DEVELOPMENT OF REGULATORY GUIDELINES FOR ADVANCED WOUND CARE AND BURN DRESSINGS

A

Thesis

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ABSTRACT

Objective: Development of regulatory guidelines for advanced wound and burn care dressings.

Methods: A total of 207 research and review articles including regulatory guidelines related to marketing of wound and burn care dressings recommended by international regulatory agencies were reviewed. To check the status of existing regulatory guidelines a comparative study of 13 countries was carried out and gaps in regulations related to their sale and distribution were identified. Statistical analysis of economic status related to their export and import was recorded. The availability of advanced dressings, their quality and usage based on opinions of physicians and pharmacists in hospitals and chemists shop dealing with wound and burn related issues in India was studied. For comparison, an innovative advanced dressing was taken and subjected for various quality control parameters such as appearance, dehydration rate, fluid handling capacity (FHC), moisture vapour transmission rate (MVTR), and stickiness. Based on the study a common set of recommendation and guidance document was prepared.

Results: The current study shows a differential analysis in regulatory requirements of different countries related to surgical dressings and highlighted the issues in existing regulations. The survey based study of physicians and pharmacist shows that mostly traditional dressings are used in India. Where advanced dressings are used, more than (90%) are imported one that causes economic burden to the users. Owing to the high cost of the imported dressings, lack of availability of regulations, these advanced dressings are unaffordable to common people. To make availability of indigenous dressing, an in-house sample was evaluated for quality parameters. The analytical results shows that in-house sample has comparable results as compared to standard. The dehydation rate of sample was found 0.000527g/min quite lower than standard dehydration rate 0.000822g/min. The FHC value of sample 27.981% that is quite high as compared to standard 5.027%. The MVTR value of sample 8667.8g/m^2/24hour and standard was 11365.8g/m^2/24hour. It was found that none of the dressings were found to have sticky property.

Conclusion: To curb above issues, need of manufacturing of indigenous surgical dressings was identified. That's why there is an urgent requirement to develop the quality guidelines so that in coming years manufacturing in indigenous country can be enhanced and new innovative product can reach to the patient bedside.

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

CHAPTER-1

1. 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 3,00,000 deaths occur each year as a consequence of fire-induced burns.[2-3] Approximately 3.5 million burn patients globally enter the outpatient health service system and receive some level of medical attention.[4] The burden of such injuries generally fall on poor patients as they cannot afford costly treatment. A primary contributing factor that leads to infection and finally to death in this population is poor hygiene.[5-6] Burn injury management is challenging, due to significant fluid loss, tissue damage and deep wounds, thus contributing to death.[7]

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.

Table 1: Estimated prevalence and growth rate of various types of wounds from 2012-2020[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%

There is a wide range of advanced and traditional wound care and burn dressings available in the market. The global wound dressing market is expected to expand at a Compound Annual Growth Rate (CAGR) of 4.5% during the forecast period from 2014 to 2020.[8] In 2013, the global wound dressing market was estimated to be greater than US$ 7.5 billion and by 2020 it is projected to it is projected to be more than US$10.1 billion.

The wound care market is composed of 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.[9-10]

1.1 Wound and burn

A wound is generally defined as a disruption in the continuity of the epithelial lining of the skin or mucosa.[11] Wound is found to be of many types and has multiple causes of occurrence.[11-12] The healing of a wound is very complex process. To prevent microbial infection and to facilitate the body's natural healing mechanisms, an optimal healing environment and an appropriate wound dressing is often required.[13-14]

Burn is a most common injury characterised by severe skin damage that causes the affected skin cells to die. Burns are generally classified on the basis of degree on burning *i.e.* first, second, third and fourth degree. The first degree of burn is the most minor and fourth-degree being the most severe. The symptoms occurring during burn generally define the degree *e.g.* red, non-blistered skin represents first -degree burn, blisters and some thickening of the skin represents second-degree of burn and third-degree burn is as when widespread thickness with a white, leathery appearance occurs. The fourth-degree burn includes all of the symptoms of a third-degree burn and also extends beyond the skin into tendons and bones.[15]

1.2 Prevalence, death rate due to burn and wound injury

Majority of the death occurs in low and medium income countries. In India, over 10,00,000 people get moderate and severe burns every year. In other countries such as Pakistan, Egypt, Columbia and Bangladesh 17% of children with burns have temporary affliction and 18% of them have a permanent affliction. Burns are the second utmost commonly reported injury in the countryside of Nepal, considering disabilities of 5%.[3-4]

The mortality rate is also high in India when burn injuries are taken into account. Large population and congested habitat results in the prevalence of such injuries. The occupation of many people falls in high-risk jobs such as cracker manufacturing, acid manufacturing, chemical manufacturing and road maintenance. The high cost of treatment, rehabilitation and shortage of dedicated burn units plays a major role in the increased mortality rate.[16] The high cost of treatment, rehabilitation and shortage of dedicated burn units plays a major role in the increased mortality rate. It is very

difficult to cater huge population with less number of beds per hospital especially with infectious diseases .[17]

1.2.1 Recovery and mortality rate

Generally, most of the burn injuries are accidental (77%) and some are self-inflicted (22%).[18] Burn injury related mortality rate varies depending on the country, season, place of injury, hospital, quality of treatment and age of the victim. Approximately, 66% of burn victims, get recover from injuries. However, about 26% die from the burns. The remaining 8% of people neglect the medical advice and cease treatment before recovery.[18-20]

1.3 Causes of death in burn and wound injury

There are various reasons of death due to burn and wound injury but burn shock and infection are the most common reasons.

Burn shock

This type of shock causes a lack of oxygen supply in the patient's body. It is very critical to treat and it may cause death due to hypovolemia or low blood volume or injured blood vessels. Burn shock might also happen as an effect of sepsis, which is the body's reaction to burn septicity.[21]

Low blood volume

Burn destructs the blood vessels, triggering fluids to leave the body. This can end in the lower volume of blood, termed as hypovolemia. A severe loss of blood and fluid stops the heart from pumping adequate blood through the body.

Respiratory failure

Huge quantity of smoke and hot air is inhaled during fire leading to burning of airways that cause difficulty in breathing. The inhaled smoke and hot air finally damage the lungs which leads to respiration failure.

Problems with bones and joints

Burn injury also leaves a person with permanent disability as deeper wounds limit the movement of bones and joints. The healed scar tissue starts contracting and pulls together resulting in contracture that prevents further movements of bones and joints.

Burn and wound infection

Due to burn injury, the skin remains open and the patient becomes more susceptible to infection. The skin is the only part of the body that prevents bacterial infection. Long-

lasting burn infection leads to sepsis, a life-threatening infection. It rapidly spreads to the bloodstream and causes failure of the organ.[22]

Ensuring the survival of a patient in the critical care stages and any interference of infections is the major challenge posed by a burn injury. Infections can delay healing, increase pain levels, increase chances of scarring and may even lead to death. Moist nature elevated temperature and the nutrient-rich environment is the ideal environment for the bacterial growth. Therefore, swift diagnosis and appropriate treatment are necessary whenever infection occurs. However, the major concern faced due to an infected burn is the difficulty in diagnosing the infection. The symptoms related to burn injuries, hyperthermia, tachycardia and hyperventilation are also observed in patients with infected wounds. The similarity in appearing symptoms makes the diagnosis of an infection much more difficult.

Table: 2 List of microorganisms responsible for infection in burn and wound patients

Infection Type	**Name of the microorganism**
Viral infections	*Cytomegalovirus*
Fungal infections	*Candida sp, Aspergillus sp.*
	Alternaria sp, Fusariumspp, Rhizopus sp, and
	Mucor sp
Bacterial infection	*Pseudomonas aeruginosa*
	Staphylococcus aureus
Sepsis and toxic shock syndrome	*TSST-1 toxin*

The most common pathogens obscured from the wounds and burn are *Staphylococcus aureus* and *Pseudomonas aeruginosa*, others may include *Streptococcus pyogenes*, *Acinetobacter baumannii and S. aureus,* which is most commonly associated with smaller burns, produces several virulence factors such as proteinases and collagenases, a variety of exotoxins which induce syndrome of toxic shock: toxin-1 (TSST-1) as well as a range of endotoxins.[20,23]

1.4 Wound and burn healing

Wound healing is a process that involves tissue regeneration and a response to injury.[11, 24] A wound can be described as a defect or a break in the skin, resulting from physical or thermal damage or as a result of the presence of an underlying medical or physiological condition.[25]

It is a quite challenging process as an acute wound may transform to chronic one if left unattended or because of lack of “ideal” wound-healing environment. Huge

figures of burns, ulcers and diseases (diabetes) cases worldwide are making wound healing a topic of large research and debate.

Healing occurs through a series of biochemical processes including 4 key phases: hemostasis, inflammation, proliferation and remodeling. Variety of cellular and matrix components act together to re-establish the integrity of damaged tissue and replacement of lost tissue.[26-27] If this process becomes distracted, healing process ceases and results in chronic wounds. In order to bring the wounds into healing cascade, wound dressings are the first line treatment, although many wound care products are also there in use.[28-29]

1.5 Wound and burn dressings

A dressing is a medical device that is used to cover the wound and burn injuries, to promote healing and further prevent harm. They are also called as surgical dressings or bandages but generally, they are different from bandages because they are designed to be in direct contact with the skin.[30]

Wound and burn dressing includes a first layer which remains in direct contact with the wound and is made up of material which should be bio absorbable, porous and adapted for serving as a scaffold for cell attachment and proliferation. The second layer which is in direct contact with the first layer comprises an absorbent, gel-forming material, which serves as a barrier to cell adhesion and penetration.[11]

The key objectives of wound care and burn dressing are the reduction of infection and pain as well as healing of wounds. Various types of materials have been used for the manufacturing of these dressings. In ancient times, natural materials like honey paste, plant and animal materials and clothes have been used for the healing purpose. [11, 31] Nowadays, novel materials like synthetic bio-compatible polymers and natural polymers are being used to improve the wound healing performance. Natural polymers having good adhesive and permeability properties like chitin and chitosan have been well investigated for wound healing. Synthetic polymers like polypeptide-poly (ethylene glycol) and copolymers have been reported to have suitable properties for wound care and burn treatment.[11, 31] The wound dressings that are prepared from synthetic polymers are generally called as advanced dressings. Various types of advanced dressings/modern dressings are now being used like hydrocolloids, hydro fibre, silicons, alginates and polyurethane etc.[31] There are other

dressings like paraffin dressing, gauze and silver sulfadiazine (SSD) called as traditional dressings but they are under criticism for causing dryness at wound site and not supporting proper healing.[32] In comparison to traditional dressings, advanced dressings have own features in achieving optimal healing and in the prevention of burn infection *e.g*. hydrocolloid dressing, one of the advanced dressing contain gelatin, pectin and sodium carboxy methyl cellulose in an adhesive polymer matrix. When the matrix comes in contact with the wound they form a gel that further facilitates autolytic debridement of wounds. Polyurethane films have their own advantage as they are permeable to water vapor, oxygen and carbon dioxide but not to pathogenic bacteria and viruses and they are not supposed to be used for wounds that are likely exudating.[33]

Traditional dressings like cotton gauze, non-woven dressings and other fibers dressing are generally used to absorb exudate and allowed for a dry site, hide the wound from view and provide a barrier to contamination. These dressings are very less preferred as compared to advanced dressings which provide a wet environment that heals wounds quickly as compared to dry state.[34]

Reasons for use of advanced dressing over traditional dressings:

1. Advanced dressings provides a wet environment to wounds
2. Can be used in chronic wounds
3. High absorption rate further reduces the accumulation of exudate at the wound site and thus overcomes microbial attack
4. Do not stick to skin and therefore no pain or trauma occurs while removing the dressing
5. Protects against microbial infection
6. Proper exchange of gases leads to quick healing of wounds

Traditional dressings have a lot of limitations but they are still being used as they are low-cost dressings.[11, 35]

1.5.1 Ideal properties of wound and burn dressings

Dressings are generally made up of different type of material, therefore they possess different properties. Hence, selection of dressing is required while treatment of particular type of wound. Not all dressings have all properties associated with them but an ‘ideal’ dressing should have following properties:

1. It should maintain a moist environment around the wound
2. Permit diffusion of gases as this is required for regeneration of skin
3. Provide mechanical support
4. Help in maintaining temperature and pH
5. Low cost and commercially available
6. Should be elastic and biocompatible
7. Should be inert and not cause skin irritation
8. Easily removable and require less frequency of change
9. Help in minimizing pain and give relief to patients
10. Easy to handle
11. Protect wound from external contamination like foreign particles and microorganisms
12. Help in exudate management and prevent saturation of dressing from the external environment

It has been reported in several studies that wound healing generally takes place faster in moist environment *e.g.* provided by hydrogel dressings as compared to gauze dressings.[11, 35-36]

1.5.2 Types of wound and burn dressings

There are basically various types of wound and burn dressings. Some are used for short-term application and some are used for long-term application. They can be further subdivided on the basis of application like partial thickness until healing occurs and full thickness wounds until autografting.[37]

Dressings can be categorized in many ways but the most preferred dressing classification is based on the nature of the material as conventional, biological and synthetic dressings. They are sub-categorized as primary dressings, secondary dressings and island dressings.[11, 38]

Primary dressing

Dressings that are used directly and comes in physical contact with injured skin.

Secondary dressing

These are the dressings that are used to cover the primary dressings.

Island Dressing

These are the dressings that are made up of a central absorbent core surrounded by an adhesive portion.[11]

1.5.3 Advanced dressings

The advanced dressings have been named according to the materials from which they are produced including like hydrocolloids, alginates and hydrogels etc.[39]

1.5.3.1 Impregnated gauze

These are the dressings that are non-adherent and moderately occlusive. Gauze dressings are impregnated with substances such as petroleum, iodine, bismuth and zinc *e.g.* Paraffin Gauze.[11, 40]

1.5.3.2 Transparent film dressings

These are thin flexible transparent sheets with the adhesive back, made up of polyurethane or co-polyester. Film dressings can be used as primary or secondary dressings and also as an outer layer in foams, hydrocolloids, composite and hydrogel dressings. Film dressing is permeable to water vapor, oxygen and carbon dioxide but impermeable to bacteria and water.[11, 41]

They have the advantage that they retain moisture at the wound site and also promote autolytic debridement. Film dressings can be used to cover sutures following surgery. They have the limitation of being non-absorbable and cannot be used in wounds with excessive exudates. Moreover, they are prone to bacterial growth because of lack of adequate drainage.

1.5.3.3 Foam dressings

Foam dressings are made up of a polyurethane base and are permeable to both gases and water vapour. Foam films help in reducing the risk of bacterial contamination. It works incredibly well for wounds of varying degrees of severity, as well as for injuries that exhibit odours. It absorbs exudates from the wound's surface, creating an environment that promotes faster healing. Their water vapor permeation property helps in keeping the area moist, promoting faster healing and prevents bacteria from entering the affected area. These dressings come in various sizes and shapes as well as in a range of adhesive and non-adhesive options *e.g*. Allevyn (Smith & Nephew), Biatain (Coloplast), Mepilex/ Mepilex Border (Molnlycke), Tegaderm foam (3M). It limits its use in wounds that dry out if there is no or too little exudate to be absorbed.

Sometimes maceration of the surrounding skin can occur if it becomes saturated with exudate.[11, 42]

1.5.3.4 Hydrogels

Hydrogels dressings are generally composed of two components, where one of the components is hydrophilic *i.e.* insoluble in water and the other is water that provides high humidity to wound area. Hydrogels dressings are found to have all properties of an ideal dressing. These are mainly beneficial for hydrating dry wound beds and softening and loosening slough and necrotic wound debris *e.g*. Gel (ConvaTec), Intrasite Gel (Smith and Nephew). Hydrogel dressings are very beneficial in burn case as they reduce the loss of body fluids. They are designed to maximize patient comfort and reduce pain while helping to heal wounds or burns and fight with infection. One of the disadvantages associated with them is they have very poor mechanical properties after swelling. Also, they are difficult to sterilize due to their high-water content. Hydrogels are unable to mineralize and cannot form chemical bonds with hard tissue such as bones. [11, 41]

1.5.3.5 Hydrocolloids

A hydrocolloid dressing is a dressing that heals the wound by providing occlusion. It is usually composed of hydrophilic colloid particles such as carboxy methyl cellulose (CMC), pectin, gelatin or an elastomer. It consists of an inner layer that is self-adhesive, gel forming and composed of hydrophilic colloid particles. After application on wound site colloidal layer absorbs exudates and swells into a gel-like mass providing the moist and thermally insulated environment. These films also have an outer layer which usually consists of polyurethane that helps in protection of wound injury. These dressings are available in a variety of sizes/shapes and also come in a paste, powder or granule form *e.g*. Duoderm (ConvaTec), NuDerm (Johnson & Johnson Medical), Comfeel (Coloplast Sween, Inc, Marietta, GA), Hydrocol (Dow Hickman, Sugar Land, TX), Cutinova (Smith & Nephew). The Patient warning is required with these dressings as initially with use of these dressings the size of the wound will get enlarged and become smelly. Some leakage takes place, therefore frequent change is required.[42]

1.5.3.6 Alginates

These dressings are generally made up of a block of copolymers of two hexauronic acid residues.The dressing forms gel in the presence of divalent cations such as calcium that further helps in keeping the wound moist. Alginates are useful because they allow gel formation which contacts with exudate wound and gives a strong absorption power and thus, prevents microbial contamination *e.g.* Aquacel/Ribbon (ConvaTec), hydrofibre dressing, Kaltostat (ConvaTec). They are generally not recommended to use where there is no exudate to react with the dressing. Physicians generally prefer to use hydrocolloid and alginates dressings in combination.[44]

1.5.3.7 Biologic dressings

These are the dressings that are made up of natural tissues like collagen, elastin and lipid. These dressings have many advantages over synthetic dressings. These dressings promote wound contraction and epithelialization by decreasing the formation of exuberant granulation tissue and they are considered bioactive *e.g.* collagen-based dressing in the form of films and sheets.

1.5.3.8 Collagen dressings

These can be used for chronic wounds, pressure sores, transplant sites, surgical wounds, ulcers, burns or injuries with a large surface area. These dressings act as scaffolding for new cells to grow and can be highly effective when it comes to healing. The collagen membranes which proved satisfactory in the healing of superficial and superficial partial thickness burns are Derma Col (Derma Rite), Endo form (Hollister), Skin Temp (Human Bio Science), Triple Helix (MPM), Bio Step (Smith& Nephew), Stimulen (Southwest Technologies). A single stretch of the membrane is not advisable to be placed on flexor surfaces as it cracks when it becomes dry and wounds visible through the membrane have given rise to apprehension amongst care givers.[45]

1.5.3.9 Silver dressings

Silver is a broad- spectrum antimicrobial agent, wound dressing impregnated with silver have been developed which along with its medicinal effect also reduce inflammation and promote tissue healing.[46]

1.5.3.10 Negative pressure wound therapy (NPWT)

It applies sub atmospheric pressure or suction to the wound bed via a unit attached to a dressing/sponge. The suction effect of the device removes excess fluid allowing enhanced circulation and disposal of cellular waste thereby reducing the risk of bacterial contamination.[47] Various types of advanced wound care dressings currently available are shown in Table 3.

1.5.4 Dressings under clinical trial

Despite the availability of advanced dressings, many innovations are still in the clinical trial phase.

Table 4 lists the upcoming innovations in the field of the wound and burn care treatment.

1.6 Quality of advanced dressings

To create an optimal environment that best facilitates healing, protection from microbial infection, promotes re-epithelialization; quality of the dressing plays an important role in the treatment of wound and burn infection. Therefore, quality evaluation of the parameters is utmost important to check the fluid handling capacity, moisture vapor transmission rate, drying rate, pore size, density, tensile strength, elongation, lateral and vertical spread, stickiness, thickness, pH value *etc.*

The launch of quality products in the market depends on the regulatory guidelines of the concerned countries.[70] Generally, the regulatory guidelines provide guidance to manufacturers and innovators. Regulatory guidance is formerly established based on the observed benefits and risk impacts. Lesser the information available, lesser the understanding and greater will be the chances of uncertainty.[72]

1.7 Regulatory status of wound and burn dressings in India

Prior to 2018, India categorized these types of dressings as drug and thus regulated as per The Drug and Cosmetic Act, 1940. The dressings that are already approved in other countries are directly eligible for sale and distribution in India.[73] Recently, the new Medical Devices Rules, 2017 has been released by the Ministry of Health and Family Welfare in Gazette of India, Extraordinary Part II, section 3, subsection (i), vide notification no G.S.R. 983(E), implemented since 01 January 2018.[74]

Table: 3 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	48-50
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	48-50
Film dressings	3M Tegaderm, Pro-clude, 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	48-50
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	48-50
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	48-49,51
Collagen	Prisma, Promogran, Stimulen (Systagenix)	Collagen	Wounds with minimal, moderate or heavy drainage	48-49,51
Therapy device:				
Negative pressure wound therapy (NPWT)				
Conventional NPWT	Vacuum Assisted Closure (VAC) therapy, Vista Versatile (Boehringer Wound Systems LLC), Engenex®	Consist of three components: porous non adhesive packing material, occlusive seal, air tight container system	Potential to accelerate healing process	48,52-55
Oxygen and hyperbaric oxygen equipment	OxyHeal (OxyHeal Health Group)	Hydrogel sheet containing glucose and an enzyme oxidase	Stimulates wound healing	48,51,53
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	48,53,56-58
Active wound care device:				
Artificial skin and skin substitutes	Biobrane, TransCyte (Smith & Nephew)	Biosynthetic skin substitute	Provides protection from bacterial influx and mechanical coverage	51-53

Type of dressing	Examples/ product brand names	Components	Intended use	References
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	48,55-57
Collagen-based sealants	Regranex, Autogel, Multidex gel (Smith & Nephew)	Comprised of collagen or hyaluronic acid	Stimulates wound healing	48,51,53
Anti-infective dressings	Silver dressing, Algidex, Aquacel Ag (DeRoyal)	Hybrid dressings that provide healing advantage	Broad spectrum activity	48,51,58-60

Table: 4 Upcoming innovative advanced dressings

Product	Innovator/Company	Material	Clinical trial	References
Dissolvable dressing	Boston University (USA)	Hydrogel	Under trial in lab rats with second degree burns	61
Colour change dressing	University of Bath (UK)	Hydrated Agarose film	Funds granted for further trials, Plans has been developed. But trails has not yet been started.	
Fish skin dressing	Federal University of Ceara (Brazil)	Tilapia Fish Skin	Trials on-going on 56 burn patients in 2017	62
Smart bandage	MIT - USA	Hydrogel and LED indicators	Under trials	63
Microlyte AG wound dressing	Imbed Biosciences (USA)	Ultrathin polymeric film with metallic silver coating	In 2017, FDA cleared MicroLyte™ Ag for use	64
Strata graft	(Stratatech Corporation, (UK)	Living tissue of human cells	Got fast track boost from USFDA	65
Omega3-rich fish skin	Keresis (USA)	Omega3-rich fish skin	Under clinical trials since 2016	66
Restorative oxygenation technology	Mednoxa (USA)	Oxygenation in skin	Received funds to develop the technology in 2017	67
Smart scar pad	Department of Rehabilitation Sciences, PolyU(China)	Pressure therapy and silicone gel	Clinical trial (2017) results showed the pads are effective	68
Wood based gel dressing	IIT Kharagpur, (India)	Unique water-based gel, wood is the main component	Under clinical trials	69

1.7.1 General treatment procedure for wound and burn injuries in India

The treatment procedure for burn injury depends upon the degree of burn and in case of wound, it depends on the depth and exudate. Both types of injury require dressings after initial medical treatments. Conventionally, it was assumed that the injury should be kept open for quick healing since the environment was clean. Now, it has been found that open wound or burn injury is more susceptible to infection that even leads to death. Hence, covering of wound and burn injury has become important.[75]

1.7.2 Steps taken by the Government of India to reduce mortality

There are many national programs that are being run by the government of India in order to reduce the mortality rate due to burn and wound injury. The National Programme for Prevention, Management and Rehabilitation of Burn Injuries (NPPMRBI) is an initiative by the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India to strengthen the preventive, curative and rehabilitative services for burn victims.

Prevention Program

National Injury Surveillance Center (NISC): This program was initiated as a result of Ministry of Health and Family Welfare (MHFW), termed as the pilot programme for prevention of burn injuries (PPPBI). The objective of this program is to ensure burn prevention of injuries and provide proper treatment.[76]

National Programme on Prevention and Management of Burn Injuries (NPPMBI)

The aforementioned pilot project was finally launched as a full-fledged program, empowered by Expenditure Finance Committee (EFC) and succeeded by Cabinet Committee on Economic Affairs (CCEA) that covered 67 medical colleges of state government and 19 hospitals of the districts. The district hospital section was further undertaken under National Health Mission (NHM).[77]

Research and Development

Indian government encourages research and development on wound healing, dressing, infections and wound management. There are efforts undertaken to set-up skin banks to develop artificial skins.

1.7.3 Need of quality guidelines for wound and burn dressings in India

It was estimated that there are an estimated 7 million burn injuries in India annually, of which 7,00,000 require hospital admission of which (1,40,000) are estimated to be fatal. According to the National Burns Programme data 91,000 of these deaths are of women. In cases of surgical site infection, the mortality rate resulted in 70 - 80%, where deep and extensive infection takes place during surgery.

