(s) and validation standard(s) used
- Proof of QMS, for example, ISO 13485 certificate, conformity to USFDA quality system regulations.

A non-sterile dressing is exempt from fees; however, the application fee for sterile dressings is $25, and there is no evaluation fee. In general, market approval for sterile dressings can be obtained within 30 working days.

- Step 3 (submission of application): The dossier is submitted in HSAGN-15 format, electronically through MEDICS.
- Step 4 (review of application dossier): The review conducted by the HSA is based on the supporting data, which have been submitted by the applicants. If clarification or additional information is required, HSA will request further information from the applicants. A regulatory decision and listing in the Singapore Medical Device Register (SMDR) for successful registration, on review of the application submitted, is made by HSA. Applications that have satisfied the registration requirements are then registered and listed in SMDR. The approval timeline for these types of dressings is 1 month.
- Step 5 (evaluation process) - full evaluation route: Surgical dressings that have not been approved by any of the H as reference agencies will be subjected to the full evaluation route.

Abridged evaluation route

Surgical dressings that have been previously registered with at least one HSA reference regulatory agency for a labeled use identical to that intended for marketing in Singapore are eligible for the abridged evaluation route. A decision tree highlighting the approval procedure in Singapore is provided in Fig. 8 [52-61].

Malaysia

The Malaysian medical device regulatory framework is based on the global harmonization trend, as promoted by GHTF, the Asian Harmonization Working Party and Medical Device Product Working Group of the Association of Southeast Asian Nations Consultative Committee for Standards and Quality, and supported by the WHO [29].

The Malaysian Medical Device Authority (MDA) is responsible for enforcing medical device regulations and medical device registration. The full approval procedure is outlined and highlighted in Fig. 9.

- Step 1 (classification): According to the Malaysian Medical Device Regulations, surgical and wound care dressings are categorized as Class A devices. Class A is further subdivided into Class A non-active and Class A active sterile groups.
  - Class A, non-active sterile dressings: Class A non-sterile devices do not require registration, but approval in the reference country is required. To market Class A non-sterile surgical dressings, it is mandatory to notify the MDA.
  - Class A, active sterile dressings: Submission of an application dossier using the Common Submission Dossier Template (CSDT) format is required.
- Step 2 (identification of regulatory requirements): The medical device registration form requires the following components
  - General information regarding the medical device
  - Information regarding the manufacturer of the medical device
  - CSDT
  - Post-market vigilance history
  - Declaration of conformity
  - Attestation for registration
  - ISO certificate
  - Labeling
  - Approval in reference countries.
- Step 3 (appointment of authorized representative): To register surgical and wound dressings in Malaysia, an authorized representative in Malaysia must be appointed.
- Step 4 (preparation and submission of dossier): The authorized representative prepares the registration application dossier and submits the application to the Malaysian MDA online.
- Step 5 (review of the dossier): An independent conformity assessment body (CAB) reviews the registration application dossier and issues a CAB certificate that is then submitted to the MDA. Fig. 9 details a decision tree for the approval procedure in Malaysia [62-66].