The high prevalence and death rate due to burn mandates the need for guidelines to be identified. The "WHY-5" concept was designed (Fig1) and applied to check the most common cause of death due to burn and wound injury and necessity of regulatory guidelines in India.[78]

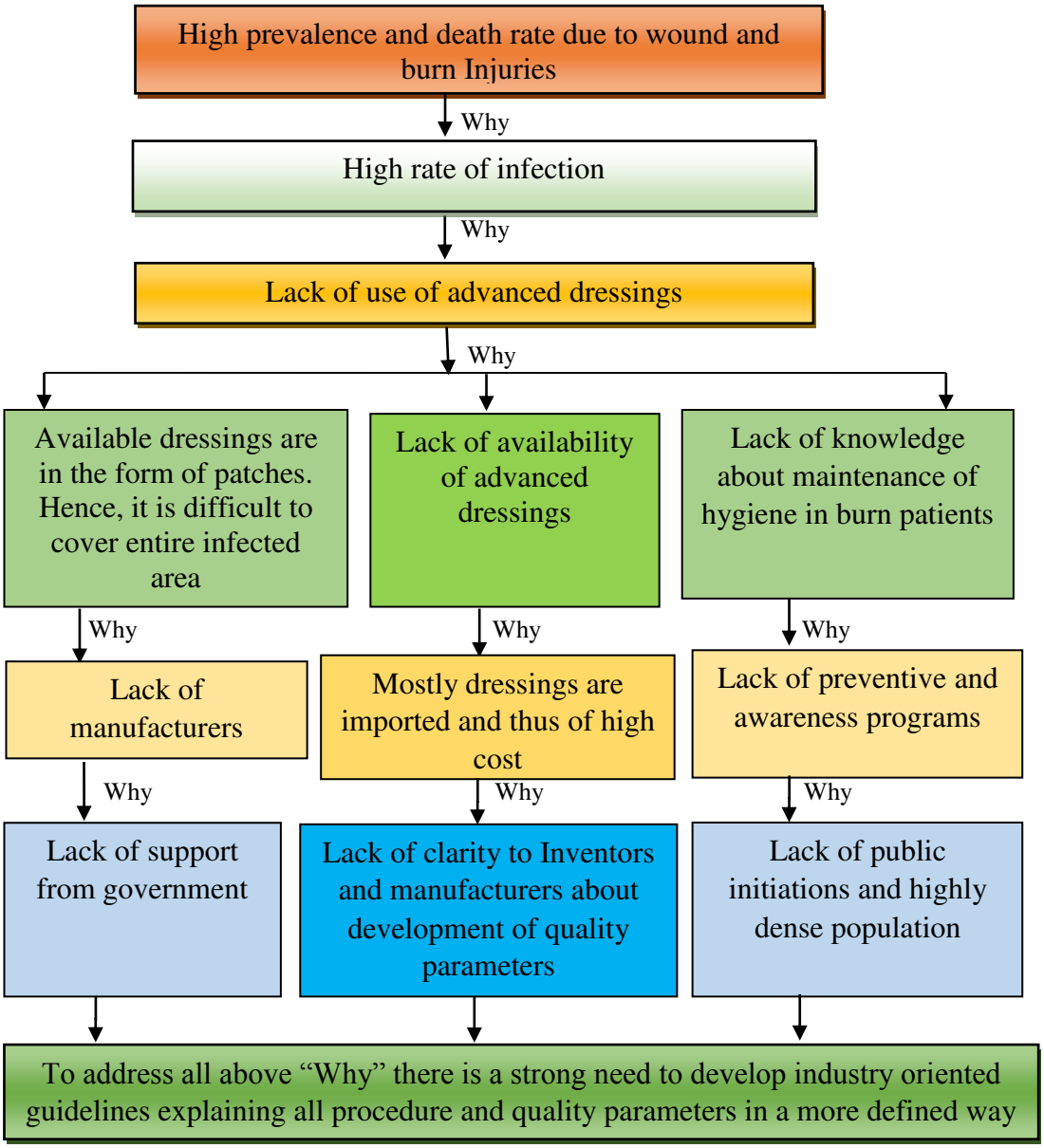


Fig.1. Need of guidelines for wound care and burn dressings

CHAPTER-2

2. REVIEW OF LITERATURE

2.1 Advancements in the study of wound care and burn injury management

This chapter aim to offer a critical investigation on the work carried out so far on advanced wound care and burn dressings. It is important to explore the advancement in the study and to know the regulatory status of such products. The study details about the infection causing microorganisms and recent studies been done so far to curb this critical care issue.

2.1.1 Wound healing methods

Rowan et al., (2015) addressed the burn and wound healing method of advanced dressing. Fig 2 illustrates the burn wound recovery strategies.

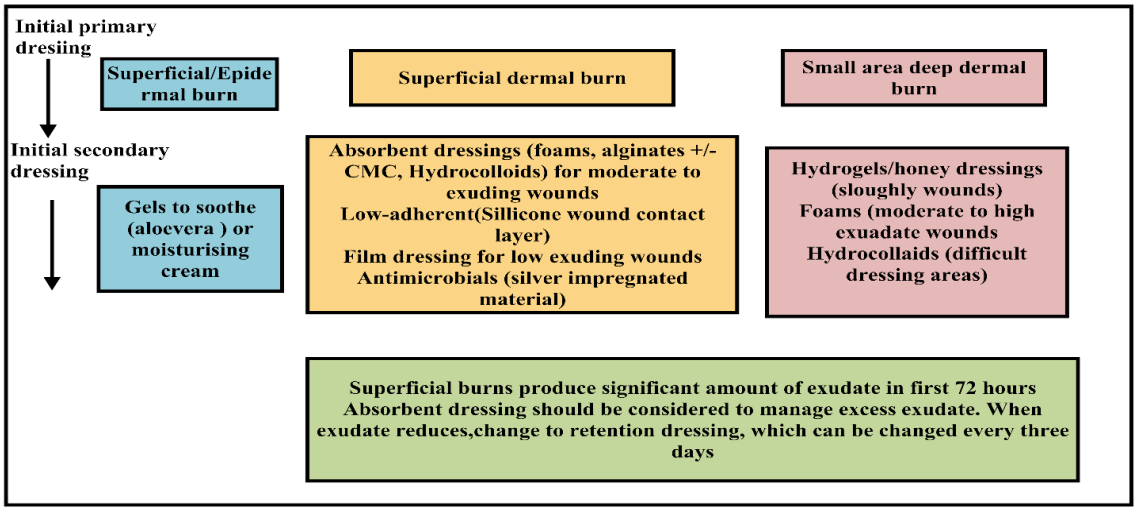


Fig. 2. Wound healing methods

They stated that the selection of suitable dressing depends on the several factors that includes seriousness of the burn, state of the wound bed, location of the wound, preferred moisture retention, drainage, rate of dressing changes and price. They also concentrated on the intake of keratinocytes besides stem cells in the proliferative stage. They concluded that in future, these products must be regulated to maintain the standard of the stem cell bank.[1]

Konieczynska etal.,(2016) established an on-demand dissolvable dendritic thioester hydrogel burn dressing. Generally, hydrogel is embraced of a lysine-dependent Dendron and a PEG-dependent cross linker. Thiol-thioester added in the dressing

stimulates exchange reaction with hydrogel for its proficiency to be dissolved on-demand.[79]

2.1.2 Advanced dressings healing process

Rashaan et al., (2014) witnessed the same results but some evidence based research concluded that silver containing dressing is effective than paraffin coated gauze dressings. Still research is on-going on this topic.[80]

Barajas et al.,(2013) reported that antibacterial prophylaxis decreases the threat of burn and wound infection, aggressive infections or mortality associated with infection. The utilization of topical anti-bacterial specifically, the usage of silver sulfadiazine (SSD) in burn injury is to be reconsidered. Since, the present indication recommends that patients treated with topical SSD have a greater threat of burn and wound infection.[81]

2.1.3 Material used in advanced dressings manufacturing

Jones et al.,(2006) addressed all advanced dressing materials currently in use for dressing preparation. This paper analyzed the drawbacks of gauze material with subject to dryness and tissue damages. In recent years, the United Kingdom has avoided using such materials in wound healing. Hence, we further move to modern technology built on the standard of creating and preserving a wet wound atmosphere. This research work briefly analyzed various advanced dressing materials.

Low adherent dressings: Suitable for use on flat, trivial wounds with small effluence

Semi porous films: Appropriate for flat, surface wounds with small to moderate effluence.

Hydrocolloids: Frequently cast-off on wounds in which the alginates have been exploited usually.

Hydrogels: Appropriate for slough or necrotic injuries.

Alginates: Beneficial in cavities and sinuses.

Foam dressings: Silicone foam dressings safeguard the area round the wound as of more damage.

Anti-microbial dressings: Used in all nearby infected wounds.

They also stated the undesirable properties of dressings. They highlighted that unsuitable use of dressings might lead to undesirable properties.[82]

Faunce and Watal (2010) investigated the regulatory issues of applying Nanosilver dressings for the treatment of external wounds, burns and ulcers. This work carefully analyzed the impacts of Nanosilver in the universal atmosphere and represented the significance of regulation for dressings. They studied the toxicity of Nanosilver on wound bed carefully. Finally, this work established that the Nanosilver must be categorized as a novel product for particular purposes and its improved usage shows severe ecological and health related risks.[83]

Pozo and Patel (2007) analyzed the biofilm-associated bacterial infections which is recognized as healthcare-associated contaminations (HAI). These are the infections that patients attain throughout the sequence of treatment for further circumstances inside a healthcare setting. Fig 3 signifies the biofilm associated infections in wounds. This research concluded that variety of biofilm-associated infections are expanding with time in the present healthcare atmosphere. It was recommended that biofilms are existing in more than 65% of all microbial infections.[84]

Fig. 3. Biofilm-associated bacterial infections in wounds

Vartak et al., (1991) suggested a new cellulose based product named as cellophane as a dressing material for split-thickness skin graft donor sites. They investigated the improvement of wounds using this material. They analyzed various merits and demerits of use of cellophane in wound and burn injury. They considered presence of pain, medical manifestation of infection, remedial time and superiority of healing for result assessment. They concluded that cellophane satisfied all the requirements of a good dressing material.[85]

Benskin (2013) reviewed the effectiveness of various dressing materials in wound healing process. He suggested moist wound environment by means of spontaneous dressings like banana leaves, food wrap and saline-soaked furniture foam. He discovered that nature based selections are higher to several viable dressings. Dressing with honey, papaya pulp and loosening jelly are suitable for treatment of debriding wounds. He studied various dressing constituents that will be effective for

healing burn and wounds. Finally, he concluded that cellophane, a semi-permeable membrane is far superior to porous petrolatum gauze in supporting the remedy of burn and wound injury.[86]

Wasiak et al.,(2013) estimated the properties of wound bandages on partial thickness injuries. The products assessed were silver sulfadiazine (SSD), silver-containing dressings, chlorhexidine impregnated paraffin gauze, bio-synthetic skin substitute bandages, hydrocolloid bandages and silicon coated dressings. They evaluated the parameters like time taken in wound healing from the day of incidence of infection.[29]

Daunton (2012) analyzed the merits and demerits of all advanced dressing materials in wound healing process. First, he started his review from ancient Egypt where donkey feces were used as dressing materials. Gauze, honey, herbal and milk *etc.* were also used. He categorized the modern dressings as semi-permeable films, spray-on dressings, hydrocolloids, hydrogels, polyurethane foam, silicone dressings, capillary action dressings and odor-absorbent dressings. He stated that Semi-permeable film (cellophane) is made up of a non-porous plasticized polyvinyl polymer. The cellophane has advantages in the aspect that it can sterilized, sustains moist environment and precludes bacterial migration. This dressing may not prevent maceration.[87]

2.2 Infection, a major problem in burn and wound injury management

Guan et al., (2015) proved that chronic subclinical infection on account of biofilm affecting the immune system. Biofilm assays are further appropriate for determining anti-biofilm presentation but are frequently inappropriate for the perspective of dressings use. An ultimate test method should reflect, how and wherever a product should be utilized. The kind of microbe(s), inoculum, constitution of artificial soil, temperature, exposure time, endpoint depth should be cautiously deliberated and validated with similar in-vivo or clinical data. “Modern Healthcare” launches several forms of invasive devices and measures to give treatment to the patients and aid them to recover.[88]

Sievert et al., (2013) reported various Healthcare-Associated Infections (HAIs) including central line-related infections of blood stream, ventilator-associated pneumonia and catheter-related urinary tract infections. Infections might also happen

at surgery spots identified as operating site infections. They suggested monitoring and preventing these infections since these pose significant risk to patient safety. Eight pathogen groups have been conveyed and found to be related with the infection. Overall 81,139 pathogens were informed from the 69,475 HAIs which includes, 90% bacteria and 10% yeasts. This report offered the action taken to prevent the HAI through the use of dressings. They suggested a strict regulation so as to avoid such infections.[89]

Tsourounis et al., (2015) focused on six main challenges in the development of regulatory guidelines.

1. Transparency of internal reviews
2. Global coordination and arrangement product directives
3. Assessments at promoter head office
4. Co-packaged products vs kits
5. Manufacturing process validation
6. Inter-center coordination

This brief work also suggested various actions required to elevate the regulations to meet these challenges. Improved transparency in the accessing center's instruction (*e.g.* topic, reviewed data, reference made to main center) would be preferred by the sponsor. The modern FDA counseling reviews are as follows:

1. Correct FDA center is recognized upon the request submitted (*e.g.*, novel submission: pre-IND, pre-IDE).
2. OCP communicated (inbox is examined regularly).
3. Once critics are allocated, suitable assessment timelines are set (*e.g.*, for original IND 30-day assessment clock).
4. Review groups should visit the site as long as possible throughout the process.
5. Pre-meetings are conducted before the assembly of industry so as to remove redundancy and unpredictability in offering associated remarks to promoters.
6. In order to improve global harmonization, FDA has discussions with other nations like Germany and Singapore, on emerging worldwide ethics for flexible arrangement of products.

This work strongly recommends developing countries to work jointly with FDA to make proper guideline for such advanced dressings.[90]

Keshk (2014) suggested that cellulose is an organic polymer which is made of polysaccharide bonds of D-glucose units. Generally, the external layer of the plant cell composed of this type of cellulose. It is the important constituent of algae and oomycetes. Generally, cellulose is found in cotton fiber (90%), wood (40–50%) and dried hemp (45%). Cellulose can be altered by various chemical and physical methods to yield products suitable for different applications. The cellulose is made available to heal the burn injuries in the form of cellophane. It is a thin, soft and transparent sheet prepared by the modified cellulose.[91]

Bolton (2004) proposed that cellulose is manufactured basically from the wood cellulose, cotton and hemp which is dissolved in carbon disulfide and alkali to prepare viscose material. This viscose is then exuded over a slit obsessed by the immersion of diluted sulfuric acid and sodium sulfate for converting in to cellulose.

The film is then disseminated over various baths to eradicate sulfur, bleach the film and to add glycerin to preclude the flick from flattering frail. Its little penetrability to air, oils, lubricants water and bacteria creates this one beneficial meant for food packing and wound dressing.[92]

2.3 International guidelines for wound care and burn dressings

The ISO document termed as ISO 14155:2011(E) defines dressings under medical devices for human subjects. Good Clinical Practice (GCP) defines surgical dressings under medical device category. It describes "medical devices as any appliance, implement, apparatus, machine, software, material, implant or similar and interrelated article envisioned through the producer to be utilized, separately or in mixture, on human beings for one or more explicit resolution of analysis, anticipation, observing, treatment or relief of disease, control over formation and refinement of medical devices." [93]

USFDA (2018) details in section 201(h) that dressings are therapeutic devices, which are subjected to pre-marketing and post-marketing directing controls. It categorizes the dressings under class A of medical devices.[94]

Well-established systems like the UK[95], European Union[96] and Australia also categorize bandages under medical device on the origin of related risk associated with them.[97]

Thyssen et al., (2007) proposed that allergy could be caused in different aspects like climate, traditional practices and regulation.[98]

Zug, Warshaw et al., (2009) founded ten most regularly optimistic allergens including topical antimicrobials neomycin (with a positive reaction rate of 10.0%) and bacitracin (9.2%).[99]

Simonsen et al.,(2011) listed various allergy related elements that are frequently used in medicines, gels and rinsing liquids (ammonium per-sulfate, gold sodium thiosulfate, thimerosal, toluene-2,5-diamine and nickel sulfate).[100]

Mallon et al., (1994) founded glyceryl rosinate cross-sensitivity with colophonium derivative utilized in dressing material of Combiderm™ that causes allergy and strongly not recommended for wounds.[101]

Fuller (2009) and Atiyeh et al., (2007) dermatitis research revealed the reaction of silver sulfadiazine and their compounds in wound care management. They found many compounds and materials which are used in manufacturing of dressings out of which few are prohibited by the various health authorities. Consequently, these strategies help in the identification of such products and prevent human life from danger. These prohibited products could be fatal for many patients. Issue arises because of the lack of regulating guidelines for medical devices.[102-103]

Indian Medical Device Rules, 2017 released by Indian Ministry of Health and Family Welfare in Gazette of India, Extraordinary Part II, section 3, sub section (i), vide notification no G.S.R. 983(E), implemented since 01 January 2018 states the well-defined procedure for import, manufacture and sale of dressings under medical device category.[104]

Calianno (2003) stated that actual wound healing will depend on choosing the exact treatment and suitable bandage for the wounds. He suggested the best dressings for arterial and venous wounds.[105]

Guidelines for managing arterial wounds:

1. Dry dressings should be selected for dry wound and stable eschar off non-infected arterial wounds.
2. For wet or draining wounds, bandages that can be frequently changed should be selected.

3. Avoid bandages that are changed every 3 to 5 days, such as hydrocolloid dressings.
4. Examine the wound type cautiously.
5. Examine regions of wound and peri wound regularly for restrained marks of infection.

Guidelines for managing venous wounds:

1. Select hydro fiber (alginates) dressings intended to absorb moderate to huge quantities of exudate over exposed wound regions.
2. Alter dressings as required to avoid effluence from leaky over the outer dressing and saturating peri-wound muscle.
3. Combination of dressings should be selected to decrease edema and enable healing (distinct level wraps: Sure Press, Ciric Aid, Setopress, Unna's boot) (multilayer wraps: Profore, Dyna-Flex).
4. Limit usage of debriding mediators.
5. Evade usage of moisture-retentive bandages like hydro-gels.
6. Observe the regions of wound and peri-wound regularly for marks of cellulitis and dermatitis.[106]

Boulton et al. (2004) suggested guidelines for managing neuropathic wounds. They advised how to analyse the wounds and how to select exact dressing material for the same.

1. Use dressings intended to absorb moderate to huge quantities of exudate over exposed wound regions, like hydro fibers which are categorized as an alginates.
2. Alter dressings as required to avoid effluence from leaky over the outer dressing and saturating peri-wound muscle.
3. Custom pressure-relieving strategies to diminish pressure from the spot of wound.
4. Biochemical debridement mediators can be utilized to eliminate slough from the wound bed, conversely fixed sharp debridement is commonly required to diminish peri-wound formation of callus.
5. Hydrogels are supportive in preserving a wet wound atmosphere for wounds with slight or no effluence.

6. Examine regions of wound and peri-wound frequently for infection signs.

Cheng (2003) examined the aids of medical device regulations. His in-depth analysis includes the requirement and benefits of guidelines, future enhancement for future innovative devices. This work listed the following benefits of guidelines:

1. Medical device safety and supervision of risk
2. Efficacy/performance of health strategies
3. Life span of a medical device
4. Post-market surveillance
5. Standard maintenance
6. International standard

Medical devices are related to the well-being of people. If there is any degradation in the product, it will lead to major concerns like medical negligence on an international level. The standard of the product should be maintained throughout the production, packing and marketing stages.[107]

Bakker et al. (2016) recommended guidelines against the utilization of prophylactic use of antibiotics to safe guard besides sepsis or cellulitis. There is no proof to prove that the usage of topical antimicrobial reduces the occurrence of infection in early stage of injury.[108]

Sibbald et al. (2006) studied the effect of anti-microbial dressings on a wound for two weeks. He found that the wound isn't being cured in spite of optimum care.[109]

Lipsky et al. (2012) stated that there is inadequate confirmation to care the predictable usage of up-to-date antibiotics as wound dressings. Risks of antimicrobial conflict and connection dermatitis are noted while using antibiotics and close monitoring of wounds is recommended to avoid any adverse response. Appropriate antimicrobial intervention (oral antibiotics) is recommended in circumstances wherever the infection is confirmed or highly suspected on individuals. For slight to modest infections, operating debridement and narrow-spectrum antibacterial are recommended. Wound infections that are simple and convoluted by serious limb ischemia are generally considered for hospitalization, parenteral broad-spectrum antibiotics and surgical intervention.[110]

Robson and Barbul (2006) concluded that wound antiseptic agents are harmful for granulating tissues. Antimicrobial dressings may be advantageous for regular or deeply injuries which reduces microbial load and helps in wound healing.[111]

Hookway et al. (2015) suggested not to choose antimicrobials (silver, iodine and honey) in routine practice. There is no medical or cost-effective indication to offer the utilization of antimicrobial dressings over non-medicated dressings to prevent or treat prolonged wounds. Indiscriminate usage should be reduced due to its toxic effects. Antimicrobial dressing may be deliberated to use to reduce bacterial quantities in wounds, conversely it should be evaded if the wound is infested.[112]

Lazarus et al. (2014) proposed that wound care clinical guidelines should target diverse forms of wounds. In general, these guidelines recommend debridement, rinsing and providing a moist wound environment at the wound site. Recommendations for dressing selection are based on patient-specific wound care needs (for example the need for exudates management or for avoidance of fluid loss). Topical antimicrobials are not typically recommended for wounds that do not exhibit medical signs of infections. Most guidelines do not state the usage of a particular kind of wound dressing and many conclude that there is little variance in effectiveness by means of wound healing consequences.[113]

2.4 Challenges in the development of regulatory guidelines

2.4.1 Political issues

Chaudhuri (2015) addressed the sociological exploration in pharmaceutical sector. Socio-political affairs are affecting the development of regulatory guidelines. Many countries have placed certain regulations to enhance the value of essential health care products. In this respect, Government of India has been executing guidelines on its production and rate controls on health care products and facilities. Conversely, modern Drug Price Control Guidelines, 2013 (DPCO 2013) (published under National Pharmaceutical Pricing Policy 2012 (NPPP 2012) actually employed by means of the National Pharmaceutical Pricing Authority (NPPA), Ministry of Chemicals and Fertilizers, Government of India) has originated to be focused on the modern deliberations. Differences in social and cultural attitudes toward healthcare risks, individual rights and governmental responsibilities influences the designing of regulatory guidelines. Diverse stages of political power can also affect harmonization

efforts. Enforcement capabilities, patent protection, health care systems, insurance coverage, governmental subsidies (to the consumer and the manufacturer), are the political issues that has an impact on the manufacturing of medical devices. This also reflected in the guideline of corresponding countries.[114]

2.4.2 Ethical issues

Chaudhuri (2007) has questioned the gap among effective origination and admittance to its profits. He also addressed success key factors of Indian pharmaceuticals and health care goods which are as follows:

1. A custom of improvement of knowledge by ethnic initiatives.
2. Setting up of public initiatives in awareness.
3. A close relationship among constructors and management through workshops.
4. The influence of obvious and manufacturing strategies in the intervening time of 1970s.

Particularly, last two points emphasize that the administration policy is a key constituent of the manufacturing achievements. He also answered the question on the lack of access benefits with the causes like availability, affordability and appropriateness. Further, he blamed that there is no proper quality control on products. Corrupt practices amongst firms on device quality control have also been described. This not only compromises health but also generating unethical monetary benefits to such enterprises.[115]

Kaplan et al., (2011) listed the remunerations of confined assembly of medical devices as below:

1. Low cost
2. Increased availability through local distribution networks
3. Local alteration of prevailing products via local firms through incremental invention efforts
4. Innovative devices and products should be established locally and custom-made to the confined population

Also, they compared the behavior of MNCs and local pharmaceutical producers and concluded that Indian organizations are organized by domestic centered arrangements and developed competences with MNCs in the following aspects: functional return

boundaries, net profit boundaries, stable strength throughput, operational assets, record stock period, and several others.[116]

World Health Organization (2011) identified the subsequent issues regarding confined production.

Human Resource Constraints

An educated and skill labour is pre-requisite to work in the health care industry. Human resources should be proficient and an approved druggist with knowledge in pharmacology and chemistry. Also, it requires biological, biochemical specialists and engineers who will be able to customize the overall systematic apparatus with precision and in accordance to commercial demand.

Poor infrastructure

Shortage of transportation network and elementary facilities like electricity and water affects the operating budgets adversely. These unfavorable scenarios increase the cost of the end products.

Lack of the collaborative linkages

Some uncertain rules and shortage of policies amongst various relevant ministries, sectors and associations impacts the local production.

High financial cost

Start-ups are being recognized as high risk.

Lack of economies

The arrangement of weak economies and indeterminate markets affects the restricted economies adversely and makes it fragile for the investors.

Production of low quality standards

Non- adherence to the laid down standards like ISOs are leading to the low quality of the products. Even few of the local prevailing standards are compromised in quality and not up to the mark. This may produce the low-cost products but at the cost of quality. Universal harmonization/synchronization is required for benchmarking the standards. These benchmarking should be accepted universally to avoid the duplication of work and to maintain the quality. Audit programs should be in place to fight against the low-quality products.

2.4.3 Harmonization issues

Harmonization of regulations is the most important aspect in making things common while bringing all think tanks on the same platform. It is missing for the regulation for medical device which is leading towards unnecessary delay and increase in cost of the product. The duplication of work is carried out across the globe like testing, dossier preparation, regulatory submissions and fee. Common methodology is to be prepared for better understanding, which should be equally suited to the regulatory authorities of all the countries. Fig 4 shows the progressive functions of harmonization in different countries.

The harmonization of regulations specially for medical device regulations should be in place that directs necessities, quality and administrative requirements. [116]

Cheng (2003) explained the importance of harmonization in the guideline of medical device regulations.

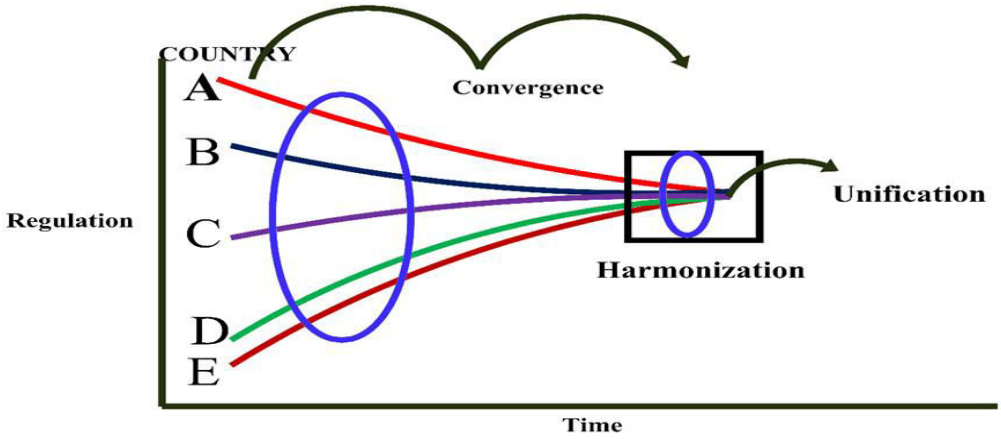


Fig.4. Harmonization process

He focused on various risk associated with device, performance of the medical device that should really be same in all countries. Further, he divided the life cycle of medical device into various stages as shown in Fig 5.

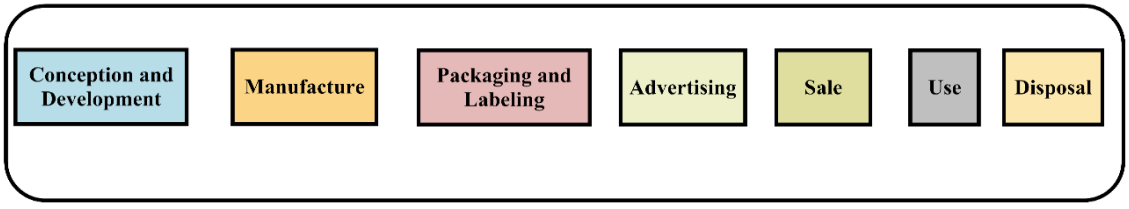


Fig.5. Life-cycle of a dressing

The basic working property of dressings should be similar and follow same general principles. The production should be managed effectively in order to maintain the quality of the product. Appropriate packaging of dressings should be done to decrease the risks associated with labeling like expiry, ingredients and its intended use. Proper removal of dressings should be assured and guidelines should be followed.[117]

Faulkner (2009) defined the essential sections that a dressing's regulation should have. This research work also emphasized that the strategies should be intended, manufactured and filled in a way in which their features and presentations throughout their use will not be unfavorably affected in transportation and storing.[118]

Pettman (2013) addressed the technical barriers to trade which is a key priority of ASEAN as a part of trade facilitation in achieving the single market and production base under the ASEAN Economic Community. The members of the community are Indonesia, Thailand, Vietnam, Singapore, Malaysia, Philippines, Cambodia, Myanmar (Burma), Brunei and Laos. This study addressed the key challenges for ASEAN in addressing the harmonization of standards which is lacking in well-established structures. The region has set ambitious goals but the ASEAN Secretariat still only has limited powers and sway over member states, as compared to the European Parliament.[119]

Advanced dressings manufacturing is the firmest emerging trades in India. Evolving market places like India and other countries of Asia can be the development drivers for leading enterprises. The improvements in advanced dressings have posed a boost in healthcare system. Therefore, Indian regulatory system requires harmonization to overcome the challenges of product inventions and manufacturing of goods.

CHAPTER-3

3. RATIONALE OF STUDY

Burn and wound injuries are recognised as a serious health problem. Various reported study details that burn and wound injuries have a major contribution in death occurring each year. According to the WHO every year more than 3,00,000 individuals died of fire-related burns and 95% of these deaths occurred in low and middle-income countries.[2] Despite having recent advancement in medical sciences the infection caused during the injury is still uncontrolled. For the successful management of burn injuries and to prevent death and deformity following burns, the systemic study of death reasons following burns and wounds has not yet been carried out so far.[119-120] Therefore, an attempt has been undertaken with a view to fill up the lacuna in regard to knowledge about burns and associated problems.

The present study offers an overview of the significance of regulatory guidelines for marketing authorization of advanced dressings for wound and burn care in India. It is important to note that burn is a serious hazard and prone to infections that can finally lead to the death of the patient. This accident is more common in India and unfortunately, the number of burn care centers are very less. Deaths due to burn are a major public health problem in a developing country like India.[3-4] Moreover, poor sanitation of burn care centers further aggravates the situation.

One of the major causes behind this is the quality and cost of advanced dressings that are being marketed in India. These are either imported or manufacturers trying to get it approved in EU/US. Further maintaining their standards related to infrastructure, approval fee, renewals finally led to increased cost of the product. India is lacking behind of their own quality regulatory standards for advanced dressings.

Hence, the treatment becomes further very costly as the dressings need to be changed regularly. This makes the purchase of such dressings non-affordable. Ultimately, this may lead to serious infection or death of the patient. Despite such alarming situation that occurs not due to the burn but due to the costly therapy. So, there is an urgent need for the development of advanced dressings without compromising its quality which is totally ignored by the Indian regulatory bodies.

Keeping all the facts, the aim of the present study is to develop quality regulatory guidelines for advanced wound care and burn dressings.

In order to achieve this aim, the following objectives have been proposed:

3.1 Brief objective of the research

1. Systematic analysis of regulatory requirements for surgical dressings in regulated and semi-regulated countries.
2. Survey of market availability of surgical dressings in India and their regulatory status.
3. Identification of gaps associated with existing regulatory guidelines for successful positioning of dressings in India.
4. Addition of parameters those are required for regulatory approval of surgical dressings.
5. Comparative study of physicians based acceptability of in-house surgical dressing and quality testing with respect to its established brand.
6. Statistical analysis of survey reports and preparation of guidance document.

3.2 Plan of work

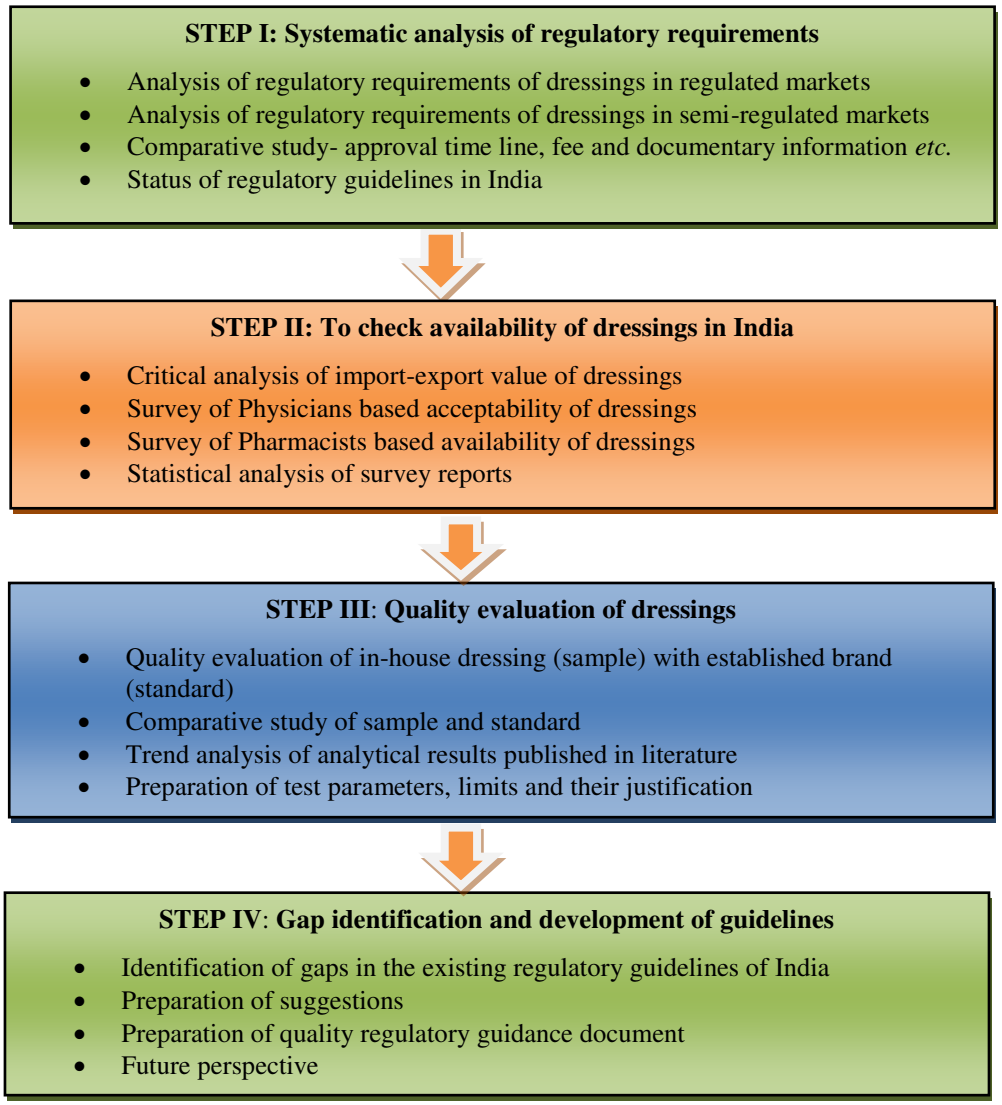


Fig.6. Plan of work

CHAPTER-4

4. GLOBAL REGULATORY ASPECTS OF WOUNDCARE AND BURN DRESSINGS

Generally, wound care and burn dressings are classified on the basis of the risk associated with the wound and are categorized as medical devices.[72] They are classified as Class I to IV and in some countries, they are classified as Class A to 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.[72] General classification is shown below in Table 5.

Table 5: General classification of wound dressings[72]

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

In regulated markets like USA, European Union and Japan, wound dressings are classified as class A 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. [121] 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 US and EU approval marks and do not ask for additional approval if products have been previously approved in these countries.[122-124]

4.1 Regulations for wound and burn dressings in 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, Class II and Class III.[125]Generally, classification depends on the complexity and invasiveness of the dressings. Examples of dressings are detailed in Table 6.

For Class I dressings, a 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, *e.g.* Oasis Wound Matrix, Prisma and

Medihoney.[126-127]Class III wound care dressings are considered to have the highest risk *e.g.* 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.

Table 6: List of dressings with their associated risks[126]

Type	Examples	Level of risk	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
	Dearma graft		Class III	Dossier is required

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.[128]

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:

Step1 Identification of classification

According to the USFDA medical device guidelines, surgical dressings are categorized as Class I, Class II and Class III medical devices.

Step2 Identification of predicate

Prior to 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.

Step3 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. Prior to submitting the application, applicants are required to complete the following:

- Quality management system
- 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 prior to final submission, a request is made to the USFDA.

Step 5 FDA feedback

FDA will review the classification of products and the similarity of claimed predicate devices.

Step6Submission 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.

Step7Issuance 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.

Step8Renewal 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 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 (CFR) Part 820.70).The full approval procedure is outlined in Fig 7.[127]

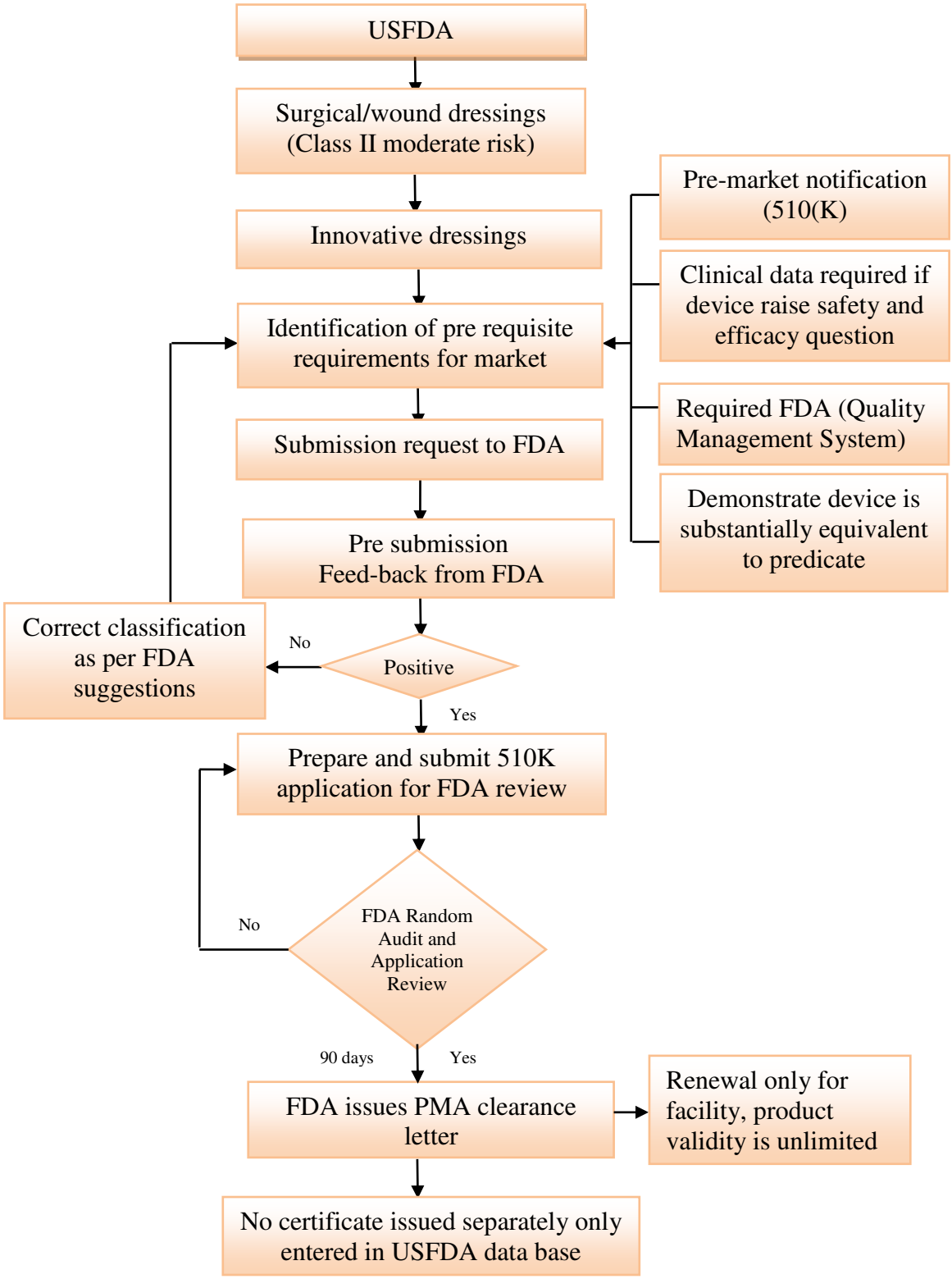


Fig.7. Decision tree for the approval process in the United States[125-128]
*Application fee ($5018) are revised annually, Updated information concerning fee can be obtained at: support@fdaagents.com. PMA; pre-market approval application, FDA; Food and Drug Administration

4.2 Regulations for wound and burn dressings in European Union

The European Medicines Agency (EMA) is the regulatory body for wound care and burn dressings within the Medical Devices Directive (MDD) 93/42/EEC. To commercialize wound care and burn dressings in the EU, a European Conformity (CE) mark certificate is needed.[129]

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, non-measuring) or Class I (sterile, measuring).

Step 2 Identification of regulatory requirements

Before submitting the application, compliance with the following regulatory requirements is needed:

- Quality management system 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 quality management system is required in accordance with Annexure-II of the Medical Device Directive and ISO 13485 standards. Manufacturers are 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

The application is submitted to the Ministry of Health (MOH) along with the specified fee.

Step5 Application Review

The Quality Management System (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, 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 three years.

ISO 13485certification 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 8.[129-134]

4.3 Regulations for wound and burn dressings in Japan

The Ministry of Health, Labor and Welfare (MHLW) in Japan, regulates wound care dressings under the medical devices category.[125,135]

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.

In order 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:

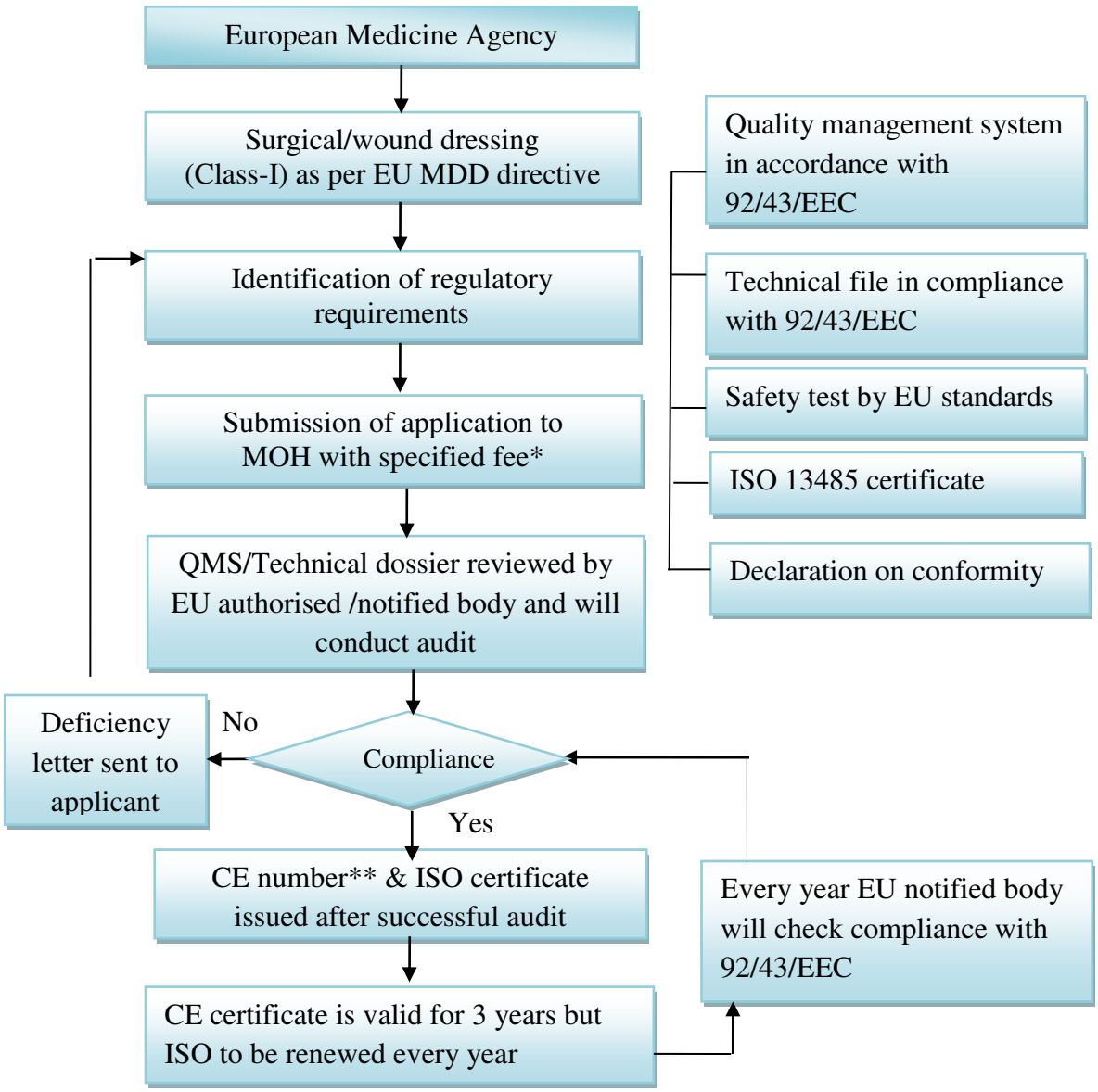


Fig.8. Decision tree for the approval process in the Europe

* Fee vary in 30 member states. More details available on: http://www.mhra.com/cost-and-fee-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

Approval procedure:

Step 1 Classification determination

According to the Japananese PAL and the Japanese Medical Device Nomenclature (JMDN) codes, wound care dressings and surgical dressings are categorized as Class 1and as general medicine–Class I medical devices.

Step 2 Identification of regulatory requirements

Before submitting an application for marketing approval, manufacturers should prepare the following documents and product information. All documents must be written in Japanese.

Information required for surgical dressings as Class1 medical devices in Japan:

- Quality Management System 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: colour photo, size and weight, components and accessories, electrical rating, and block diagram
- Raw materials: quantity (weight, %),materials specification (chemical and/or physical characteristics)
- Product specifications (defined according to each product) *e.g.* appearance and/or physical characteristics
- Directions for use and storage conditions and shelf life
- Manufacturer(s) and manufacturing method
- 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

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 5Certification or renewal and validity

After one month, a decision regarding approval/rejection is reached by the PMDA. No separate certificate is issued for Class1 devices and approval is valid until there is any change in the QMS. The full approval procedure is outlined in Fig 9.[13]

4.4 Regulations for wound and burn dressings in 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." These are regulated under Medical Devices Regulations (MDR) and wound care dressing classifications depend on their intended use or the risk associated with the use of dressings. 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 below as in Fig10.[136-137]

Approval procedure

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

Prior to application for market approval, manufacturers should make available the documents listed below:

- Medical Device Establishment License (MDEL)with list of manufacturers
- ISO 13485:2003 Quality System Management (QMS)
- 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.

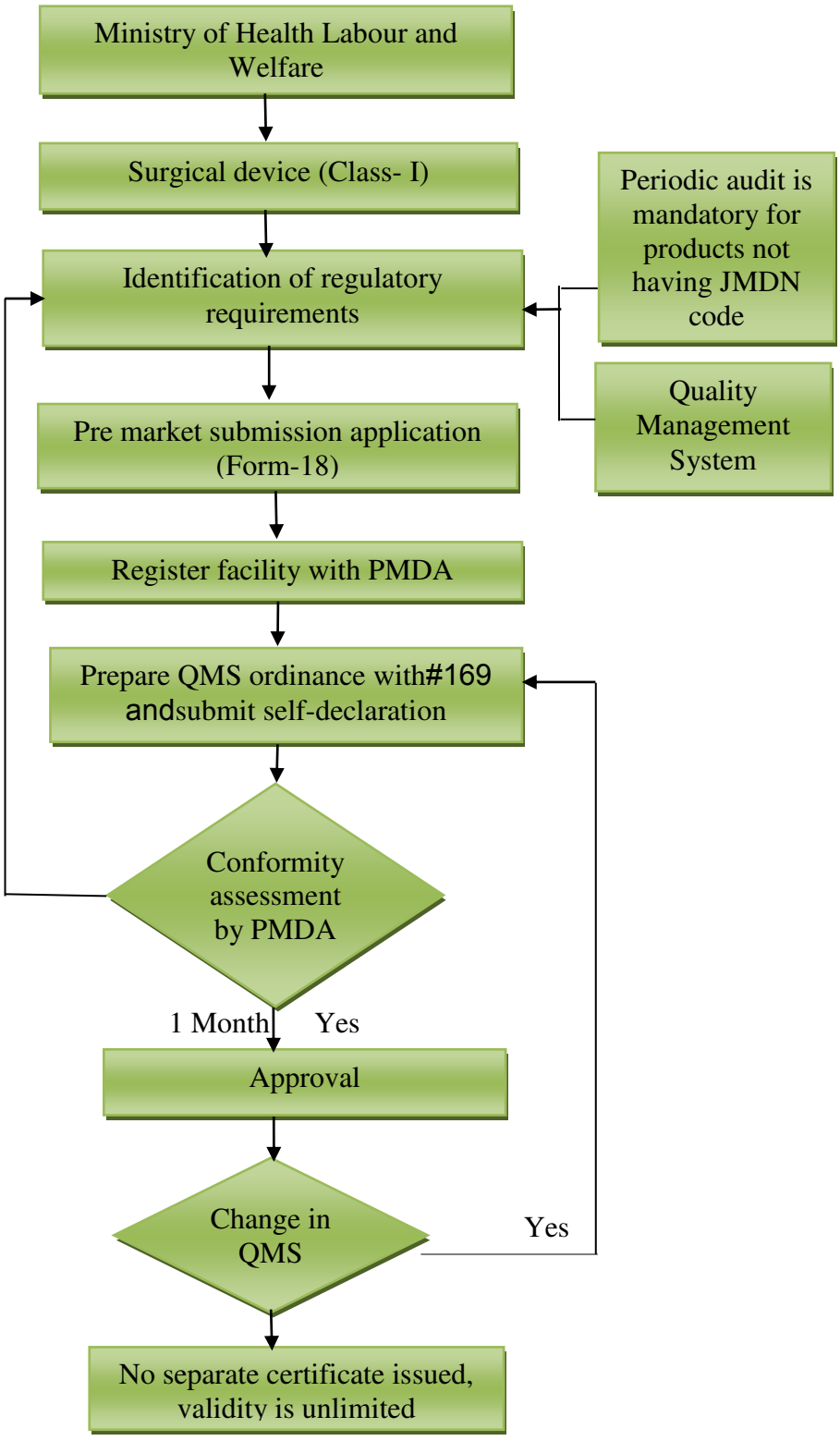


Fig.9. Decision tree for approval procedure in Japan [134]
PMDA; Pharmaceutical and Medical Device Agency, JMDN; Japanese Medical Device Number, MAH; Marketing Authorization Holder

Step 4 Fee submission

After submitting an MDEL application, a 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. 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 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. 10.[136-138]

4.5 Regulations for wound and burn dressings inAustralia

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 in the Australian Register of Therapeutic Goods (ARTG). Regulations and classification of wound care dressings are similar to those in Europe. [125,139]

The full approval process, along with the necessary requirements for application is outlined below and in Fig 11.