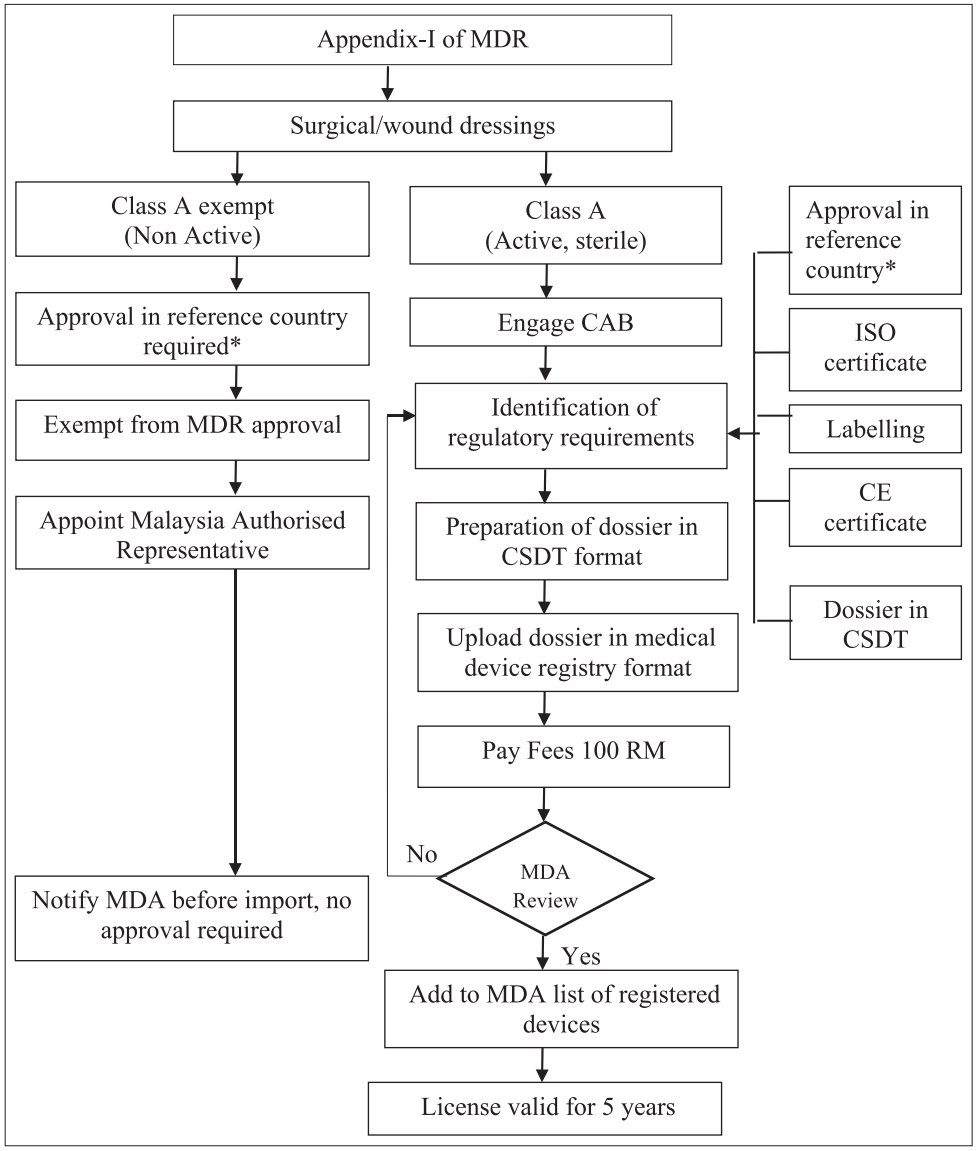

Fig. 9: Decision tree for the approval procedure in Malaysia. CAB: Confirmatory Assessment Body. *Recognized reference markets include: Australia, Canada, EU, Japan, and USA

Mexico

In Mexico, wound care and burn dressings are classified on the basis of the risk associated with their use. They are classified as medical devices and are regulated by the Federal Commission for Protection of Sanitary Risks (Comisión Federal para la Protección contra Riesgos Sanitarios, or "COFEPRIS"), which is a division of the Secretariat of Health (Secretaría de Salud).

Foreign manufacturers are not permitted to submit registration applications directly to COFEPRIS and instead must appoint a Mexican distributor or local Mexican registration holder (MRH) to act on their behalf. The full approval procedure is described below and a detailed flowchart is provided in Fig. 10.

- Step 1 (classification determination)
  The first step for registration in Mexico is to determine the class of the device. Wound care and burn dressings are categorized as Class I, that is, low-risk medical devices. Products within this category have been previously well-established, with a long-standing history of registration, approval, and proven safety and effectiveness, and are generally not introduced into the body. These products must be registered; however, technical data are not required to support registration.
- Step 2 (identification of regulatory requirements)

The following list outlines the documents that manufacturers must prepare, before applying for registration:

- Application form
- Device information
- Scientific and technical information
- Testing requirements
- Evidence of home-country approval
- Labeling in accordance with NOM-137 SSA-1-2008
- Instructions for the use of the device
- Description of the manufacturing process
- Valid GMP
- Product structure and bibliography.

- Step 3 (appointment of a local registration holder)
  An MRH must be appointed, who is licensed by COFEPRIS and located in Mexico, and who will submit the application to COFEPRIS. The appointed MRH will also be responsible for coordinating importation of the device; therefore, the MRH must maintain warehouses that comply with COFEPRIS' specifications.
- Step 4 (COFEPRIS review)
  A third-party reviewer (TPR) is a private commercial entity authorized by COFEPRIS to conduct an initial review of an application

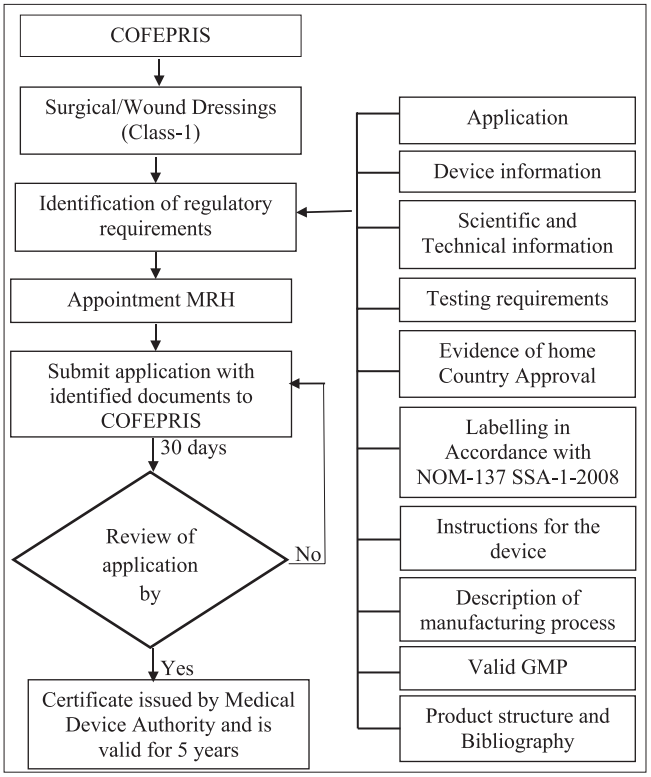

Fig. 10: Decision tree for the approval procedure in Mexico Fees is set by the authority on the basis of risk assessment, according to the federal law on fee payment. MRH: Mexican Residence Holder. # SLA: State Licensing Authority, CLA: Central Licensing Authority. *Audit of Facility by Notified body is carried out after approval of Class A medical device