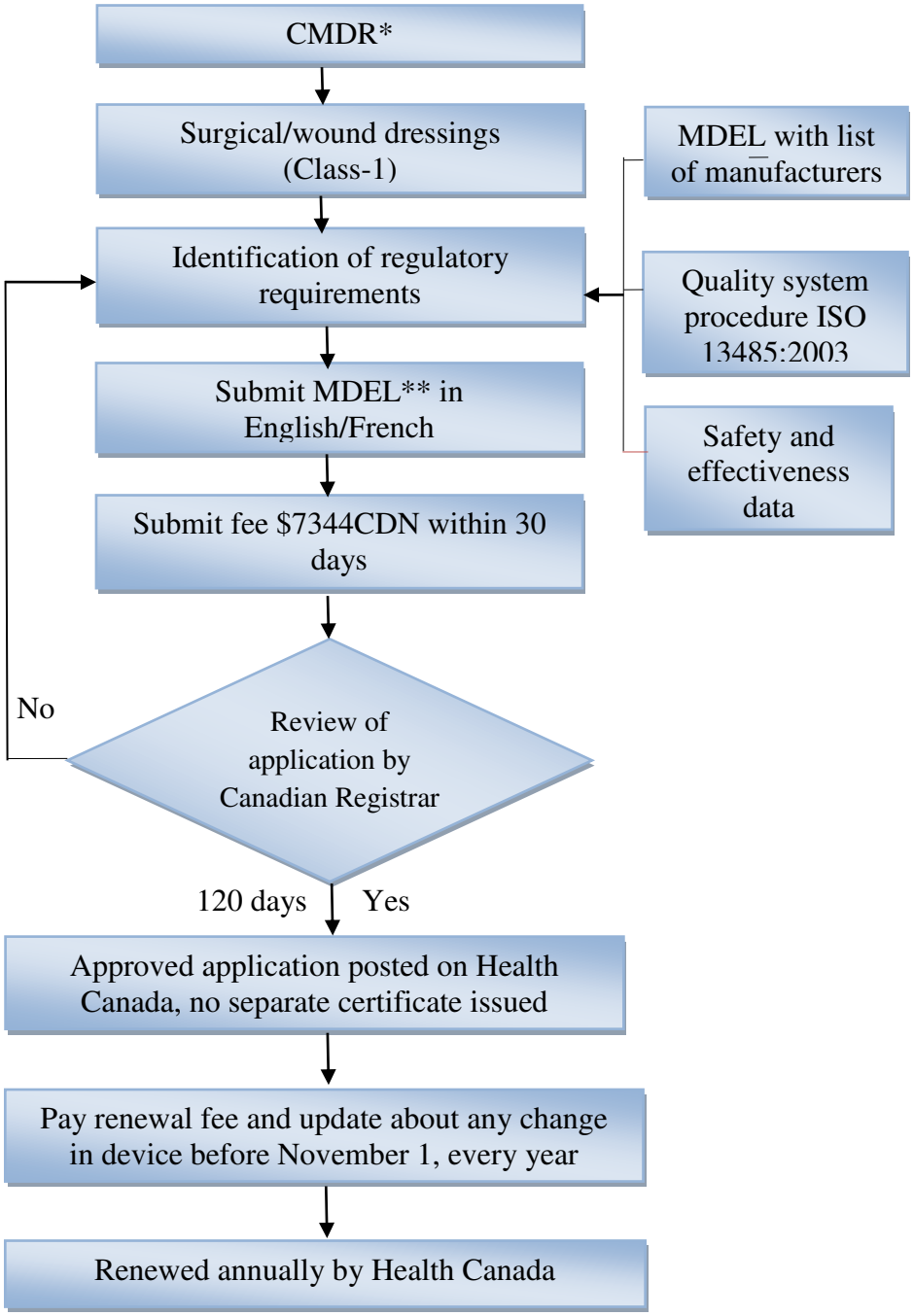


Fig.10. Decision tree for approval procedure in Canada
*Canadian Medical Device Regulation;**Medical Device Establishment License

Approval procedure:

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, non-measuring) or Class I (sterile, measuring).

Step 2 Identification of regulatory requirements

Prior to 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 e-Business Services system
- Australian sponsor
- Audit fee

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 4Application 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.

Step5 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.[139-142]

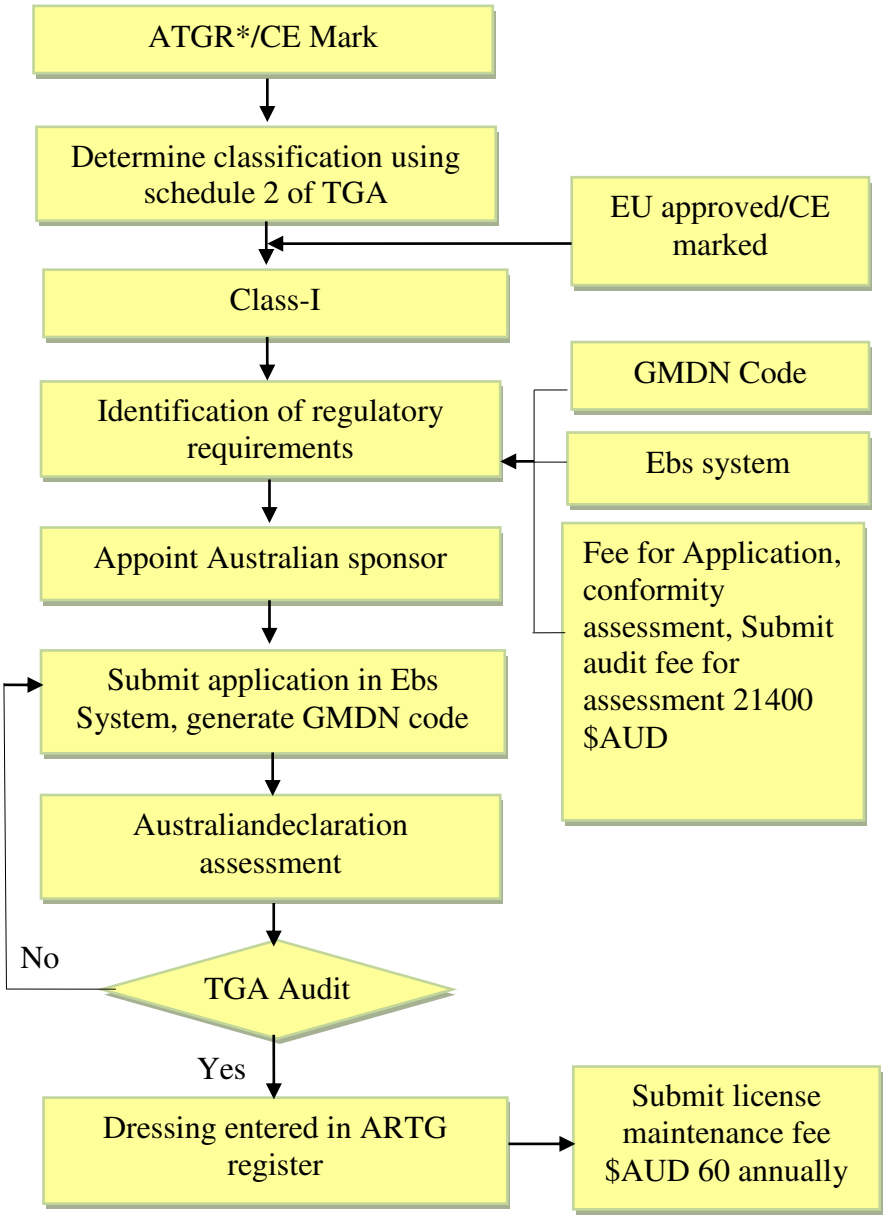


Fig.11. Decision tree for approval procedure in Australia
*Australian Therapeutic Goods Regulations, ARTG; Australian Register for Therapeutic Goods

4.6 Regulations for wound and burn dressings inBrazil

In Brazil, approval is required from MOH to market any health, domestic or imported products. The National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA), a federal agency subsidiary to the Ministry of Health 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. [125,143]

Surgical device manufacturers are required to obtain ANVISA (Agency National de Vigilance Sanitaria) approval prior to selling their products in Brazil. The regulatory requirements for approval are similar to those identified in the European MDD 93/42/EEC 65.

Approval procedure:

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 Cadast roprocess pertains to lower risk devices. As such, wound care dressings require approval via the Cadastro approval process. This review process has a simpler application pathway and typically requires less time than Registro approvals .[143-146]

Step 2 Identification of regulatory requirements

The following are required:

- Manufacturing unit prepared in line with Brazilian Good Manufacturing Practices (BGMP)
- Labelling 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 country of origin approval.

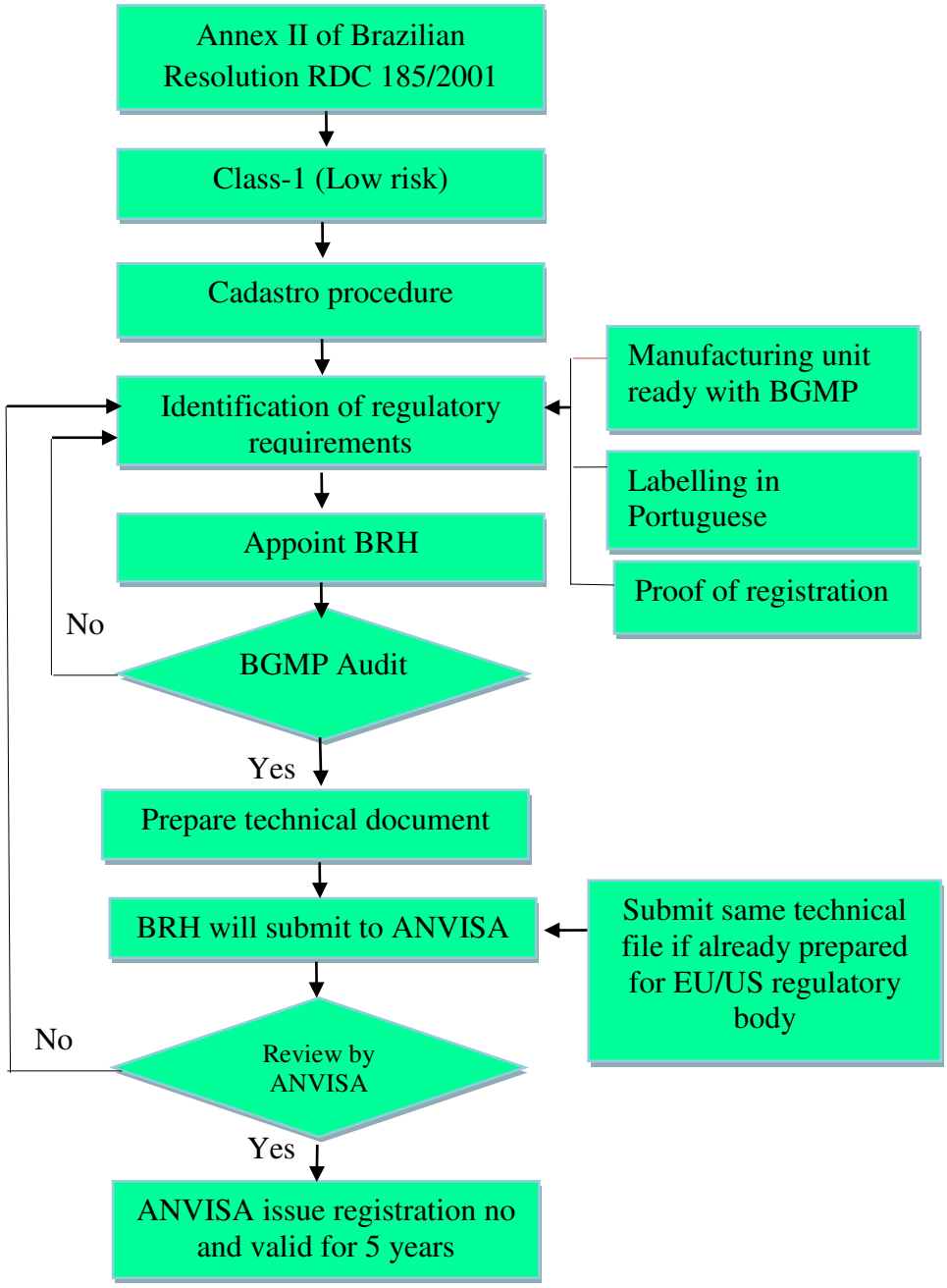


Fig.12. Decision tree for approval procedure in Brazil
BGMP; Brazilian Good Manufacturing Practices, BRH; Brazilian Registration Holder, ANVISA; National Health Surveillance Agency, Brazil

Step 3 Appointment of a Brazilian registration holder

Company that holds a company working allowance permit from ANVISA should be appointed as a Brazilian Registration Holder (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 (DOU). Registration is valid for five years. The full procedure is outlined in Fig 12.[143-156]

4.7 Regulations for wound and burn dressing inChina

The China Food and Drug Administration (CFDA) is responsible for the registration of wound care and burn dressings. It is mandatory to obtain pre-market approval from the State Food and Drug Administration (SFDA). The Centre 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.[125,147]

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

The full procedure is outlined below and in Fig 13.

Approval procedure:

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

Prior to 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 ofUS$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 the 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 fee have been paid, the test laboratory will issue a report (valid for six months) to be submitted as part of the medical device registration.

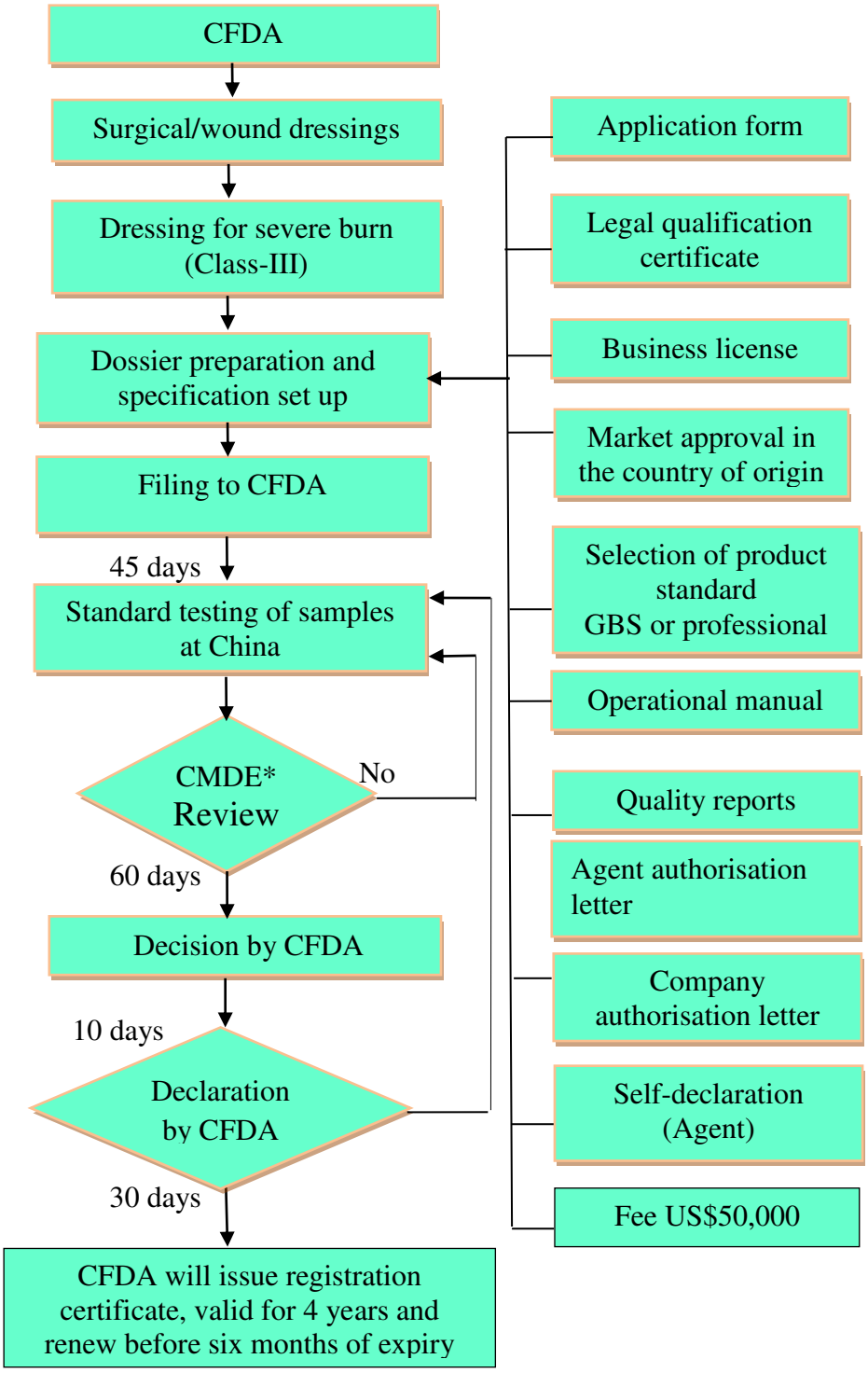


Fig.13. Decision tree for approval procedure in China

*CDME; Centre 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 the device registered in terms of structure, performance and safety.

Step6Evaluation

Technical evaluation involves systematic examination that focuses on the safety and effectiveness of the medical device. The evaluation is performed by internal Center for Medical Device Evaluation (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 13.[147]

4.8 Regulations for wound and burn dressings inSingapore

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 prior to 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 prior to their placement in the Singapore market. [148]The full approval procedure is detailed below in Fig 14.

Approval procedure:

Step1 Classification of surgical dressing

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 prior to entering the Singapore market.

Class A, sterile dressings

Class A, sterile dressings require submission of an application dossier via the Medical Device Information and Communication System (MEDICS) and a payment of an application fee is immediately required upon submission.

Step 2Identification of regulatory requirements

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 via MEDICS
- Submission of fee

Documents required for Class A (sterile) dressings

- Letter of authorization
- Proposed device labelling
- 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 *e.g.* ISO 13485 certificate, conformity to USFDA, Quality System Regulations non-sterile dressing is exempt from fee; however, the application fee for sterile dressings is $25 and there is no evaluation fee. Generally, 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 via 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 upon 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 one month.

Step5 Evaluation process

Surgical dressings that have not been approved by any of the HA 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 labelled 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 14.[148-158]

4.9 Regulations for wound and burn dressings inMalaysia

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. [125]

The Malaysian Medical Device Authority (MDA) is responsible for enforcing medical device regulations and medical device registration. The full approval procedure is outlined below and highlighted in Fig 15.

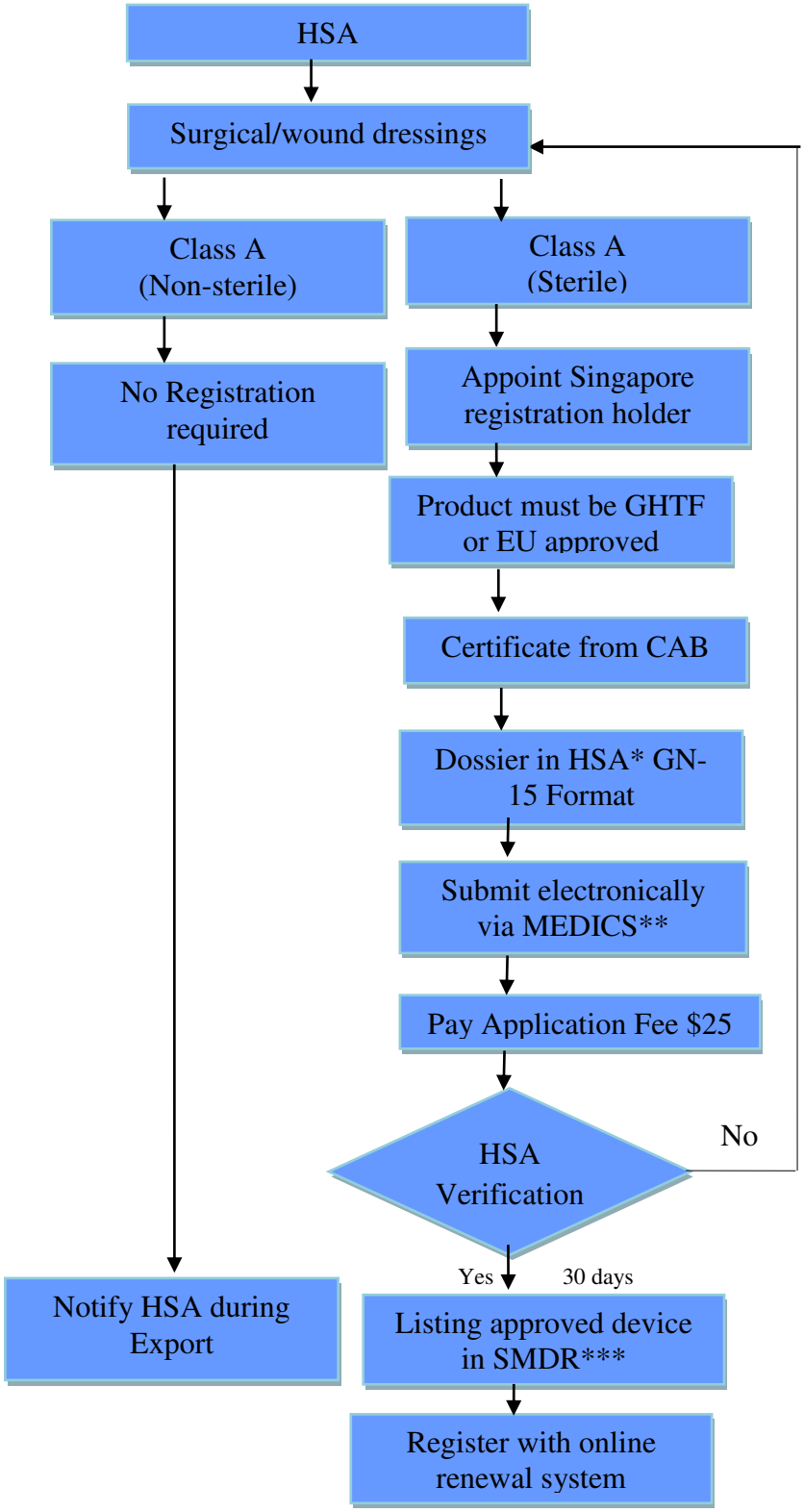


Fig.14. Decision tree for approval procedure in Singapore
*Health Science Authority; ** Medical Device Information and Communication System ***Singapore Medical Device Register**;** CAB: Confirmatory Assessment Board

Approval procedure:

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
- Labelling
- Approval in reference countries

Step3Appointment of authorized representative

To register surgical and wound dressings in Malaysia, an authorized representative in Malaysia must be appointed.

Step4 Preparation and submission of dossier

The authorized representative prepares the registration application dossier and submits the application to the Malaysian MDA online.