and, if satisfied, write a technical report for COFEPRIS recommending approval. While an additional cost is incurred for a TPR, typically no additional information will be required by COFEPRIS after the TPR issues their report. In addition, as TPRs are commercial entities, they may be more responsive and review applications more quickly, resulting in a shorter review process overall. After reviewing the report, if there are no further requests for information, COFEPRIS will issue the final registration certificate within 30 days.

- Step 5 (issuance of the certificate of approval)
  Once COFEPRIS approves an application and issues a certificate, confirmation and registration number are posted on the MOH website. If COFEPRIS has any concerns with the registration, it will inform manufacturers in writing. On such occasions, the time limit for approval is lifted and longer time may be required to approve a registration. A decision tree for the approval procedure in Mexico is shown in Fig. 10.
- Step 6 (renewal and validity)
  The certificate is valid for 5 years [67,68].

India

Wound care and burn dressings in India are currently included in the new Medical Devices Rules 2017, under subsection (1) of section 12 and subsection (1) of section 3 of the Drugs and Cosmetics Act, 1940 [69].

Burn dressings are not classified separately in the Medical Devices Act, however, according to the medical device classification detailed in Schedule I, Part I, they are classified on the basis of their intended use.

- Step 1 (identification of classification)
  Wound care and burn dressings are categorized as Class A-D medical device as in contact with injured skin. In addition, subject to clause (c), a non-invasive medical device in contact with injured skin shall be assigned a Class B categorization, as it is principally intended for the management of the microenvironment of a wound.
- Step 2 (identification of regulatory requirements)
  The domestic manufacturer or authorized agent shall submit a signed form along with the following information pertaining to the manufacturing site as provided in Table 5.
- Step 3 (submission of application)
  The State Drugs Controller serves as the State Licensing Authority (SLA) and shall be the competent authority for enforcement of the rules relating to the manufacture of Class A or Class B medical devices and the sale, stocking, and exhibition of medical devices, and other related functions. Class C and D high-risk devices are regulated by the Central Licensing Authority (CLA), which oversees the clinical investigation and clinical performance evaluation of medical devices and has other related functions. If the manufacturer intends to manufacture a predicate medical device, the manufacturer must receive approval from CLA before applying to the SLA.
- Step 4 (issuing the license)
  The manufacturing site of the applicant, in respect to a Class B device, shall conform with the QMS requirements, as specified in the fifth schedule, and the applicable standards, as specified under these rules, and such conformance shall be verified through an audit by a notified body as referred to under rule 13 before granting the license.
- Step 5 (validity and renewal)
  A license issued using the MD-5 form shall remain valid in perpetuity, subject to payment of a license retention fee, as specified in the second schedule before completion of the period of 5 years from the date of its issue; unless it is suspended or canceled by SLA or CLA [68]. A decision tree for the approval procedure in India is provided in Fig. 11.

Israel

Israel is one of the world's leading centers for the development of innovative medical devices [71]. In Israel, wound care dressings are categorized as medical devices. All regulations related to medical devices are also applicable to wound care and burn dressings. Wound care dressings manufactured or marketed in Israel must be registered with the MOH Registrar (AMAR - the Medical Device Division of the Israeli MOH) [72].

Registration of wound care dressings in Israel is based on prior approval in one of the following countries: Australia, Canada, EU, Iceland, Norway, New Zealand, Switzerland, Japan, or USA.

The registration procedure for wound care dressings is described and the process flow is shown in Fig. 12.

- Step 1 (identification of classification)
  Wound care dressings are categorized as medical devices, and all regulations regarding medical devices are applicable.
- Step 2 (identification of regulatory requirements)
  Manufacturers of wound care dressings should make available the following documents before applying for registration:
  - FDA 510 (k) pre-market approval
  - Prior approval by GHTF is mandatory
  - CE marketing certificate by European notified body
  - Proof of ISO 13485 certification
  - Certificate of free sale.
- Step 3 (appointment of an Israeli registration holder [IRH])
  Following determination of the category, a local IRH must be appointed, licensed and located in Israel. The appointed IRH will also coordinate importation of the device and must maintain warehouses that comply with Israeli specifications. The IRH will submit the applications to AMAR.
- Step 4 (application submission)
  The IRH will submit the above-listed documents to the AMAR-Medical Device Division of the Israeli MOH.
- Step 5 (review of application)
  AMAR will review the application within 120 days; however, registration is usually completed within 6–9 months because