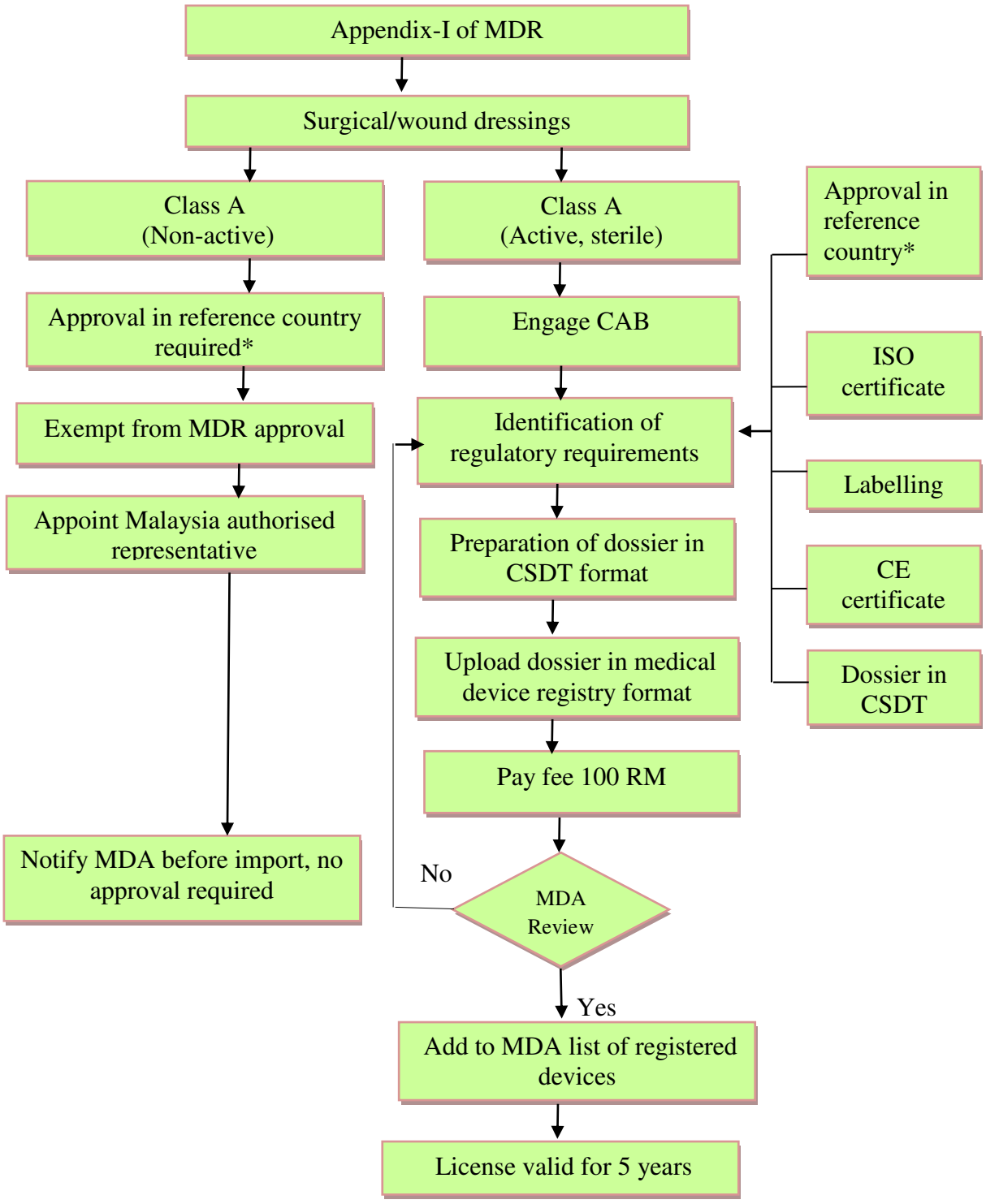


Fig.15. Decision tree for approval procedure in Malaysia
CAB; Confirmatory Assessment Body,* Recognized reference markets include: Australia, Canada, EU, Japan, and USA.

Step5Review 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. Fig15 details a decision tree for the approval procedure in Malaysia. [159-163]

4.10 Regulations for wound and burn dressings inMexico

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 16.

Approval procedure:

Step1Classification 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, which is a low-risk medical device. 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.

Step2Identification of regulatory requirements

The following list outlines the documents that manufacturers must prepare prior to applying for registration:

- Application form
- Device information
- Scientific and technical information
- Testing requirements
- Evidence of home-country approval
- Labelling in accordance with NOM-137 SSA-1-2008
- Instructions for use of the device

- Valid Good Manufacturing Practices (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 4COFEPRIS review

A third-party reviewer (TPR) is a private commercial entity authorized by COFEPRIS to conduct an initial review of an application 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.

Additionally, 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 5Issuance of the certificate of approval

Once COFEPRIS approves an application and issues a certificate, confirmation and registration number are posted on the Ministry of Health's 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 16.

Step 6Renewal and validity

Certificate is valid for five years.[164-165]

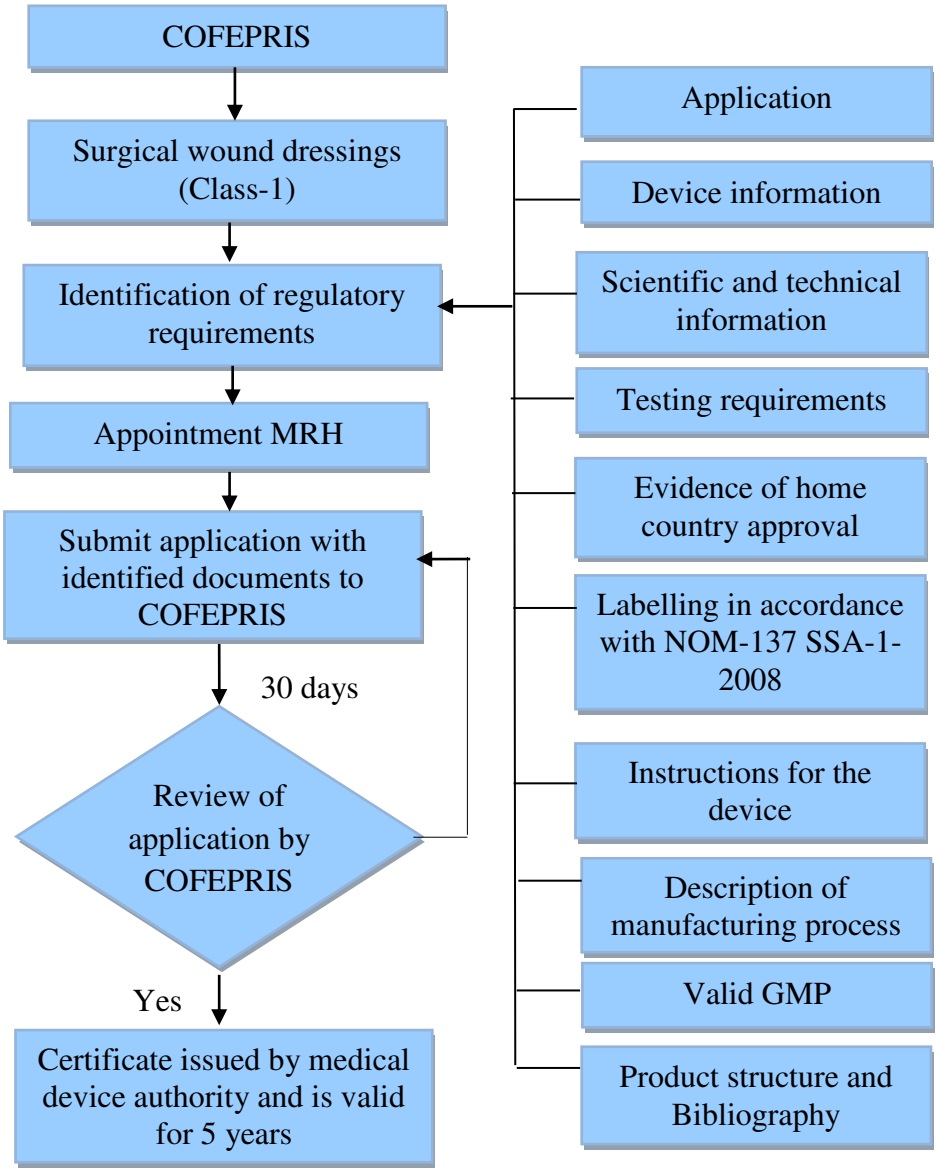


Fig.16. Decision tree for approval procedure in Mexico

Fee are set by the authority on the basis of risk assessment, according to the federal law on fee payment.
MRH; Mexican Residence Holder

4.11Regulations for wound and burn dressings inIsrael

Israel is one of the world's leading centres for the development of innovative medical devices.[71]

Approval procedure:

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 prior to applying for 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 Ministry of Health Registrar (AMAR – the Medical Device Division of the Israeli Ministry of Health). [166-167]

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 below and the process flow is shown in Fig 17.

Approval 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

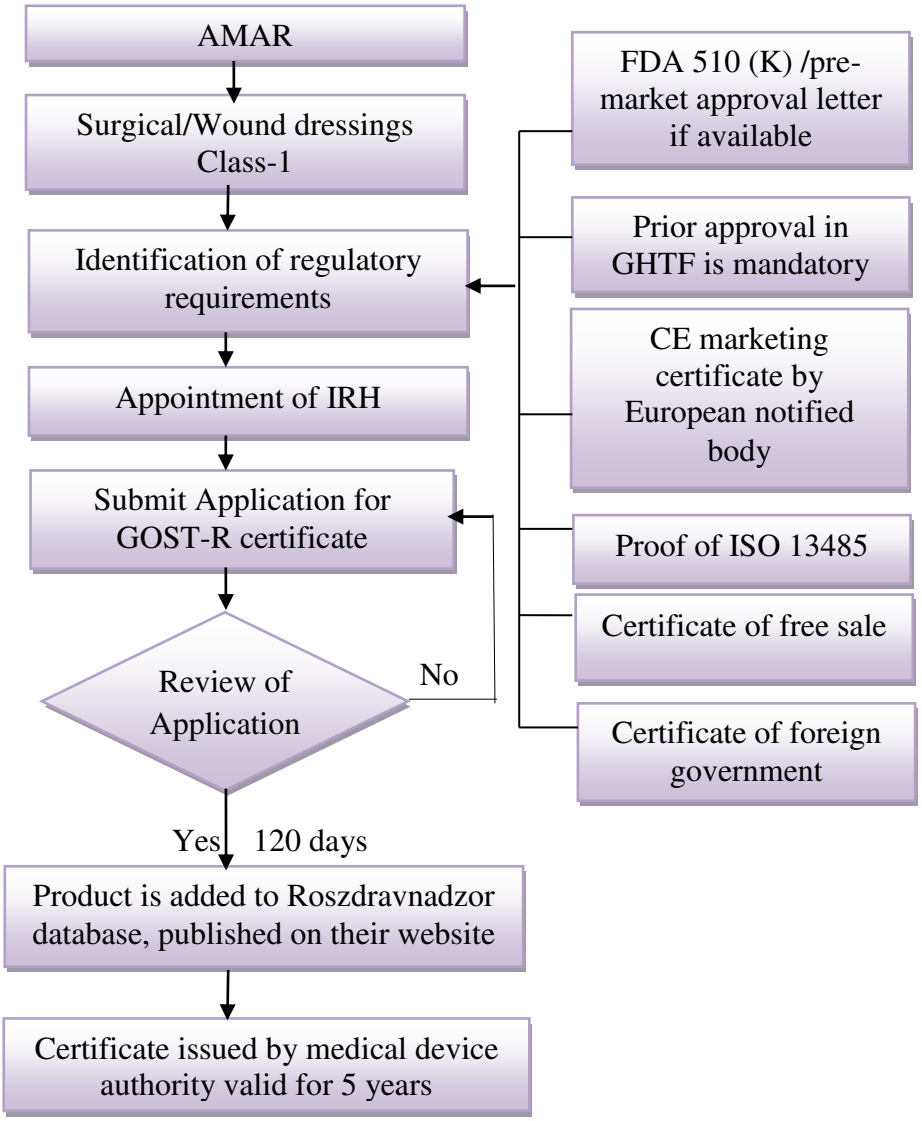


Fig.17. Decision tree for approval procedure in Israel[166-167]
GHTF; Global harmonization task force, AMAR; a department within the Israeli Ministry of Health responsible for licensing medical devices, IRH; Israeli Residence Holder

Step 4 Application submission

The IRH will submit the above-listed documents to the AMAR-Medical Device Division of the Israeli Ministry of Health.

Step 5 Review of application

AMAR will review the application within120 days.

However, registration is usually completed within 6-9 months because 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 five years. The license expiration date is based on the current regulatory certificate and is subject to the device's CE mark or FDA approval.

4.12Regulations for wound and burn dressings inRussia

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).[168]

Approval procedure:

Step1 Identification of classification

In accordance with Government Standardization GOST R51609-2000 medical products, surgical dressings/wound care dressings are categorized as Class 1(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.[169]

Step2 Identification of regulatory requirements

- Certificate from the country of origin
- Proof of compliance
- ISO13485
- Gosudarstvennyy standard 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 medical device authority.

Step 4 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 centres within Russia. Preparation of the registration dossier should include testing results and medical reports. All documents should be submitted to the relevant officials.

Step 5 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 18 details the decision tree for the approval procedure in Russia. [168-170]

4.13 Regulations for wound and burn dressings inIndia

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.[171]

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 can be classified on the basis of their intended use.

Approval procedure:

Step 1Identification of classification

Wound care and burn dressings are categorized as Class A,B, C and D medical device as in contact with injured skin. Additionally, 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.

Step2Identification 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 7

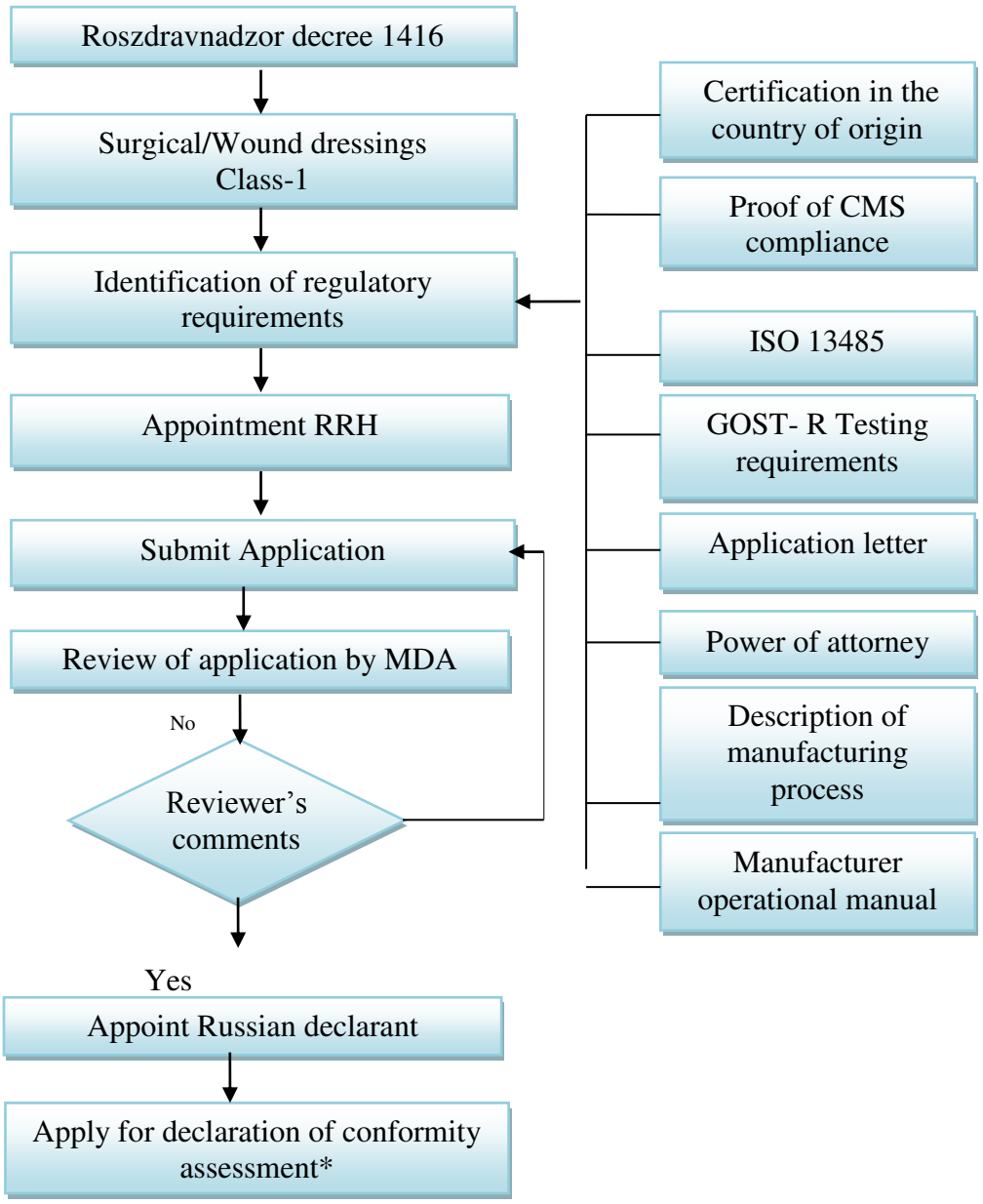


Fig.18. Decision tree for approval procedure in Russia

Roszdravnadzor Federal service for control over health care and social development, RRH; Russian Resident Holder
*Conformity Assessment: A declaration certifying that the product conforms to Russian Regulatory Requirements.

Step 3 Submission of application

The State Drugs Controller serves as the State Licensing Authority and shall be the competent authority for enforcement of the rules relating to the manufacturing 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 State Licensing Authority (SLA).

Step4 Issuing the license

The manufacturing site of the applicant, in respect to a class B device, shall conform withthe 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 prior to granting the license.

Step5 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 five years from the date of its issue, unless it is suspended or cancelled by SLA or CLA. [171-172]Theapproval procedure in India is provided in Fig 19.

4.14 Comparative studyof global regulatory approval process for dressings in different countries

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 in dossier content submission, as well as in evaluation procedures. Differences, regarding dossier submission format are detailed in Table 8.

The comparative study (Table 9) shows that the complete regulatory assessment for advanced dressings in regulated and semi-regulated markets. The detailed information regarding fee, timeline and regulatory requirements have been well defined. Manufacturers and innovators can make use of it during their business planning.

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.

Table 7: List of documents required for manufacturers registration and for importation of dressings

Class A	Class B, Class C and Class 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
Working principle and use	Device master file	results
of novel technology, if any	Essential principle checklist for	Reliability test results
Label package inserts	demonstrating conformity for safety	Validation of software
User manual	and performance	Performance test results
Summary of ADR	Quality control data	Biocompatibility test results
Site master file	Signed undertaking agreement	Risk management data
Firm details	stating that the manufacturing site is	Animal performance data
Signed undertaking	compliant with schedule	Pilot and pivotal clinical
agreement		investigation data
Analytical performance		Regulatory status and restrictions
		in use
		Proposed instructions for use
For importation:		
Notarized copy of overseas manufacturing site or FSC		
Notarized copy of QMS		
Self-attested whole sale license		
Copy of latest inspection report		

Table 8: Differences in content and format of dossier required in regulated and semi-regulated countries [125]

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.
European Union (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 are required. Compliance with QMS accordance with # 169 is required.
Canada (Health Canada)	Class I	Dossier in French is required.
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 fee, 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 Health Authority Specific format, HASFis required.
Mexico (COFEPRIS)	Class I	Dossier with specific labelling required, in accordance with regulation NOM-137 SSA-1-2008.
Israel (Medical Institutions and Device Licensing Department)	Class 1	Prior registration with Global Harmonisation Task Force (GHTF) is mandatory.
Russia (Federal Services on Healthcare Supervision)	Class 1	Testing in the country of origin is required.

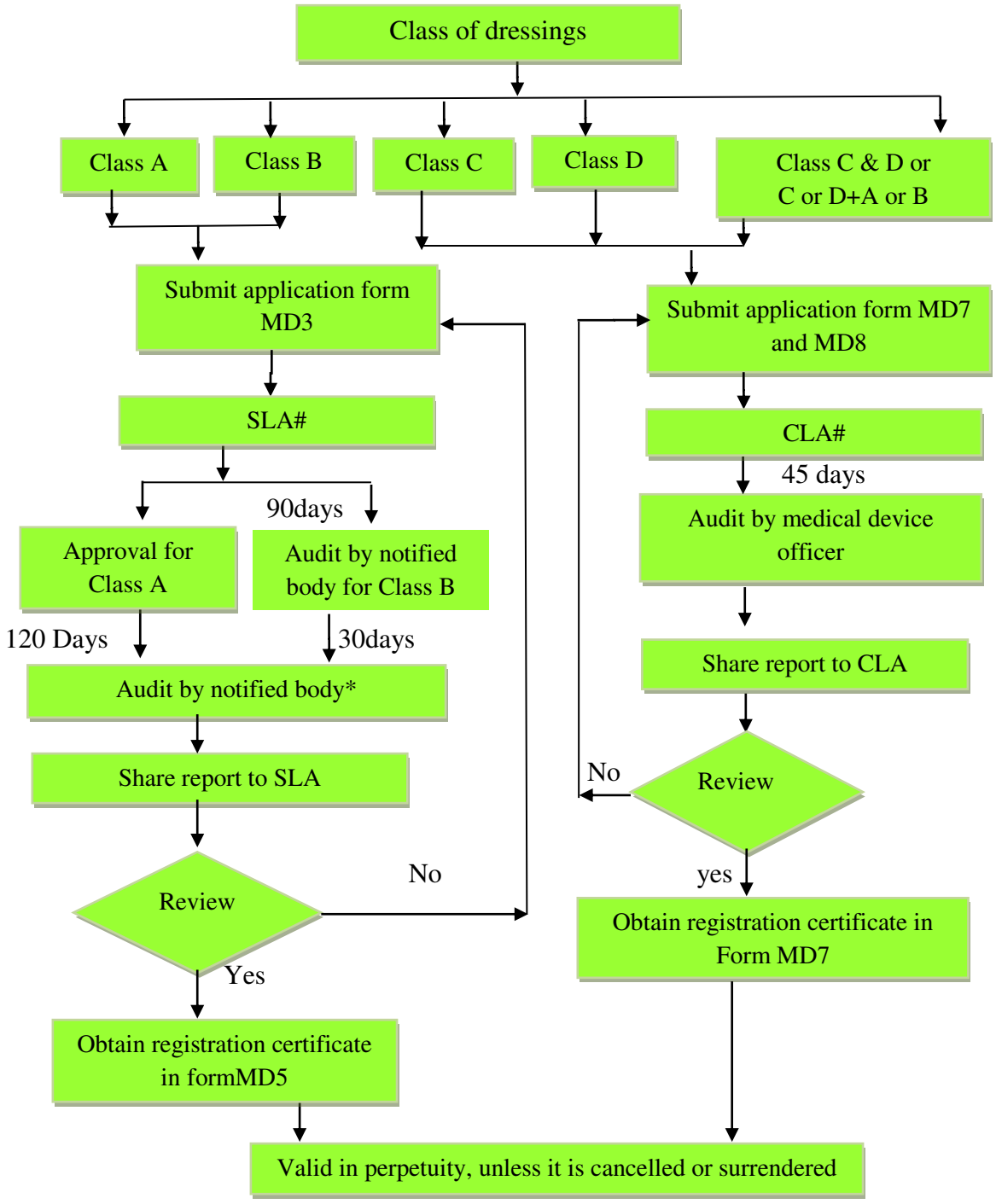


Fig.19. Decision tree for approval procedure in India [171-172]

SLA- State Licensing Authority, CLA – Central Licensing Authority; *Audit of Facility by Notified body is carried out after approval of class A dressings

Table 9: Comparative study[125,173-174]

Country Name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Fee	Approval time line	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. Quality management system 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	Approx. 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 like size, appearance, raw material quality standards, microbial limit, heavy metals if any, ash content, pore size, required for wound dressings are not well addressed in guidelines.
European Union	EMA	Council Directive 93/42/EEC	Class II	1.Quality management system 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	Fee vary in different member states	Not defined	Three 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 fee during the approval process.
Japan	Minister of Health, Labor and Welfare, PMDA	Japanese Pharmace-utical Affairs Law	Class I (low risk associated with wound care dressing)	1. Form No 18 2. Quality management system 3.Self-declaration in Japanese language	Fee: ¥ 664500	36 month	Unlimited validity until there is a change in QMS	A streamlined registration process.	The application process appears costly and time-consuming (requires between 1-3

Country Name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Fee	Approval time line	Registration validity	Pros.	Cons.
									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 fee for class 1 devices; however, MDEL fee:CAD$7344	120 days	Valid for one 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	Therapeutic Goods Administration	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 fee: AUD $21,400 License maintenance fee: AUD$60.00annually	Not defined	Not defined	A well-defined classification and summary of the guidance document is available.	Approval fee are high, and it appears to be very difficult to place standard medical devices in the Australian market.
Brazil	ANVISA	Brazilian resolution RDC No 185/2001	Class I (low risk)	1.Device registration certificate or free sale certificate(FSC) 2.Proof of registration in any other two countries 3.FSC/Proof of registration in other countries	No fee for class I	Not defined	Valid for five years	Manufacturing permitted only for manufacturers who have the unit ready with the audit. Separate	Quality parameters required for wound dressings are not well addressed in the guidelines.