Table 5: List of documents required for manufacturer registration and for importation of dressings

Class A	Class B-D	Dressing other than predicate
For manufacturing		
Device description	Constitution details of domestic	Data analysis
Intended use	manufacturer or authorized agent	Design input/output documents
Specification	Site or plant master file	Mechanical and electrical test results
Working principle and use of	Device master file	Reliability test results
novel technology, if any	Essential principle checklist for	Validation of software
Label package inserts	demonstrating conformity for safety and	Performance test results
User manual	performance	Biocompatibility test results
Summary of ADR	Quality control data	Risk management data
Site master file	Signed undertaking agreement stating that	Animal performance data
Firm details	the manufacturing site is compliant with	Pilot and pivotal clinical investigation data
Signed undertaking agreement	schedule	Regulatory status and restrictions in use
Analytical performance		Proposed instructions for use
For importation		
Notarized copy of overseas manufacturing site or FSC		
Notarized copy of QMS		
Self-attested wholesale license		
Copy of latest inspection report		

FSC: Free sale certificate

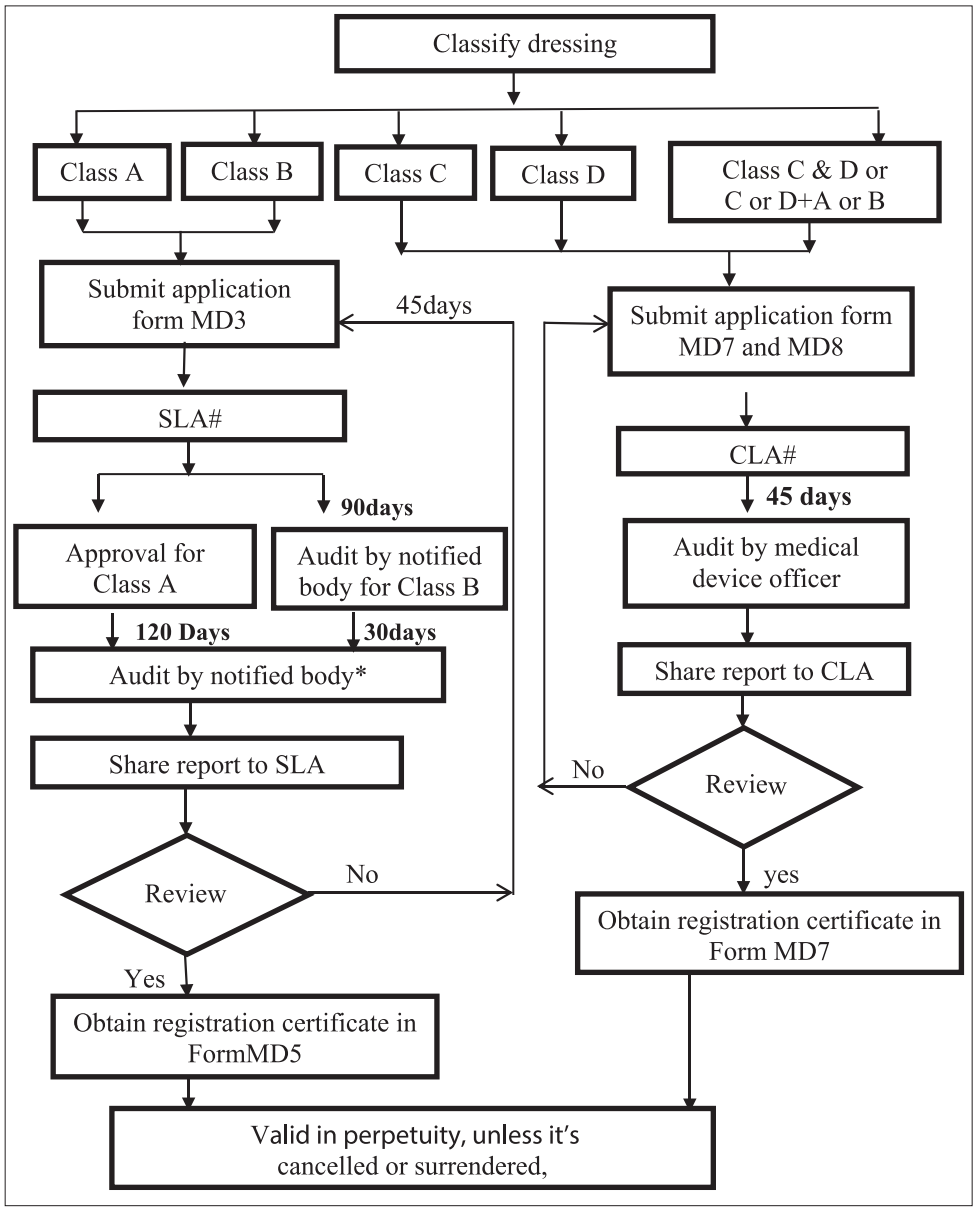

Fig. 11: Decision tree for the approval procedure in India [69-71]