Country Name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Fee	Approval time line	Registration validity	Pros.	Cons.
				4. BGMP audit				approval procedure is well defined.	
China	China Food and Drug Administration, Centre 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$50 000	105 days	Valid for four 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 labelling 3. Patient information leaflet 4. Proof of quality management system 5. Manufacturing process- flowchart 6. Information on sterilization method 7. Conformity of quality management system- USFDA, Japan, Canada, Australia 8.Certificate from	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

Country Name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Fee	Approval time line	Registration validity	Pros.	Cons.
				conformity assessment board 9.Prepare dossier in MEDICAS electronically					guidelines.
Malaysia	Malaysian Medical Device Authority (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 five 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. Labelling 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 check list 5. Quality control data	INR 5000	9 months	Manufacturing license validity - five years	The draft medical device rules are very effective.	Burn dressings-Quality guidelines concerning burns dressings remain not well

Country Name	Regulatory body	Regulatory guidelines	Wound dressing classification	Approval requirement	Fee	Approval time line	Registration validity	Pros.	Cons.
				6. Underrating 7. MDA dossier appendix-II					defined within the draft medical device rules.
Israel	Division of Medical Devices and Accessories under the Israeli Ministry of Health (IMOH)	Israel Medical Devices Act (2012)	Surgical dressings are regulated as medical devices within class 1 category	1. FDA 510(k) or pre-market approval application 2.Certificate to foreign government (CFG) 3.CE marketing certificate issued by a European-notified body 4. Proof of ISO 13485 certification 5. Require registering device with AMAR, the Israeli Ministry of Health Medical Device Regulation Unit 6. Prior approval in GHTF 7. Certificate of free sale	No fee for class 1	120 days	Valid for five 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.
Russia	Federal Service for Control over Healthcare and Social Developme nt, more commonly known as Roszdravna dzor	Government Regulation No. 1416	Federal Law on Fundamentals of Healthcare 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 fee for class I devices	Four months	One year	Similar to the EU.	Guidelines are available in Russian language only. A dossier is also required, in Russian language only.

CHAPTER-5

5. TREND ANALYSIS OF DRESSINGS IN INDIA

5.1 Import-export market of dressings in India

The global wounds market is poised to expand from a value of USD 5.5 billion and expected to grow up to USD 9.4 billion by 2022, growing at a common annual growth rate (CAGR) of 7% and expected to grow at the rate 8.1% by 2022.[175] The Indian wound care market is growing at a CAGR of 7.4% which is quite higher in comparison to rest of the world.[176] The traditional and advanced wound dressings together constitute a major market share. Currently, dressings market is dominated by international companies and many more are expected to enter to Indian market very soon as both factors are growing *i.e.* population and living standard.[175-176] The major players are Molnlycke Health Care, Convatec, Inc. B. Braun, Melsung AG, Medline Industries Inc., Kinetic Concept Inc., Systagenix Wound Management Ltd., Smith and Nephew, 3M Health Care, Coloplast A/S, Derma Science Inc., Paul Hertman AG. The market entry trends of Indian wound care dressings are given in Fig 20.[175]

The key factors responsible for this growth is rising chronic disease, growth of the geriatric population, increase in healthcare expenditure, patient awareness, rising incidents of wound infections and growing demands in emergency cases. [175-176] Fig 21 details different type of dressings and their contribution in Indian market segment.

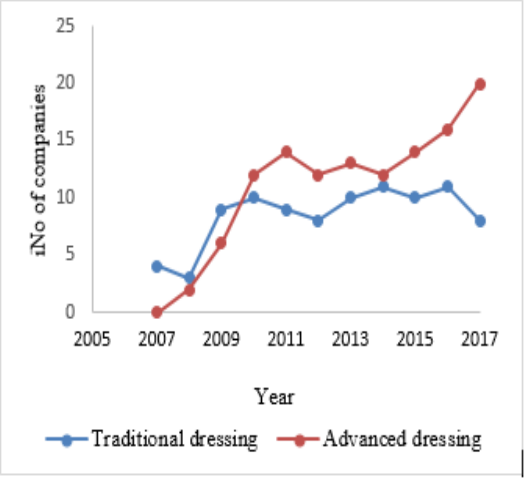


Fig.20. Market trends of wound care dressings

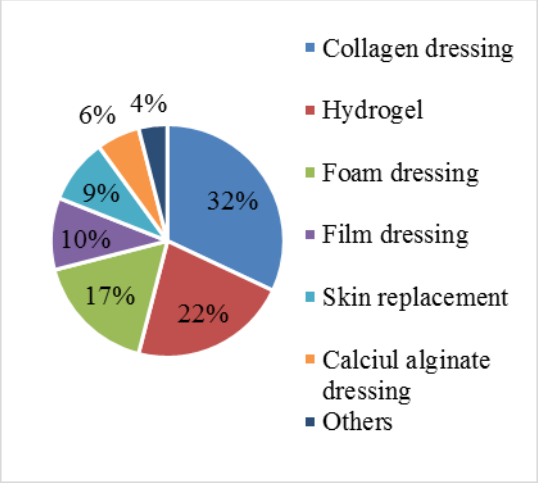


Fig.21. Wound care segments

The wound care market in India is still in its growth phase and is quite a fragmented one. It is characterized by the presence of several manufacturer's fierce

competition existing between them. These companies had a strong portfolio along with strong distribution system and promotion strategies that enable to keep hold their market shares.[176]

This chapter provides a complete analysis of import-export value of wound care and burn dressings in India. It helps in preparing growth strategies, knowledge about leading players, recent developments, business strategies and manufacturing status of the wound care and burn dressings in India.

5.2 Trend Analysis

The recent trend of burn care and treatment has shifted to a more comprehensive approach, which not only focuses on recovery from injury but also on improvement in long-term infection and form of the healed injury & quality of life. Owing to this trend, the demand for skin grafts and other skin substitutes for the treatment & management of acute injuries are expected to show an upward shift during the forecasted period. Increasing awareness level among people regarding various treatment options related to burn management is anticipated to boost the market growth. The rising disposable income and willingness to opt for new advanced wound care products, especially in case of patients affected with burns are contributing towards the increasing demand.[177]

As the well said saying goes "the necessity is a mother of invention". To feel the necessity of the subject commodity (wound and burn dressings) an import-export analysis is a prerequisite. To analyze the trends on expenditure on the wound and burn dressing the import-export data of the year 2008-2017 were collected from various market research analysis websites and import-export analysis is done on the same. The detailed analysis reveals that India is a growing market for wound and burn dressing and spending a lot of exchequer on importing the subject commodity.

5.3 Import and export analysis of dressings from 2008-2017

In India wound care and burn dressings are imported and exported with HS code-30061010 for wound dressings and 30059050 for burn dressings. A critical analysis of import-export market (Table 10) of wound care dressings was carried out for a period of last ten years i.e. 2008-2017.[178]

Table 10: Import-export data (2008-2017)

Year	Export value (approx.) (Lac INR)	Import value (approx.) (Lac INR)
2008	3295	2177
2009	1792	2369
2010	1642	2622
2011	2978	4361
2012	1744	4882
2013	2926	6005
2014	3260	6841
2015	3350	7576
2016	3514	7656
2017	3416	5842
Total	27917	50271

Fig 22 shows a comparative data of dressing imported and exported during these years. It shows that India is import dependant.[177-180]

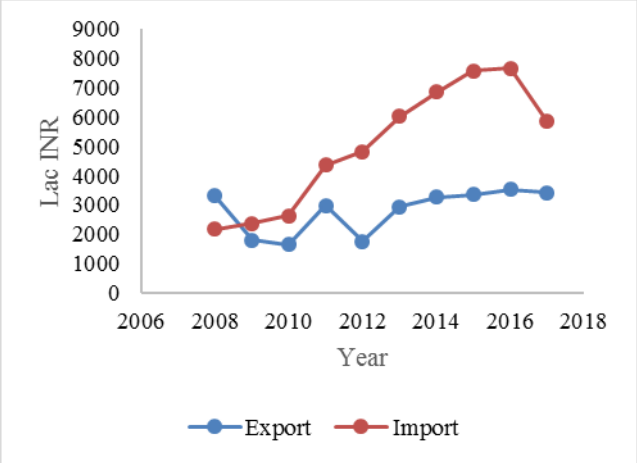


Fig.22. Import-export value 2008-2017

5.3.1 Export of dressing from India

Wound dressing export is averaged to approximately same from 2013 to 2017. India has seen a continuous rise in wound dressing export since 2013. It averaged approx. INR 2791 lac from 2008 to 2017 and it attained its all-time high of INR 3514 lac in 2016 and record low of INR 1642 lac in 2010 (Fig 22).

5.3.2 Import of dressing to India

According to the statistical data, the import of wound dressing fell in 2017 as compared to 2016. It is decreased by about INR1814, however, in last eight years; it follows the tendency to increase. Overall, India saw a rise of wound dressing import over the past 10 years. It averaged INR 50271 lac from 2008 to 2017 and it reached its all-time high of INR 7656 lac in 2016 and record low of about INR 2177 lac in 2008.

The import value was found high as compared to export as shown in Fig 22. The overall trend shows the import need of the country for these dressings.

5.4 Analysis of major imported-exported dressings from 2014-2016

The major dressings imported and exported during a period of 2014-2016 to India are discussed, especially for advanced dressings like:

i. Aquacel AG SCD DRS (foam dressing soaked in gel)
ii. Polypropylene optimized composite mesh

On the other hand, there is a sizeable quantity of low-cost burn and wound care dressings which are exported from India. The prominent amongst these dressings are:

i. Sterile surgical burn Tulle dressings
   Paraffin gauze dressing B.P (PARAGEL)
ii. Medicated wound dressings
   Chlorhexidine gauze dressing B.P. (BACTI GUARD)
   Povidone-Iodine non-adherent Tulle dressing (GLOBIDINE)
   Povidone-Iodine and Metronidazole non-adherent Tulle dressing (POVI PLUS)
   Triple antibiotic Tulle Gras dressing-sterile (POLYBACIN)

The detailed analyses are as follows:

5.4.1 Major imported-exported dressings

5.4.1.1 Major imported dressings

From 2014 to 2016 the overall yearly import never came down below INR 980 lac (Fig 23) that itself reveals that there is a huge import of wound and burn dressings and relatively higher consumption over the production within the country. The import has touched the peak of INR1718 Lac in 2014 and INR 1533 Lac in 2016. The average import comes out to be INR 1410 Lac which anyhow attracts the exporters of the commodity to expand their business in India. But for Indian self-reliance point of view, this trend needs to be encountered with the local production which can compete for the subject commodity at the international market. For that India need to have advanced dressing which should be of a better quality on all surgical parameters and obviously of low cost.[181]

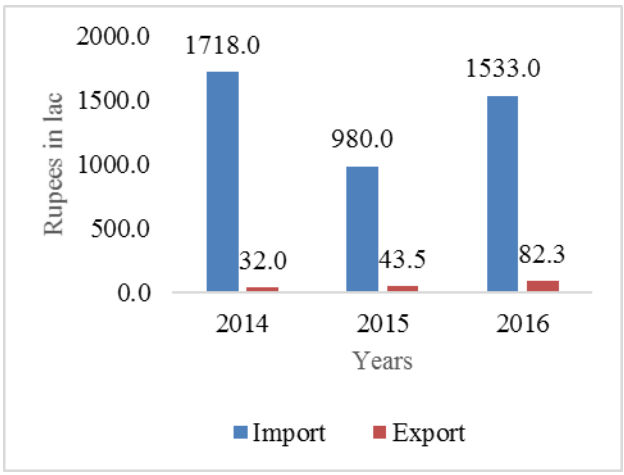


Fig. 23. Import-export of major dressings

Table11: Major imported dressings in 2014

Description	Qty (Nos)	Value (INR Lac)
Composite mesh	9259	681.83
Fenestrated drape	182	1.63
Foam dressing soaked in gel	64111	1022.16
Blanket soaked in gel	59	12.12

5.4.2 Imports by item quantity and value: 2014

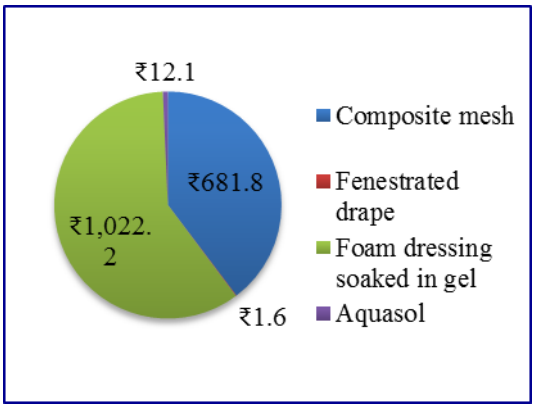


Fig.24. Import value (INR lac) 2014

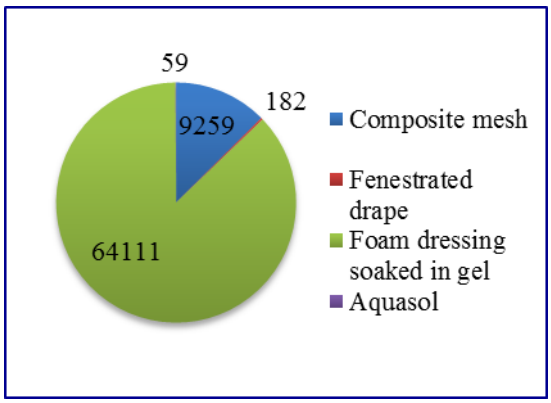


Fig.25. Import quantity 2014

From Fig 24 and 25 it is revealed that Composite Mesh and Aquasol dressings (dressings soaked in gel) were the highest imported items by quantity as well as by value in the year 2014. For ready reference the numerical data is tabulated in Table 11. From Fig 26 and 27, it is evident that the composite mesh and dressing soaked in gel (Aquasol) has a major share in terms of numbers as well as in value. The numerical data is tabulated as in Table 12.

5.4.3 Imports by item quantity and value: 2015

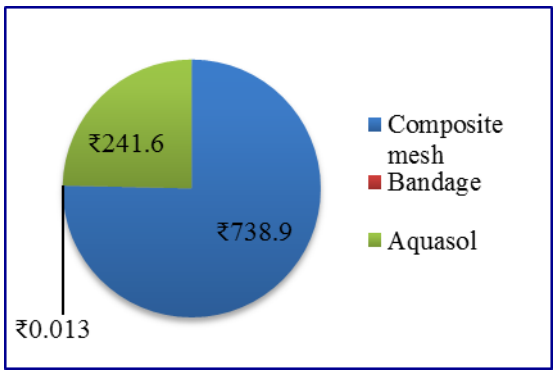


Fig.26. Import Value (INR lac) 2015

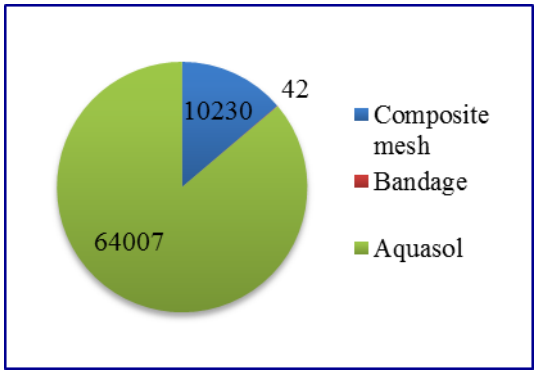


Fig.27. Import Quantity 2015

Table 12: Major imported dressings in 2015

Description	Quantity (Nos)	Value (INR Lac)
Composite mesh	10230	738.91
Bandage	42	0.013
Foam dressing soaked in gel	64007	241.62

5.4.4 Imports by item quantity and value: 2016

Fig 28 and Fig 29 manifest that composite mesh is dominating in the import of the year 2016. The dressing soaked in gel (Aquasol) takes the second position. Quantity vis-a-vis cost data for the year 2016 is tabulated in Table 13. Data reveals 100% jump in the import of composite mesh. Blankets soaked in the gel was the other significant import this year but overall composite mesh and dressing soaked in the gel have again dominated in import market of the subject commodity. In all three years period, these two type of dressing flipping in the review of imports of dressing in India. That ignites for a country's think tank to take the challenge, to curb this trend to control the outflow of foreign currency.[182]

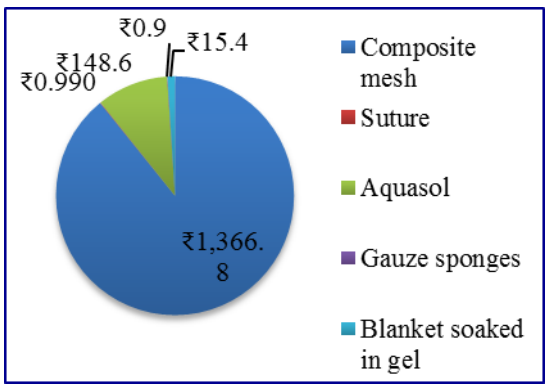


Fig.28. Import Value (INR lac) 2016

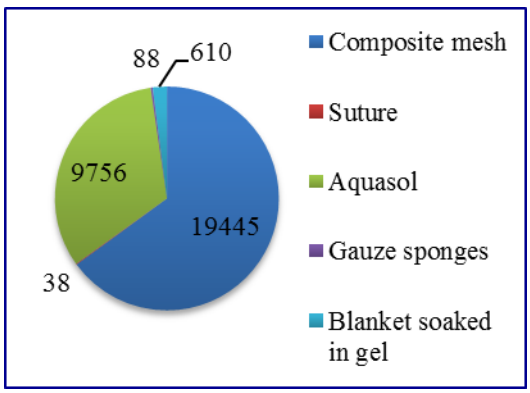


Fig.29. Import Quantity 2016

Table 13: Major imported dressings in 2016

Description	Quantity (Nos)	Value (INR Lac)
Composite mesh	19445	1366.75
Suture	38	0.990
Foam dressing soaked in gel	9756	148.62
Gauze sponges	88	0.89
Blanket soaked in gel	610	15.38

5.4.5 Month wise import in 2014

To know the in-depth trend of the import of the subject commodity the month wise data is plotted from the year 2014 till the year 2016. The year 2014 has the highest import of burn and wound dressings in India in last few years which contributed approx. 1718 Lac of INR to the total import of the nation. Fig 30 shows the month wise import cost of the subject commodity for the year 2014. The year has seen the import hikes in the month of January, February, September and October.[180-182]

5.4.6 Month wise import in 2015

As depicted in Fig 31, the import continues to grow for the first quarter of the year and then a sudden dip was observed in the month of May onwards and again a knee-jerk boost was observed in the month of September and then the trend slowed down for the rest of the year. Overall a significant dip has observed in 2015 and that almost 50% of the year 2014 imports which contributed approximately INR 980 Lac in the total import of the country.[183]

5.4.7 Month wise import in 2016

A favorable slowing down trend was started from the normal import data of 135.8 Lac but a sudden rise in the trend was observed from July till October and then nil import was there for the rest of the year. This year once again saw imports growing rapidly. Total imports touched as high as 1533 Lac this year compared to <10 crores in 2015 (Fig 32).

5.4.8 Port wise import in 2014

To know the contribution of different countries in the interested commodity imports, it is prerequisite to analyze the port wise import data. For the same purpose, the data from the year 2014 to 2016 was drawn on the Pi-charts to know who is contributing how much in our imports of the interested commodity. In the year 2014, France and USA remain the largest suppliers of burn and wound dressings. The UK and Costa Rica also played an important key role in import contribution (Fig 33).

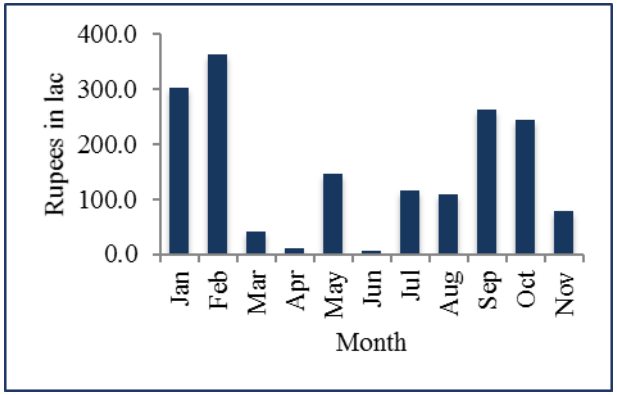


Fig.30. Import data in months 2014

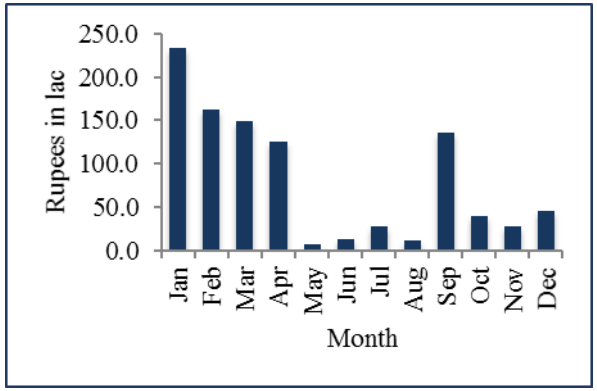


Fig. 31. Import data in months 2015

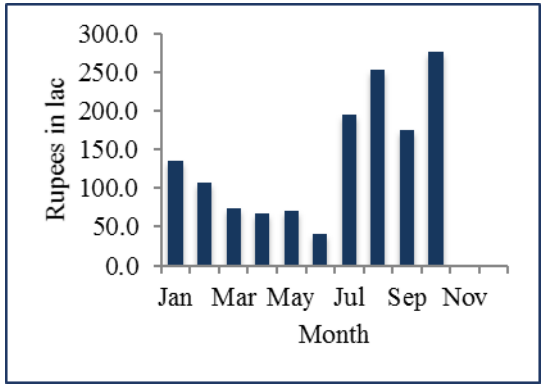


Fig.32. Import data in months 2016

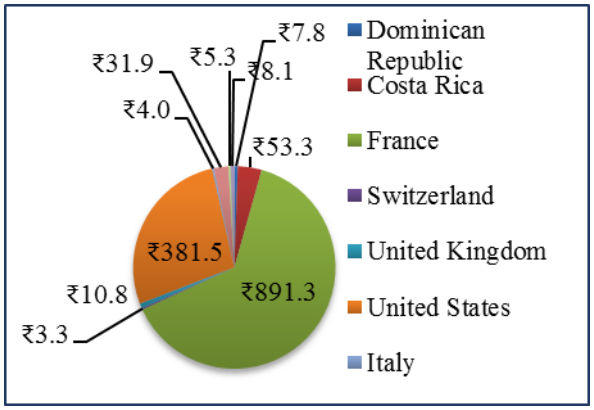


Fig.33. Port wise import 2014

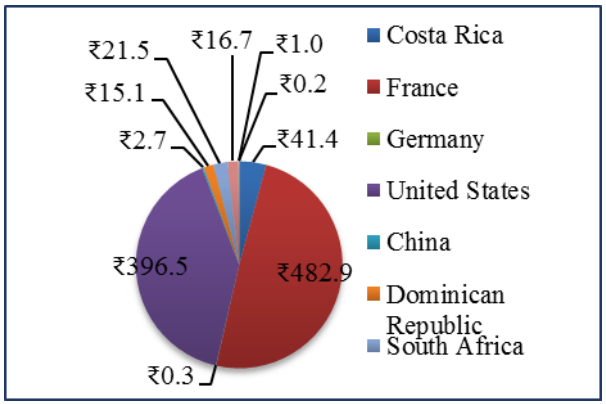


Fig.34. Port wise import 2015

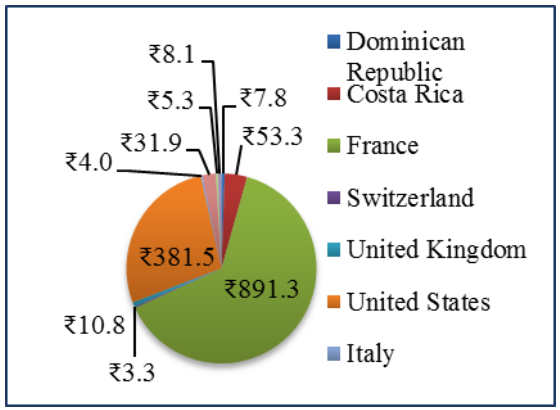


Fig.35. Port wise import 2016

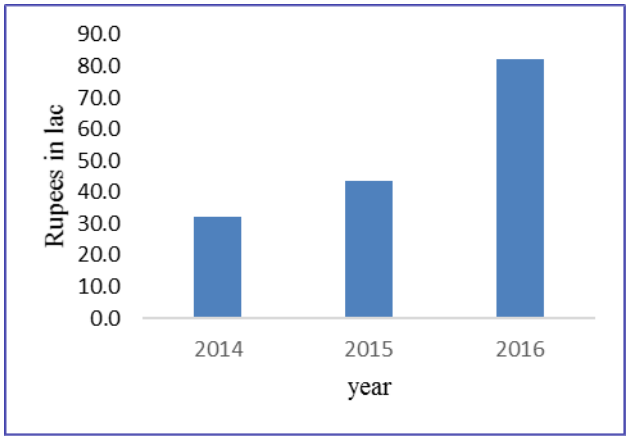
5.4.9 Port wise Import in 2015

Though the overall imports dipped this year in terms of quantity as well as amount yet France and the United States were again the major suppliers during this year (Fig 34).