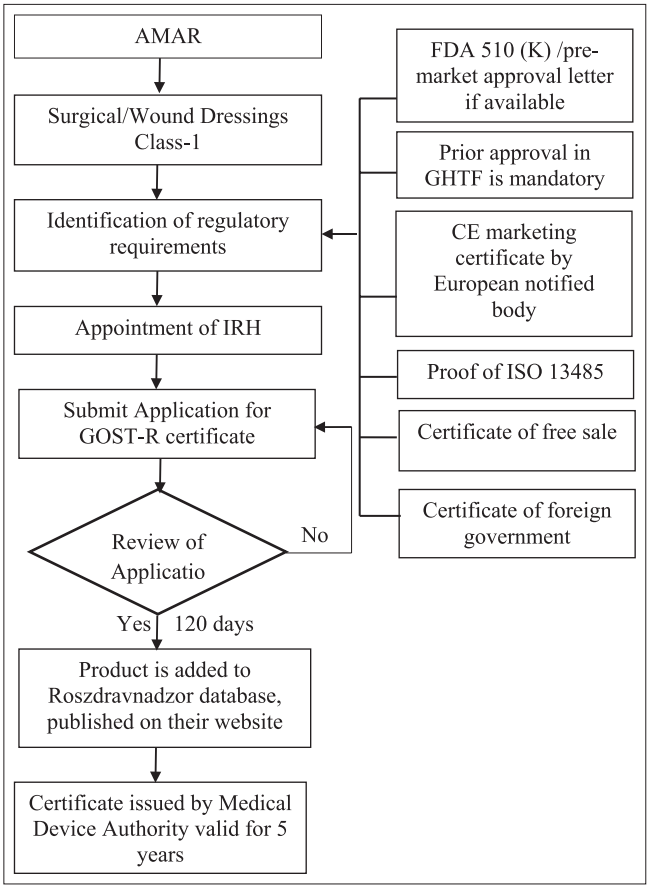

Fig. 12: Decision tree for the approval procedure in Israel [71,72]. GHTF: Global harmonization task force, AMAR; a department within the Israeli MOH responsible for licensing medical devices, and IRH: Israeli Residence Holder

authorities will often require further documentation during the course of the evaluation.
- Step 6 (issuance of certificate and validity)

After successful completion of all evaluation steps, AMAR will issue the registration certificate, which is valid for 5 years. The license expiration date is based on the current regulatory certificate and is subject to the device's CE mark or FDA approval. Fig. 12 details approval procedures in Israel**.**

Russia

In the Russian Federation, all wound care and burn dressings are categorized as medical devices. For diagnostic and therapeutic use, they must be registered in Moscow, at the Central Department of Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor) [73].

- Step 1 (identification of classification)
  In accordance with Government Standardization (GOST) R 51609-2000 medical products, surgical dressings/wound care dressings are categorized as Class I (products with a low risk for environmental, individual, and public health). Examples are medical devices used in hygiene, diagnostics, medication and nursing, single-use linen, dressing materials except for special and high-standard dressing materials, retentive bandages, and appliances. Applicants should determine whether a previously approved and/or equivalent device exists in the Russian Federation and confirm the classification of the device [74].
- Step 2 (identification of regulatory requirements):
  - Certificate from the country of origin
  - Proof of compliance
  - ISO13485
  - Gosudarstvennyy standart Russian (GOST-R) testing requirements
  - Application letter
  - Power of attorney
  - Description of manufacturing process
  - Manufacturer operational manual
  - Testing requirements of the product.
- Step 3 (appointment of a Russian registration holder [RRH])
  Following determination of classification, a local registration holder should be appointed. An RRH must be licensed and located in Russia. RRHs coordinate importation of the device and must maintain warehouses that comply with Russian specifications. The RRH will submit applications to the Russian MDA.
- Step 3 (Dossier preparation)
  If testing is required, an application for an import license for the samples is required, and sample testing is conducted at government-authorized testing and medical centers within Russia. Preparation of the registration dossier should include testing results and medical reports. All documents should be submitted to the relevant officials.
- Step 4 (application review)

Review of the application is undertaken within 120 days, and a certificate is issued if all test results and submitted documents have been approved. Fig. 13 details the decision tree for the approval procedure in Russia [73-75].

The comparative study (detailed below in Table 6) shows that some countries have heavy fees levied on the MAH for product registration and license maintenance that restrict the marketing of innovative products despite posing no risks to health.

DISCUSSION

From the details provided above, it is apparent that, for all countries mentioned, wound care and burn dressings are categorized under medical devices, and therefore, respective regulations are applicable on wound care and burn dressings. Despite the similar classification system in several countries, differences remain in various documentation requirements and dossier content submission, as well as in evaluation procedures. Differences, regarding dossier submission format, are detailed in Table 7.

The main difference in the content and format of import and export licenses for regulated and semi-regulated countries lies in the different classification of the same dressing. Some countries share a harmonization process; if a device is approved in one country, it may then be exported, due to mutual recognition agreements. Australia generally requires products with a CE mark. In India, dressings with FDA approval or EU mark may be approved and marketed more readily.

The various challenges encountered while drafting quality guidelines prevent the development of these guidelines, and also restrict manufacturers from maintaining the quality of the products. The following gaps/challenges are identified:

Wound size and type

Quantitative measurements of wound sizes are routinely used to assess an initial wound pre- and post-debridement. There are no standardization/validation guidelines for instruments such as Doppler sonography and filament testing used in the assessment of wound types [78].

Unavailability of quality testing parameters/guidelines/ monographs

To harmonize the quality of new products, there should be suitable test procedures in monographs [78].

Absence of suitable guidelines for clinical trials

The included patient population in clinical trials should be appropriate for the type of wounds to be studied. The selected patient population

Table 6: Comparative study [29,76,77]

Country name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Approval fees	Approval timeline	Registration validity	Pros.	Cons.
United States	USFDA	21 CFR Part 820	Fabric dressings: Class I Advanced wound care dressings: Class II and III	1. Premarket approval (PMA) 510(k) application 2. Clinical data, if required 3. QMS 4. Substantial equivalent predicate device 5. Random audit by USFDA 6. Pre-submission feedback from FDA 7. Before marketing, an FDA clearance letter is required	USD$5018	Approximately 90 days	Only facility renewal is required, and product validity is unlimited	Wound dressings are well defined and classified. No clinical safety data are required.	Quality parameters such as size, appearance, raw material quality standards, microbial limit, heavy metals if any, ash content, pore size, and required for wound dressings are not well addressed in guidelines.
EU	EMA	Council Directive 93/42/EEC	Class II	1. QMS 2. Technical file in compliance with 92/43/EEC 3. Safety test by EU standards 4. ISO certificate 13485 5. Declaration on conformity 6. CE number 7. Audit by notified body	Fees vary in different member states	Not defined	3 years	Well-defined regulations for dressings containing or not containing medicinal products.	Difficult to determine whether wound dressings are categorized as medical devices or medicinal products. An error in classification incurs heavy cost in fees during the approval process
Japan	MHLW, PMDA	Japanese PAL	Class I (low risk associated with wound care dressing)	1. Form No 18 2. QMS 3. Self-declaration in Japanese language	Fee: ¥ 664500	36 months	Unlimited validity until there is a change in QMS	A streamlined registration process	The application process appears costly and time-consuming (requires between 1 and 3 years), and requires clinical trial data
Canada	Health Canada	Medical device and equipment guidelines	Class 1 (dressings that act as a barrier against pathogens and antimicrobial agents are known as devices)	1. Quality system 13485:2003 procedure ISO 2. MDEL with list of manufacturers 3. Safety and effectiveness data	No fees for class 1 devices; however, MDEL fee: CAD$7344	120 days	Valid for 1 year	Well-defined classification and guidelines available for registration of surgical dressings	Quality parameters required for wound dressings including size, appearance, raw material quality standards, microbial limit, heavy metals, if any, ash content, and pore size, are not well addressed
Australia	TGA	Australian Therapeutic Goods Regulations	Class I (non-sterile) Class II (sterile)	1. EU Approved/CE marked 2. GMDN code 3. Conformity assessment 4. eBS system is required 5. TGA audit	Assessment fees: AUD $21,400 License maintenance fees: AUD $60.00 annually	Not defined	Not defined	A well-defined classification and summary of the guidance document is available	Approval fees are high, and it appears to be very difficult to place standard medical devices in the Australian market

(Contd...)

Table 6: *(Continued)*

Country name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Approval fees	Approval timeline	Registration validity	Pros.	Cons.
Brazil	ANVISA	Brazilian resolution RDC No 185/2001	Class I (low risk)	1. Device registration certificate or FSC 2. Proof of registration in any other two countries 3. FSC/proof of registration in other countries 4. BGMP audit	No fees for Class I	Not defined	Valid for 5 years	Manufacturing permitted only for manufacturers who have the unit ready with the audit Separate approval procedure is well defined	Quality parameters required for wound dressings are not well addressed in the guidelines
China	China FDA, Center for Medical Device Evaluation	Medical Devices Act	Class III	1. Application form 2. Legal qualification of manufacturer 3. Copy of business license 4. Approval in the country of origin 5. Letter from competent institution 6. Operational manual 7. Test reports 8. Product quality guarantee 9. Authorization letter of delegating agent 10. Self-declaration	USD$50000	105 days	Valid for 4 years	Classification of medical devices can be obtained from the SFDA website. Errors in classification can be avoided and money waste in evaluation can be minimized	Quality parameter information required for wound dressings such as size, appearance, raw material quality standards, microbial limit, heavy metals if any, ash content, and pore size, are not well addressed in the guidelines
Singapore	Health Science Authority	Health Product Act or medical device regulations	Class A (Non-sterile) Class A (Sterile)	1. Letter of authorization 2. Proposed device labeling 3. Patient information leaflet 4. Proof of QMS 5. Manufacturing process- flowchart 6. Information on sterilization method 7. Conformity of QMS - USFDA, Japan, Canada, Australia 8.Certificate from conformity assessment board 9. Prepare dossier in MEDICLAS electronically	Fee for sterile Class A devices: SGD $21.00	30 working days	Not defined	All information regarding approval and importation is available at SMDR. The status of the application can be readily viewed and followed online.	Quality parameter information required for wound dressings such as size, appearance, raw material quality standards, microbial limit, heavy metals if any, ash content, and pore size are not well addressed in the guidelines.