5.4.10 Port wise Import in 2016

France and USA continue to be the largest suppliers with greater than 90% share of total imports of the subject commodity (Fig35). Both countries dominated in the field of dressings have taken the lion's share of the import in all three years.[181, 184-185]

5.5.1 Major exported dressings



*YOY – Year on year

Fig.36. Major exported dressing 2014-2016

The export of a commodity by a country shows the domination of the country in the international market of that commodity. Obviously, export gives earning to the nation and proves hike to its Gross Domestic Product (GDP) and Gross National Product (GNP). Ideally per commodity country should be in the positive side; it means export should always be more than the import. Before putting import and export on the same platform for comparison and conclusion, let us discuss the exports of the commodity at a length as we have discussed imports in section 5.4 and its subsection in the chapter. Data from the year 2014 till 2016 is taken for the analysis as have done for the import analysis.

Exports of sterile surgical burn Tulle dressings (Paraffin gauze dressing) and medicated wound dressings like (Sterile Biogras Chlorhixidine gauze dressings) have seen a steady growth in the three years. Though there is a hike in the trend but the amount at which the hike is observed is very less as compared to the import. Still, hike in the export shows the growth of the industry for that commodity. Starting from

32 Lac in the year 2014 the growth reached at 82.3 lac in 2016, which shows a good sign but the overall amount still remains at a very low level and contributes negligibly in the overall export of the country (Fig 23).[185]

5.5.2 Exports by item quantity and value: 2014

From the Fig 37 and 38 it is evident that in the year 2014 the Gauze and Tully grass dressings are dominating in the export field. Almost 95% of the export of burn and wound dressings in the year 2014 was Sterile Paraffin Gauze dressings. The quantity and value wise data is tabulated below in Table 14.

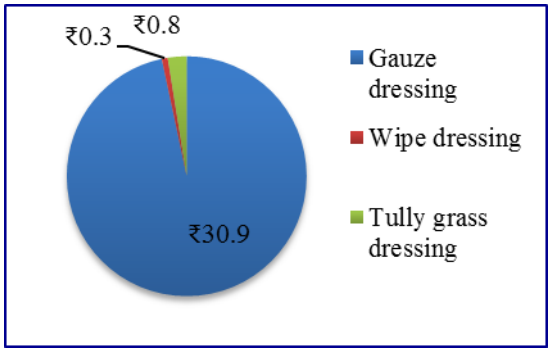


Fig.37. Export value (INR lac) 2014

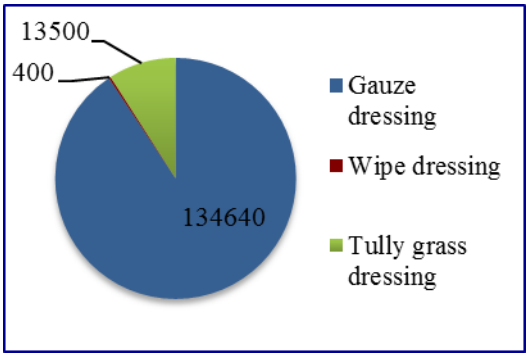


Fig.38. Export quantity 2014

Table 14: Major exported dressings in 2014

Description	Quantity	Value (INR Lac)
Gauze Dressing	134640	30.94
Wipe	400	0.26
Tully Grass Dressing	13500	0.81

5.5.3 Exports by item quantity and value: 2015

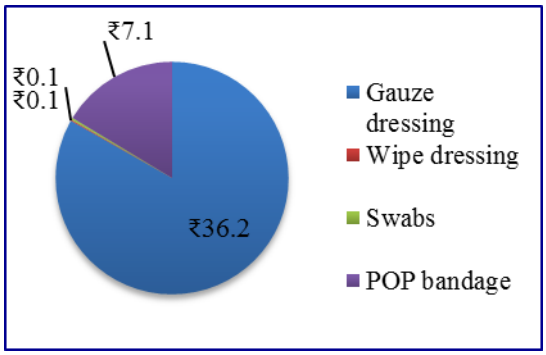


Fig.39. Export value (INR lac) 2015

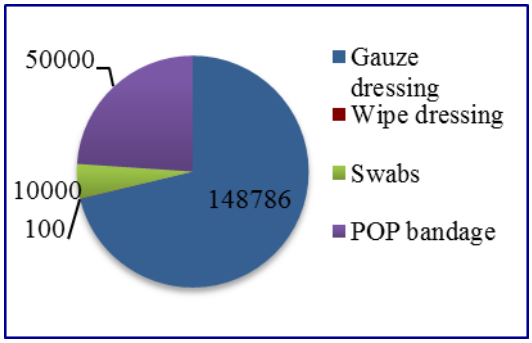


Fig.40. Export quantity 2015

Above plotted Fig 39 and 40 depicts that gauze dressings and POP bandages have taken the major portion of the subject commodity in exports. In specific to type; gauze dressing's export saw a steady rise in comparison to the year 2014 exports while POP

bandage was much in demand in other emerging markets like in Bangladesh. The quantity and value wise data is tabulated below in Table 15 for ready reference.[186]

Table 15 : Major exported dressings in 2015

Description	Quantity	Value (INR Lac)
Gauze dressing	148786	36.19
Wipe dressing	100	0.07
Swabs	10000	0.13
POP bandage	50000	7.10

5.4.4 Exports by item quantity and value: 2016

From the Fig 41 and 42 it is evident that gauze dressing has wiped the market in the year 2016. Sterile Paraffin Gauze dressing's exports saw a whopping rise from INR 36.19 lac in the year 2015 to INR 81.6 lac in the year 2016.[186] Export data in quantity and market value is tabulated below Table 16 for ready reference.

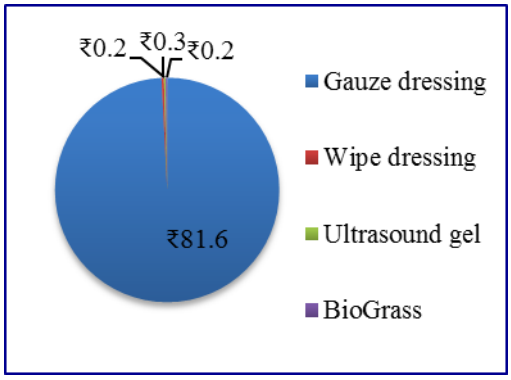


Fig.41. Export value (INR lac) 2016

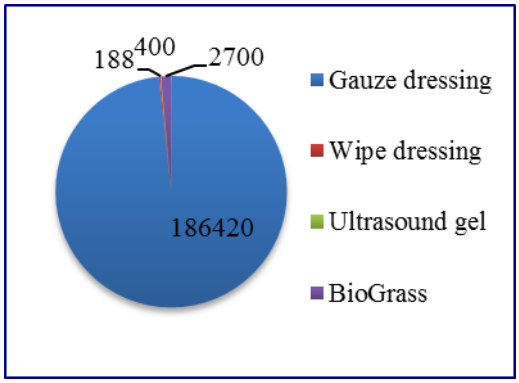


Fig.42. Export quantity 2016

Table 16: Major exported dressings in 2016

Description	Quantity	Value (INR Lac)
Gauze dressing	186420	81.60
Wipe dressing	400	0.28
Ultrasound gel	188	0.21
Biograss	2700	0.17

5.5.5 Month wise export in 2014

To know the in-depth trend of the export of the subject commodity the month wise data is plotted from the year 2014 till the year 2016 as have done for the imports. Subject commodity (burn and wound dressing) contributed 32 lac of INR to the total export of the nation. Fig 43 shows the month wise export of the subject commodity for the year 2014. The year has seen the export hikes in the month of January and July.

5.5.6 Month wise export in 2015

As depicted in Fig 44, the export picked a knee-jerk in Jan, Jun and Oct. Overall a significant hike has observed in 2015 and that almost 50% of the year 2014 exports which contributed approximately INR 43.5 Lac in the total export of the country. Although, this hike shows the demand of the product yet the total value of 43.5 lakh is insignificant. Therefore, commenting on this aspect is not appropriate.

5.5.7 Month wise export in 2016

Fig 45 depicts the exports were 300% higher in June 2016 as compared to previous year. The overall exports also went nearly 200% of the previous year. A hike is always favorable for the export for our subject commodity. The trend is continuously rising in the years of assessment. But the percentage and the total asset value is very less in the international market.

5.5.8 Port wise export in 2014

To know the gain from the different countries in the interested commodity exports, it is prerequisite to analyze the port wise export data. For the same purpose the data from year 2014 to 2016 was drawn on the Pi-charts to know who is contributing how much in our exports of the interested commodity. In year 2014 Bahrain, Bangladesh and Sri Lanka remain the largest importers of burn and wound dressings from India. Percentage wise 70% exports in this year were to emerging economies like Bangladesh, Srilanka and Bahrain. UAE also has played a key role in export contribution (Fig 46).

5.5.9 Port wise export in 2015

Though the overall export hiked by approx. 50% by this year in terms of quantity as well as amount, yet the overall amount remains at the lower value. Bangladesh continues to be one of the largest importers of the subject commodity from India. Turkey also emerged as a new player for our commodity (Fig 47).

5.5.10 Port wise export in 2016

Turkey emerged as the largest buyers with greater than 70% share of total exports of the subject commodity from India. Overall in last two years Turkey has shown a lot of interest to import of these dressings from India (Fig 48).[184-186]

The above wound care dressings report provides details about products, consumption value and volume of import-export in India. It also clearly shows the demand growth

of such imported products in India and also the demand growth of low-cost Indian products in other emerging economies. Wound care dressings report also provides a detailed analysis of the export market structure along with the specific details of wound care products being exported from India. It includes country-level analysis of the market with respect to the market size from import and export perspective. In addition to the above, this report also provides profiling of key products in demand in India; comprehensively analysing their usage patterns month on month basis and drawing a comparative landscape for global suppliers of such products.

The Indian wound care market is dominated by international players, with Johnson & Johnson (India) and Beiersdorf India together accounting for a highly dominant value share in 2017. From the import-export analysis, it is evident that the import has to dominate the export of the subject commodity. For self-reliance on the medical devices like burn and wound care dressing, our country should give a push to the production. The motivation factor of the producers to be boosted for the subject commodity. A sequential guideline should be available that boosts the product from innovative phase till production phase and finally end product should compete in international market.

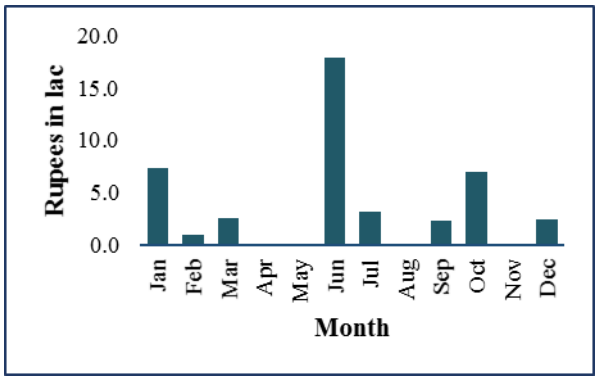


Fig.43. Export data in months 2014

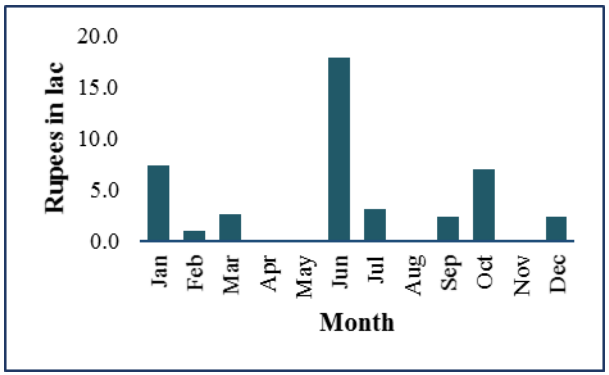


Fig.44. Export data in months 2015

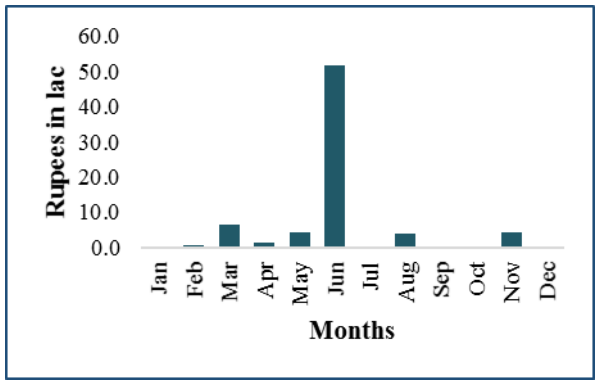


Fig.45. Export data in months 2016

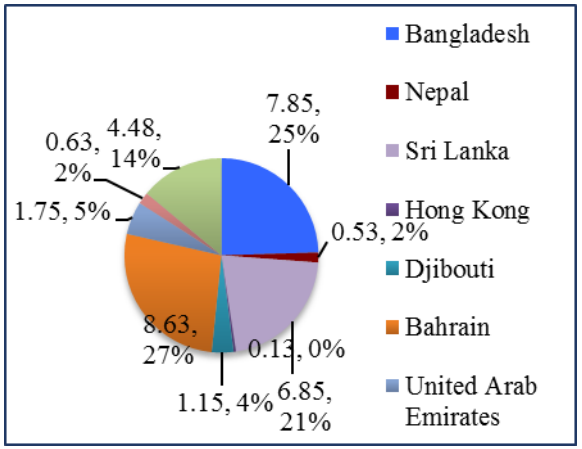


Fig.46. Port wise export 2014

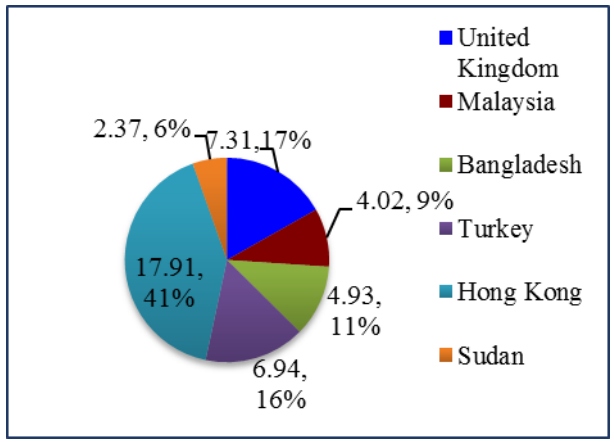


Fig.47. Port wise Export 2015

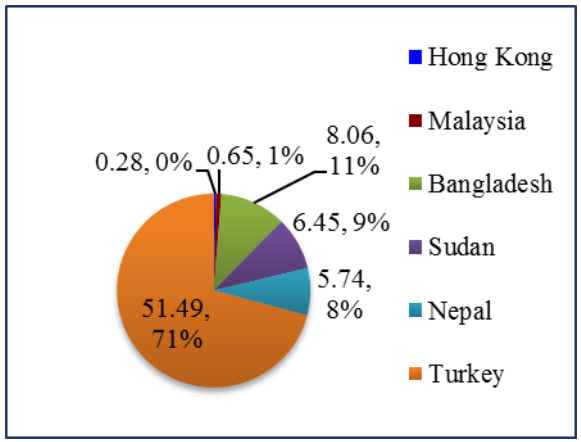


Fig.48. Port wise export 2016

CHAPTER-6

6. SURVEY OF PHYSICIANS AND PHARMACISTS

From the import-export study of burn and wound care dressings (Chapter-5), it is very much clear that import of the dressing is dominating over the exports and producing the deficit in Balance of Payments (BOP).[187] Exports are not touching even a one crore value which means there is no export per say for the commodity. That directly states that the country does not stand anywhere in the market of the concern commodity. It is a matter of concern for all. Apart from this, to know the ground reality of the requirement of our subject commodity (burn and wound care dressings), there are many questions (Annexure-1) which need to be answered, which will lead to the actual requirement of the advanced dressing. To know the answers of most of the dressing related questions, a questionnaire was made and the answers were requested form 50 physicians and 100 pharmacists. The entire survey is endorsed in this chapter. The raw data are kept with the student of this thesis as the confidentiality of data providers was promised while requesting the data. All data were provided under the seal of the physician and pharmacists. Analysis of this report supports the need of advanced dressing in India.

6.1 Sample size calculation

The sample size is calculated on the basis of margin of error or confidence intervals. The confidence level of 95% with margin of error 10% is set for the analysis. The crucial number is the population size, N.

Sample Size (N) = $(z^2 \times p\ (1\text{-}p)/e^2)/(1 + (z^2 \times p\ (1\text{-}p)/e^2N))$

Where, z is the number of standard deviations a given proportion is away from the mean (which is determined by the confidence level desired), p is the percentage of positive response, e is the margin of error, and N is the population size.

6.1.1 Sample size calculation for survey of physicians

The actual number of physicians surveyed is 50, about half of the required sample size. A reduced sample size basically widens the margin of error. However, the actual margin of error is also dependent on the actual proportion of the positive findings. The effect of the decreased sample size in the current study is analysed, on the margin of error around the actual findings.

Table 17: Calculation of margin of error

Parameter	Response (%)	Calculated margin of error
Infection as cause of death	46	13.75
Either infection or lack of advanced dressing as cause of death	100*	2.74
Current practices rated as difficult	40	13.51
1 month as the likely duration of hospital stay	68.8	12.78
Advanced dressings can prevent death due to infection	98	3.86

* For the purpose of calculation the response of 100% is entered as 99%.

As we can see, at higher percentages of the positive findings, the margin of error actually decreases. Even in the middle range of findings such as 40-70%, there is only a small widening of the margin of error. Therefore, a small sample of size 50 physician was selected.

6.1.2 Sample size calculation for survey of pharmacists

The sample size of the pharmacist was taken as 100, based on their availability and nature of products they are dealing. Pharmacist handling especially the surgical products were found to be less and some of them denied to take part in the survey study due to fear of loss of information from their shops. Therefore, pharmacist's shops near to wound and burn care hospitals was preferred.

6.2 Survey of physicians

6.2.1 Most common cause of death due to burn

From the Table 18, it is concluded that, both infection and non-availability of advance dressing leads to death, where 46% of the respondents have agreed to it. Further, 46% of the people have also revealed that infection is the most common cause of death, when the burn is not treated well. Further 8% responded that infection caused due to non-availability of dressings. Both main parameters have equal area in the pie chart drawn below in Fig 49.

6.2.2 Current practice to treat burn patients on 1-5 scale

The current treatment practices were observed as easy, moderate, difficult and very difficult on a scale of 1 to 5 (Table 19). The maximum practice is moderate (42%) followed by difficult (40%).

Table 18: Which is the most common cause of death due to burn

	Reasons	Frequency	Response (%)	Valid %	Cumulative %
	Infection	23	46.0	46.0	46.0
	Non-availability of dressing	4	8.0	8.0	54.0
	Both	23	46.0	46.0	100.0
Total		50	100.0	100.0	

The same is represented in the pie chart (Fig 50) for the highest and second highest percentage in red and green color respectively. Further, the lowest percentage response to treat burnt patients is easy (6%) and 12% reported as very difficult. Overall it is concluded that presently, physicians are considering the treatment available for burn and wound patients is moderate to difficult.

Table 19: Current practice to treat burn patient's ratings on a scale of 1-5

	Type	Frequency	Response (%)	Valid %	Cumulative %
	Easy	3	6.0	6.0	6.0
	Moderate	21	42.0	42.0	48.0
	Difficult	20	40.0	40.0	88.0
	Very difficult	6	12.0	12.0	100.0
Total		50	100.0	100.0	

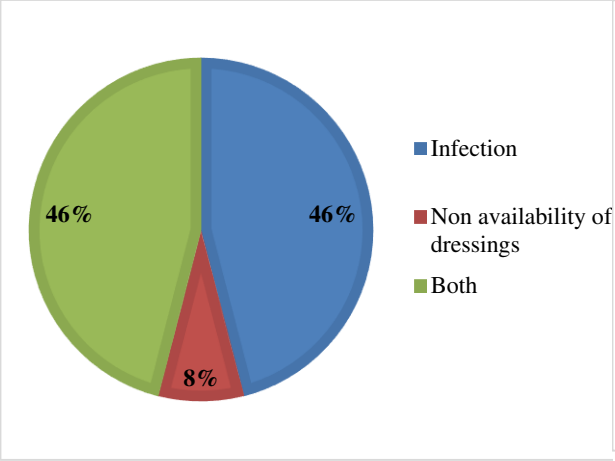


Fig.49. Most common cause of death due to burn

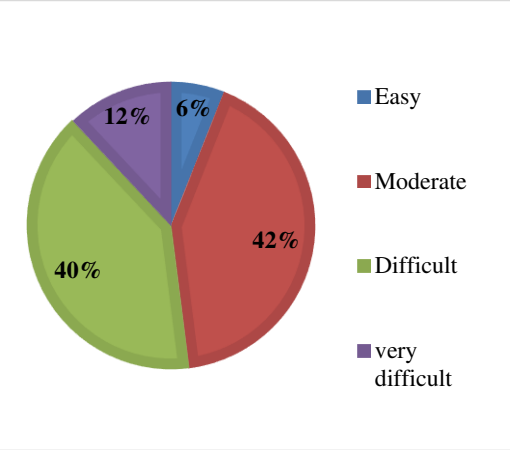


Fig.50. Current practices to treat burnt patients rating on a scale of 1to 5

6.2.3 Most likely duration of patient hospitalization in burn case

From the Table 20, we can conclude that 33 (66.0%) of response for 1 months is the most likely duration for patient hospitalization in burn case. It is also represented in the pie chart (Fig 51) in blue. Further, from the Table (20) it is well understood that as the duration for the patient hospitalization in burn cases increases the frequency along with the response percentage decreases. It is well depicted in the pie chart as red and green area for the 14 (28%) and 1 (2%) months duration of hospitalization of patients

in burn cases respectively. From the given table it can also be found that there is a missing system component which shows a percent response of 4% when the data among the respondents is recorded based on the duration of patient hospitalization in burn cases.

Table 20: Most likely duration of patient hospitalization in burn case

	Patient hospitalization	Frequency	Response (%)	Valid %	Cumulative %
	1 month	33	66.0	68.8	68.8
	3 months	14	28.0	29.2	97.9
	6 months	1	2.0	2.1	100.0
No response		2	4.0	100.0	
Total		50	100.0		

6.2.4 The common frequency to change the dressing in a burnt patient

From the Table 21, it is concluded that 30 (60%) of response for 18-24 hours are the most common frequency followed 11(22%) obtained to change the dressing in 8-10 hours in a burnt patient. The time period between 4-6 hours has 5 (10%) of responses which is shown in blue in the pie chart (Fig 52) followed by the lowest time period covered by others in the table with 2 (4%) of response shown in violet in the below-mentioned pie chart. From the data provided (Table 21) it can be interpreted that patients recovering from burn injuries in hospitals would require frequent dressing of the wounds for better and faster recovery.

Table 21: Common frequency of change of dressings during treatment

	Change of dressings	Response	Response (%)	Valid %	Cumulative %
	4-6 hours	5	10.0	10.4	10.4
	8-10 hours	11	22.0	22.9	33.3
	18-24 hours	30	60.0	62.5	95.8
	Others	2	4.0	4.2	100.0
Total		48	96.0	100.0	
No response		2	4.0		
Total		50	100.0		

6.2.5 Most common problem associated with use of advanced dressing

From the Table 22, it can be concluded that cost is the most common problem associated with the use of advanced dressing. From the data collected it can be interpreted that cost has 60% of the resultant response (Table 22) which is also represented in blue in the given pie chart (Fig 53). Further, the response found to decrease with availability (30%) and size of dressing (10%) respectively among the patients. Therefore, the decrease in response is interpreted in green and red color in the pie chart respectively.

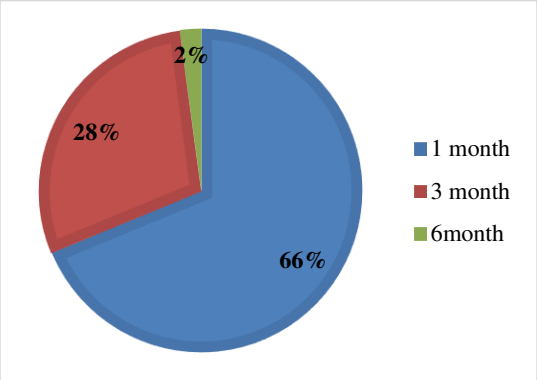


Fig.51. Duration of patient hospitalization in burn case

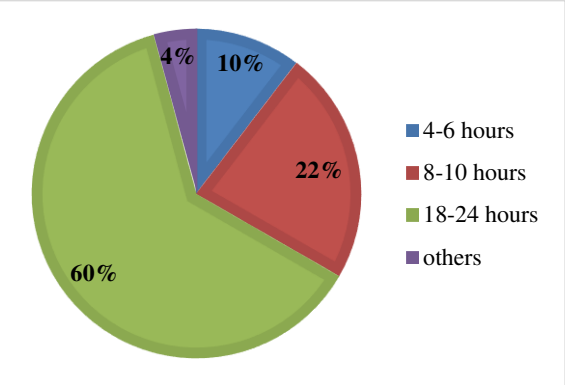


Fig.52. Most common frequency to change the dressings of a burn patient

Table 22: Most common problem associated with the use of advanced dressings

	Common problem	Frequency	Response (%)	Valid %	Cumulative %
	Cost	30	60.0	60.0	60.0
	Size of dressing	5	10.0	10.0	70.0
	Availability	15	30.0	30.0	100.0
Total	Total	50	100.0	100.0	

6.2.6 Most common challenge to treat patient with open wound treatment

From the Table 23, it is concluded that 35 (70%) of the response of infection control is the most common challenge in treating patients with open wound treatment. It is also represented in red color in the pie chart (Fig 54). Again, we found from the table that skin loss due to peel and dressing change has 24% and 6% of response for the most common challenges to treat patients with open wound consecutively. In the pie chart, the colored areas in green and blue (Fig 54) show the percentage response for 24% and 6% respectively. The interpretation suggests that in burnt cases, there is a high risk of death due to infections on an open wound and it is again considered as one of the top challenging and tough treatment practice in medical science.