(Contd...)

Table 6: *(Continued)*

Country name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Approval fees	Approval timeline	Registration validity	Pros.	Cons.
Malaysia	Malaysian MDA	Medical Devices Act 2012 (Act 737) and subsidiary legalization	Surgical dressings fall under Class A (non-active) or Class A (active, sterile)	1. General information on medical devices 2. Manufacturer information 3. Common submission dossier template 4. Post-market vigilance data 5. Declaration of conformity 6. Attestation for registration	RM 100	Not defined	Valid for 5 years	Before HA approval, CAB approval is required	MDA has not yet specified which documents CAB needs to review Products in transition are not very well defined
Mexico	COFEPRIS	General Health Law and Regulation of Health Supplies	Class 1 (low-risk devices)	1. Application form 2. Scientific and technical information 3. Testing requirement 4. Evidence of home country approval 5. Labeling in accordance with NOM-137 SSA-1-2-2008 6. Instructions for the device 7. Description of the manufacturing process 8. Valid GMP 9. Product structure and bibliography	USD$650-1200	30 days	Valid for 5 years	A fast-track process is available.	Direct registration of a product with the Mexican authority is not possible, and the requirement to appoint a local MRH is mandatory.
India	Central Drug Standard Control Organization	Draft Medical Device rules (2016)	Class B	1. MD - application form 2. Site master file 3. Device master file 4. Essential checklist 5. Quality control data 6. Underrating 7. MDA dossier Appendix-II	INR 5000	9 months	Manufacturing license validity - 5 years	The draft medical device rules are very effective	Burn dressings-Quality guidelines concerning burns dressings remain not well defined within the draft medical device rules
Israel	Division of Medical Devices and Accessories under the Israeli MOH (IMOH)	Israel Medical Devices Act (2012)	Surgical dressings are regulated as medical devices within Class I category	1. FDA 510(k) or pre-market approval application 2. Certificate to foreign government 3. CE marketing certificate issued by a European-notified body 4. Proof of ISO 13485 certification 5. Require registering device with AMAR, the Israeli MOH Medical Device Regulation Unit 6. Prior approval in GHTF 7. Certificate of free sale	No fees for Class 1	120 days	Valid for 5 years or until CE mark FDA approval	Products with CE mark and USFDA approval easily obtain approval	In Israel, device registration is based on prior approval in one of the GHTF countries.

(Contd...)

Table 6: *(Continued)*

Country name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Approval fees	Approval timeline	Registration validity	Pros.	Cons.
Russia	Federal Service for Control over Health care and Social Development, more commonly known as "Roszdravnadzor"	Government Regulation No. 1416	Federal Law on Fundamentals of Health care in the Russian Federation, 4 categories	1. Certificate of origin 2. Proof of CMS compliance 3. ISO 13485 4. Ghost-R testing requirements 5. Application letter 6. Power of Attorney 7. Description of manufacturing process 8. Manufacturer operational manual 9. Testing requirements for the product	No fees for Class I devices	4 months	1 year	Similar to the EU	Guidelines are available in Russian language only. A dossier is also required, in Russian language only

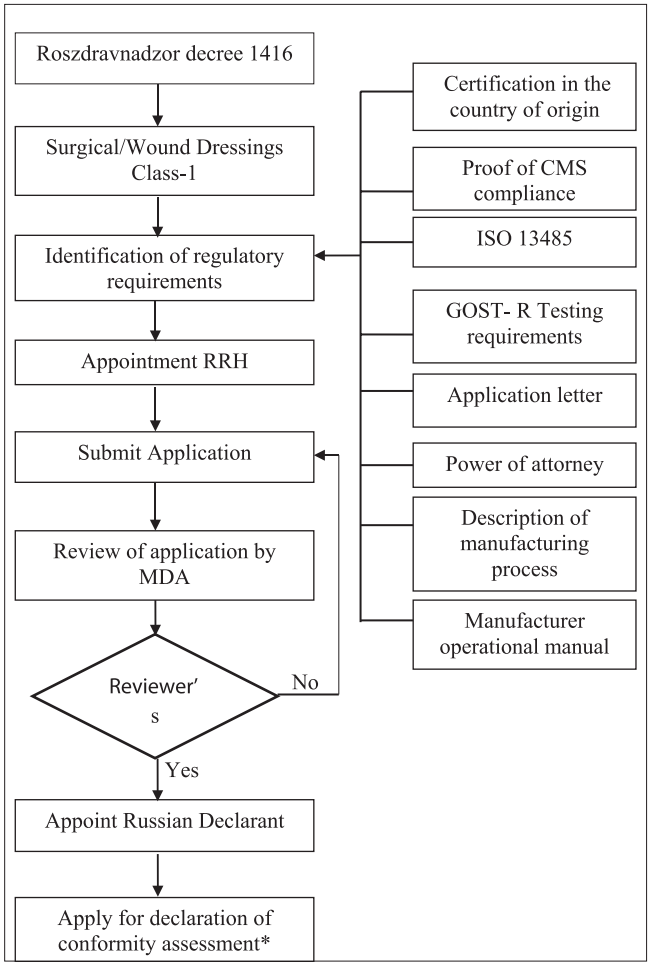

Fig. 13: Decision tree for the approval procedure in Russia. Roszdravnadzor; Federal service for control over health care and social development, RRH: Russian Resident holder. *Conformity Assessment: A declaration certifying that the product conforms with Russian Regulatory Requirements

should contribute to the optimization of the study's capacity to detect a treatment effect. There are no available ideal animal models for chronic/extensive wounds to assess the activity of wound treatment products. There are no ideal animal models for chronic wounds to estimate *in vivo* distribution and pharmacokinetic (BD/PK) profiles, which generally provide helpful data for the design of toxicology studies including carcinogenicity, and reproduction, and genotoxicity studies [78].

Microbial control

There is no specific procedure for the sterilization of different wound care products [78].

Missing suitable selection procedures for the use of dressings

Selection of wound care dressings generally depends on the type of wound. For burns, the selection procedure should include the burn site, extent of burn, type of first aid used, patient ability to manage the dressings, cause of the burn, associated pain, urgency of time healing, and cost [78].

Miscellaneous challenges

According to Bairy *et al.* [79], "burns afflict all segments of society, the rich, the poor, men and women, and children and old may fall victim to it." Scientists and firms face various challenges in the development of new therapies or products for wound care and burn dressings. Clearly, this is a complicated and difficult process with many potential pitfalls. It is difficult to acquire sufficient funding and navigate the

Table 7: Differences in content and formatting of forms in regulated and semi-regulated countries [29]

Country name (regulatory agency)	Classification	Dossier submission format for approval
United States (USFDA)	Class II	Application in 510(k) format is required, FDA QMS is mandatory. A plant audit is to be undertaken by the FDA
EU (EMA)	Class I (non-sterile) Class I (sterile)	No dossier submission is required, compliance with directive is sufficient, and the CE mark can be used
Japan (PMDA)	Class I	No certification or dossier is required. Compliance with QMS accordance with # 169 is required
Canada (Health Canada)	Class I	Submit the dossier in French
Australia (TGA)	Class I	Submission of available CE mark or the FDA QMS is sufficient. A conformity assessment certificate should be provided
Brazil (ANVISA)	Class I	Dossier in accordance with RDC 185/2001, copy of payment of fees, identification of manufacturer, free trade certificate, and declaration of conformity
China (CFDA)	Class III	A sample and specification are required with the dossier; QMS is not mandatory
Malaysia (MDR)	Class A	Dossier is required in an electronic format
India (CDSCO, DCGI)	Class A, B, C, D	Dossier submission in the form of a technical list
Singapore (HAS)	Class A	Dossier submission in electronic form and an HASF format is required
Mexico (COFEPRIS)	Class I	Dossier with specific labeling required, in accordance with regulation NOM-137 SSA-1-2008
Israel (Medical Institutions and Device Licensing Department)	Class I	Prior registration with GHTF is mandatory
Russia (Federal Services on Health-care Supervision)	Class I	Testing in the country of origin is required

HASF: Health Authority Specific F, GHTF: Global Harmonization Task Force

regulatory environment. Furthermore, when increasing production, addressing logistics, and managing the cost of goods, manufacturing sites may compromise profitability and risk the long-term viability of the enterprise [76-78].

Systems for approving advanced dressings must clearly define pathways to market important innovations while also ensuring that patients are adequately protected. To achieve these goals, there should be a combination of premarket testing and post-market vigilance but with some marked contrasts in their approaches. Features of both environments require reform, as well as continuous research to assess policy changes.

CONCLUSION

Wounds are inescapable events in life. Wounds may a rise due to physical, chemical, or microbial agents [80]. Our study reveals that wound care dressings are classified as medical devices and are categorized based on the risks associated with their use. Despite categorization as medical devices, wound care dressings are not clearly defined in any country. Most current challenges include the lack of a proper definition, quality standard specifications, requirements for preparation of the dossier, drawings and designs, and the quality of materials to be used. It has been identified that there is no specific or common dossier format available globally for market approval of such dressings. Systematic guidelines regarding wound care dressings are likely to help overcome delays in regulatory approval and will provide a better understanding to manufacturers and innovators about the specific requirements.

AUTHOR'S CONTRIBUTIONS

Vibhu Yadav: Gathered data and prepared the manuscript. Parikshit Bansal and Amit Mittal: Provided the idea, supervision, and guidance for this work. Sachin Kumar Singh: General formatting and preparation of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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