Table 23: Most common challenge to treat wound and burn patients

	Reasons	Frequency	Response %	Valid %	Cumulative %
	Dressing Change	3	6.0	6.0	6.0
	Infection Control	35	70.0	70.0	76.0
	Skin loss due to peel off	12	24.0	24.0	100.0
Total		50	100.0	100.0	

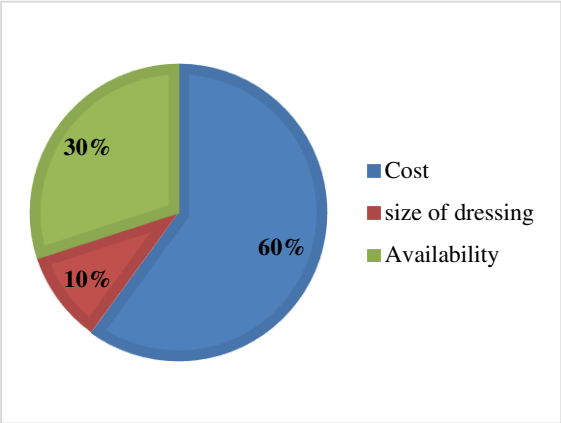


Fig.53. Most common problem associated with the use of advanced dressings

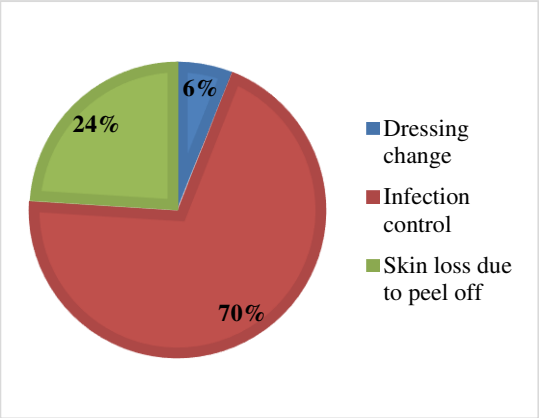


Fig.54. Most common challenge to treat patient with open wound treatment

6.2.7 Advanced dressing can prevent death due to infection

From the Table 24, it is concluded that 49 (98%) of "Yes" response is for advanced dressings to prevent death due to infection. It is also represented in blue in the given pie chart. And there is only 2% of "No" response which is very minimum and is represented in red colored area in the pie chart (Fig 55). As the respondents have provided a maximum positive response in support of the application of advanced dressing that can prevent death due to infection among patients with a very minimum response against the statement, it could be inferred that there is an urgent need for better medical equipment and tools in the hospitals to prevent death among patients due to burn injuries.

Table 24: Advanced dressings can prevent death due to infection

	Options	Frequency	Response %	Valid %	Cumulative %
	Yes	49	98.0	98.0	98.0
	No	1	2.0	2.0	100.0
Total		50	100.0	100.0	

6.2.8 Most preferred advanced dressing in burn and wound care treatment

From the Table 25, it is concluded that Bactigras with 23 (46.0%) is the most preferred advanced dressing among the respondents followed by cellulosic dressings with 17(34%), alginate dressing 5 (10%) and primapore 2 (4%) respectively. The preferred advanced dressings are well depicted in the form of the pie chart as blue, violet, green and red colored areas respectively (Fig 56).

Table 25: Most preferred advanced dressings used in burns and wound care

	Preferred dressings	Frequency	Response %	Valid %	Cumulative %
Response	Bactigras	23	46.0	48.9	48.9
	Primapore	2	4.0	4.3	53.2
	Alginate dressings	5	10.0	10.6	63.8
	Cellulosic dressings	17	34.0	36.2	100.0
	Total	47	94.0	100.0	
No Response		3	6.0		
Total		50	100.0		

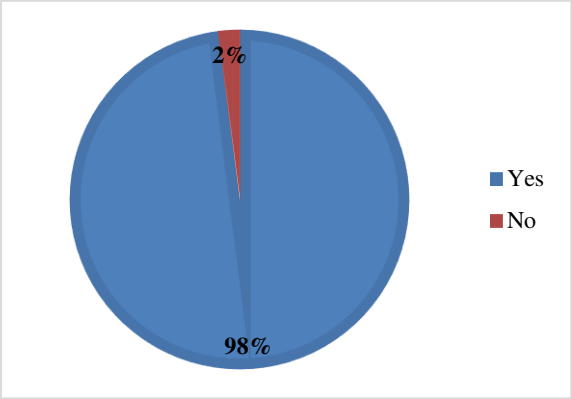


Fig.55. Advanced dressings to prevent death due to infection

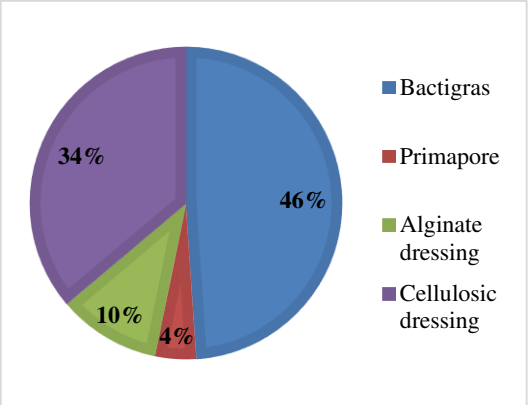


Fig.56. Most preferred advanced dressing

6.2.9 Dressing procedure for burn and wound patient

The respondents were asked regarding the way in which they dress the burn and wound patients, to which most of the respondents replied that they use paraffin gauze with SSD ointment. It was found that (Fig 57) the respondents also used bactigrass dressing, sterile dressing and antibiotic cream *etc.* Most of the respondents agreed (Table 26) that they dressed the burn or wound daily with ointment and creams (Neosporin/Fucidin/Silverx). It represents that there are still use of old traditional dressings.

Table 26 : Dressings currently in use during burn and wound care treatment

Type of dressings	Frequency	Response %	Valid %	Cumulative %
Paraffin gauze + SSD	25	50	50	74
Advanced dressing - bactigrass and cellulose dressing	12	24	24	94
Others- ointments and creams	10	20	20	100
Not replied	6	6	6	

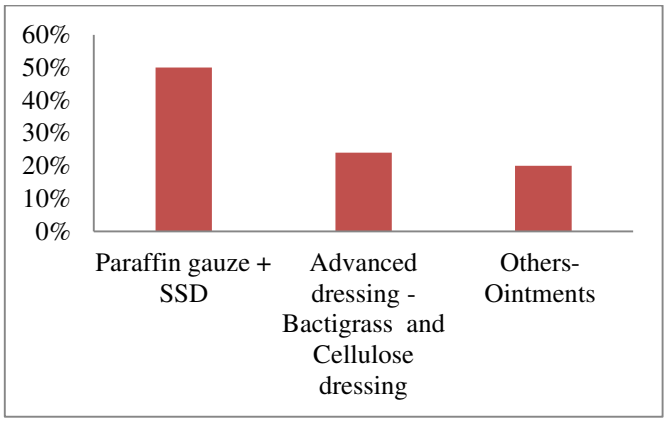


Fig.57. Dressings currently in use during burn and wound care treatment

6.2.10. Expectations from health authority of India

Most of the respondents expected the Indian health authorities to provide less costly advanced dressings which are highly effective. Further, they expect the instigation of awareness programs to assist people in understanding the requirement of burn injury management. Further, advanced technology and more efficient methods of treatment should be used to ensure adequate treatment of the patient. Few respondents (Table 27) suggested to prevent the indiscriminate use of antibiotics which is a major cause of drug-resistant organisms in burn and wound injuries (Fig 58).

Table 27: Physician's expectation from health authority of India

Expectations	Response	Valid %	Cumulative %
Cost should be reduced	15	30	30
Improve hygiene & increase awareness	6	12	42
Increase burn units & transportation to nearest medical centre	5	10	52
Better sterilization of dressings, maintenance of aseptic area	7	14	66
Size of dressings should be enhanced	4	8	74
Prevent indiscriminate use of antibiotics	4	8	82
Not responded	2	4	86
Increase the availability of advanced dressings	7	14	100

6.3 Chi – square test on physician data

Chi-square test of independence determines whether there is an association between categorical variables or whether the variables are independent or related. It is a non-parametric test. It is done to understand how an observed distribution is due to the chance. It is designed to analyze the categorical data which refers that the data has been counted and divided into categories.

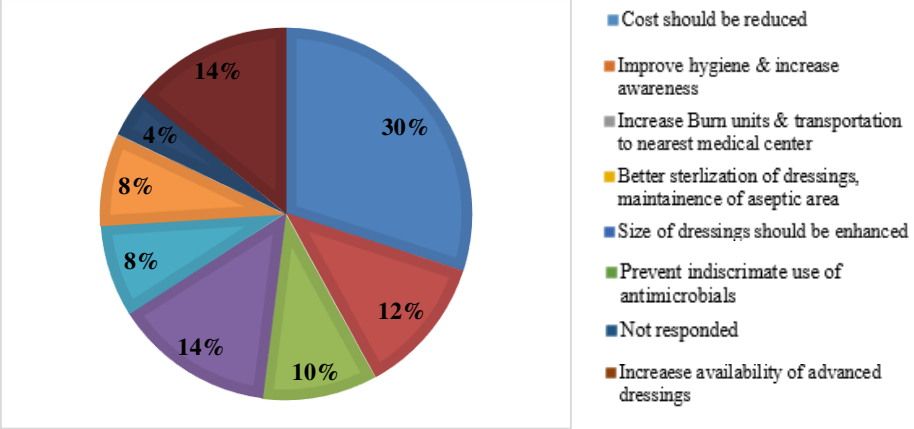


Fig. 58. Expectation of physicians from Health Authority of India

This test utilizes a contingency table to analyses the data *i.e.* is called as crosstab in which data is arranged according to categorical variables. One variable is represented in row and other in Column. The Chi-square is conducted using SPSS software to find out the relation between two variables. Three hypotheses were derived based on analyzing the data as given in Table 28, 30 and 32.

To create a crosstab and perform a chi-square test of independence: click analyze> descriptive statics>crosstab in SPSS software. Enter the variables in row and column. Open the statics window and check on Chi-square box. Check the crosstab cell display to control the displayed output in the cells. Set the statistics column for expected observed and expected observations.[188]

Criteria for the acceptance and rejection of hypothesis

If the p-value is below 0.05 then we reject the null hypothesis and if the p-value is above 0.05 then we accept the null hypothesis.[189]

6.3.1 Hypothesis-1: The Association between the most cause of death due to burn and the common challenge to treat patient with open wound treatment

Table 28: Hypotheis-1 Most common challenge to treat burn and wound patients

What is the most common challenge to treat patient with open wound treatment?					
		Dressing change	Infection control	Skin loss due to peel off	Total
Reasons	Infection	1	21	1	23
	Non-availability of advance dressing	0	4	0	4
	Both	2	10	11	23
Total		3	35	12	50

Table 29: Chi-Square tests on hypothesis-1

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	15.041[a]	4	0.005
Likelihood ratio	17.081	4	0.002
Linear-by-linear association	6.449	1	0.011
Number of valid cases	50		

a. 5 cells (55.6%) have expected count less than 5. The minimum expected count is 0.24.

Interpretation:

The value of chi-square test is 15.041 with df = 4 having p = 0.005 < 0.05 of significance level. It means there is an association between the most cause of death due to burn and the common challenge to treat patient with open wound treatment. The Null hypothesis is rejected here as there is significance relation found between the two statements.

6.3.2 Hypothesis-2: An Association between the most cause of death due to burn and advance dressing can prevent death due to infection

Table 30: Hypothesis-2 Advanced dressing can prevent death due to infection

Do you think advanced dressings can prevent death due to infection?				Total
		Yes	No	
Reasons	Infection	23	0	23
	Non-availability of advance dressings	4	0	4
	Both	22	1	23
Total		49	1	50

Table 31: Chi-Square test on hypothesis-2

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.198[a]	2	0.020
Likelihood ratio	1.577	2	0.003
Linear-by-linear association	1.087	1	0.020
Number of valid cases	50		

a. 4 cells (66.7%) have expected count less than 5. The minimum expected count is 0.043.

Interpretation:

The value of chi-square test is 1.198 with df = 2 and have p =0.043 < 0.05, significance level. From the values it could be interpreted that there is association between the most cause of death due to burn and advance dressing can prevent death due to infection. Here, the null hypothesis is rejected and the statement given is to be accepted and is considered to be true.

6.3.3 Hypothesis-3: An Association between the most cause of death due to burn and the most preferred advanced dressing.

Table 32: Hypothesis-3 Most preferred advanced dressing in wound care and burn treatment

Which is the most preferred advanced dressing						Total
Bactigras		1	2	3	4	
Primapore	1.0	7	2	3	9	21
Alginate dressings	2.0	1	0	0	2	3
Cellulosic dressings	3.0	15	0	2	6	23
Total		23	2	5	17	47

(66.7%) have expected count less than 5. The minimum expected count is 0.13

Table 33: Chi-square test on hypothesis 3

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	7.257[a]	6	0.298
Likelihood Ratio	8.235	6	0.221
Linear-by-Linear Association	2.844	1	0.092
Number of Valid Cases	47		

Interpretation:

The value of chi-square test is 7.257 with df = 6 having p value = 0.298 > 0.05, significance level. It means there is no any association between the most cause of death due to burn and the most preferred advanced dressings. The null hypothesis made is accepted here.

6.4 Key points evaluated from survey with pharmacists

The market survey has been carried out to analyses the availability of advanced dressings currently used in hospitals for burn and wound care. Major hospitals *e.g.* in Delhi (AIIMS, GangaRam, Safdarjung, Apollo), Gurgaon (Civil Hospital, Medanta, Artemis Fortis), Chandigarh (PGIMER, GMCH, Max super specialty hospital), Rohtak (PGIMER) are selected. The data was collected by conducting a personal interview of pharmacists available nearby hospitals and personal interview with doctors. Some information was collected by contacting burn trauma centers through email. The format of the market survey form has been attached at the end of report as Annex-1. Approximately 100 Pharmacists were visited, to analyze the availability of dressings in India. The critical analysis was done to check the type of dressings available in India are approved by Indian Authority or from Foreign Authority.

6.4.1 Market availability of approved dressings

From the below Table 34 and Fig 59 it was found that more than 76% dressings available in India are approved by EU regulatory body and only 24% products are Indian origin and approved by the regulatory body of India. Most of them are old dressings like Gauze, Than dressing and cotton swab.

Table 34: Approved dressings available in India

Approving Authority	Number of dressings*	Valid %
EU approved	76	76
Indian approved	24	24

* Number of EU/Indian approved products reported by pharmacist sample size 100

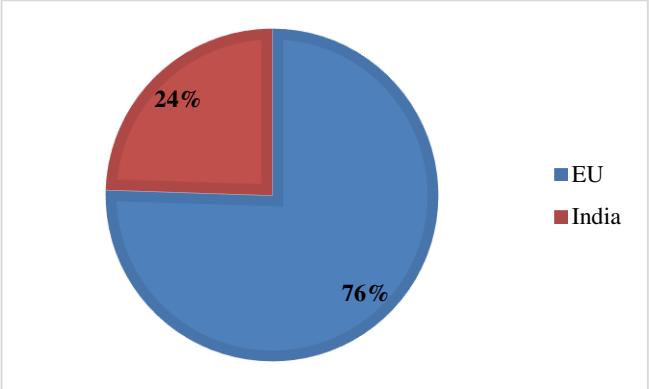


Fig.59. Availability of approved dressings in India

Table 35: Companies hold on dressing market In India

Company Name	Number of products*	Valid %
Smith & Nephew Healthcare Limited	44	44
ConvaTec Ltd.	15	15
3M Health Care Ltd	15	15
Mölnlycke Health Care	12	12
Coloplast	8	8
Insense	6	6

*Number of shops (N=100) reported advanced dressings with their company name

From the Fig 60 it was found that from the above imported products Smith and Nephew holds the major market share followed by ConvoTec and 3M Health Care ltd.

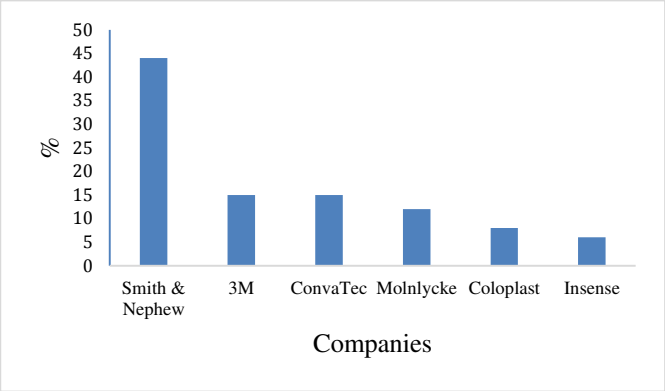


Fig.60. Companies holding dressings market in India

6.4.2 Calculation of cost effectiveness of advance dressings

Further from the pharmacist survey the approximate cost of the dressings was identified. As it was tough to calculate the exact cost because the different size of dressings was found to be of different cost. Also, it was not possible to check the cost of particular packing because the similar packing was not available with other brands. Therefore, harmonizing all parameters and a box of ten pieces was selected to calculate the approximate cost as given in Fig 61. It was found that advanced dressings were costing very high as compared to traditional dressings.

Table 36: Approximate cost of dressings in India

Sr. No.	Name of Product	Approximate cost (Rupees) *
1	Comfeel plus	13000
2	Aquacel	6000
3	Acticoat	20000
4	Algisite M	10000
5	Allevyl	6000
6	Bactigras	300
7	Tegaderm +pad	3750
8	Primapore	1400
9	Mepilex	3500
10	Paraffin gauze	1800
11	Mepore	1129
12	Mepiform	12655
13	Traditional dressings gauze, swab, Ointments, Gamzee rolls and drapes	200

*Approximate cost of one box containing 10 pieces or one roll

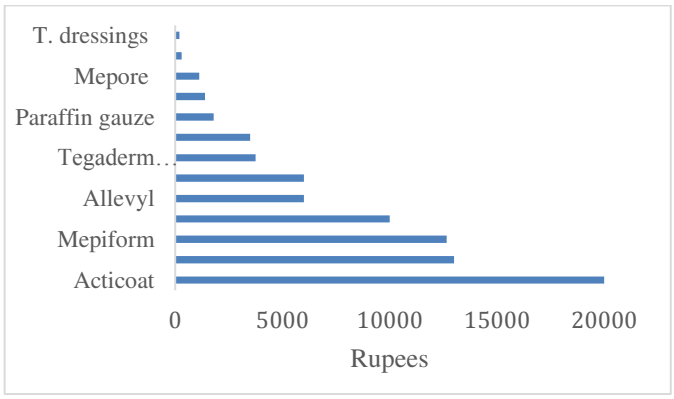


Fig.61. Approximate cost of advanced dressings in a box of 10 piece

As from the data analysis, it can be interpreted that there is an urgent need for advancement in the technology of the dressings. From the above discussion, it is concluded that the innovations in the field of advanced dressings are very much necessitated and necessity is a mother of invention. Innovators need to be motivated to carry out innovations and there have to be guidelines that need to adhere for testing and approval of prototype in the minimum time. To prove the same on the practical sample, an in-house test sample was taken and tested. All evaluated parameters were compared with one of the marketed advanced dressing in next chapter.

CHAPTER-7

7. QUALITY EVALUATION AND SIGINIFICANCE OF DIFFERENT TEST PARAMETERS

All dressings are made of different type of materials and therefore possess a different type of properties. Some dressings claim to have good fluid handling capacity and some having good moisture vaporisation rate. Selection of appropriate dressings depend on their quality results obtained during testing *e.g.* fluid handling capacity of dressing helps in the exudate management. Poor fluid handling capacity of dressing will lead to leakage and further produces discomfort to the patient. Similarly, a moist environment is mandatory for quick healing. Therefore, moisture vaporisation rate evaluation is necessary for dressings that specially designed to provide a moist environment at wound bed. Similarly, other properties as associated with the dressing should be evaluated.[70] No well-defined criteria available for analysing the quality of wound and burn dressings in India. This chapter details the specific parameters, suitable for measuring the dressing performance and to recommend laboratory evaluation to determine the quality of dressing. An in-house product was evaluated for their quality parameters and certain limits were recommended based on the analytical results obtained during the evaluation and in available literature. This chapter provides guidance to the innovators and manufacturers in the development of their product in the Indian market.

7.1 Quality parameters of dressings

Not all parameters are applicable on all type of dressings but parameters that directly affect the healing of wound should be evaluated and reported in the certificate of analysis. For comparative study two samples of dressings were taken. First sample is in-house sample named as sample in this chapter and another sample is chosen from one of the available market product which is available in the Indian market named as standard in this chapter. Both the samples were evaluated based on the following parameters: [70]

i. Appearance
ii. Dehydration rate or drying rate
iii. Fluid handling capacity
iv. Moisture vapour transmission rate

v. Stickiness

7.2 Evaluation of sample and standard

7.2.1 Sample and standard

From the market survey report as done in chapter 5 and survey report with physicians and pharmacists as in chapter 6, it was found that the major imported dressings and dressings in use are Bactigrass, Tegaderm, Mepore, Primapore *etc.* The characteristics and functional properties were compared with the sample. The most resembling standard was selected for the further comparative study.

7.2.1.1 Selection of sample and standard

The in-house sample (NANOKIN) is a sandwich type comprising two cellulose membranes with a central core of wetting material *e.g.* viscose. The cellulosic material used is fully transparent and non-microbial. The limitations relating to use of non-microbial cellulosic membranes as dressings pertain mainly to drying out of the membranes when in contact with mammalian body; lack of transparency when combined with any other material. These problems have been reduced in the sample (NANOKIN). The cellulose membranes have a pore size of about 3-10 nm and are thus semipermeable. This pore size easily allows water and air to pass but does not allow the passage of bacteria and viruses. To enable the pores of the cellulose membrane to remain open, the cellulose membranes have to be kept wet.

The standard TEGADERM^{TM} (3M) was purchased from market. The results of sample (NANOKIN) was compared with the standard (TEGADERM).

7.2.1.2 Solution Preparation

Solution 'A' was prepared using Sodium chloride (NaCl), Calcium chloride dihydrate ($CaCl_2.2H_2O$) and de-ionised water.[70, 190-192]

7.2.1.3 Method

Selected wound dressing specimens were individually tested and analysed to determine a comprehensive understanding of their fluid handling properties, dehydration rate, dispersion characteristics, vertical wicking, air permeability, swelling characteristics and pH. Prior to all the testing, the dressing specimens were conditioned for 48 hours in 65% relative humidity and at a temperature 20°C. As a preliminary test fluid, solution 'A' was used which consisted of sodium chloride 2.298g/l, calcium chloride dihydrate 0.368g/l and de-ionised water.[70,191-193]

7.2.2 Appearance

Standard

3M Tegaderm™ Hydrocolloid thin dressing are sterile wound dressings which consist of a hypoallergenic, hydrocolloid adhesive with an outer clear adhesive cover film.

Sample

It is a sandwich type cellulose membrane composite dressing for burn and wounds. It comprises of two cellulose membranes with a central core of wetting material *e.g.* viscose. The cellulosic material used is fully transparent and non-microbial.

7.2.3 Drying rate or dehydration rate

The drying rate was determined by measuring the difference between the mass of wet and dry specimens. The specimens were dried in an incubator for 24 hours at 37±1°C. The mass of dry specimens was determined before submerging them in the excess volume of solution 'A' at 37±1°C for 30 minutes. The specimens were taken from fluid and suspended by a corner for 30 seconds for free drainage. After draining these were re-weighed and put into petri dishes and kept in an incubator for 24 hours at 37±1 °C.[70]

Test solution 'A' 2.298g Sodium chloride, 0.368g Calcium chloride dihydrate were added to 1 liter of de-ionised water.[70]

Table 37: Observations of weight of sample

Sr. No.	Weight of empty petri dish (gm)	Weight test sample with petri dish (gm)	Weight of sample (gm)	Weight of sample after drainage(gm) (W)	Weight of sample after drainage (24hr)(gm) (D)	After drying sample weight with petri dish (gm)
1	45.5342	45.6200	0.0858	46.2687	45.5729	45.5760
2	45.5120	45.5916	0.0796	46.2870	45.4982	45.4980
3	45.4340	45.5152	0.0812	46.3120	45.5193	45.4870
Average				46.2892	45.5301	45.5203

7.2.3.1 Drying rate of sample

Dehydration rate (g/min) = (W - D) / T

Dehydration rate (g/min) = (46.2892-45.5301) / 1440

= 0.000527g/min

Where W is the wet mass of specimens, D is the dry mass of specimen and T is the time.

7.2.3.2 Drying rate of standard

Table 38: Observations of weight of standard

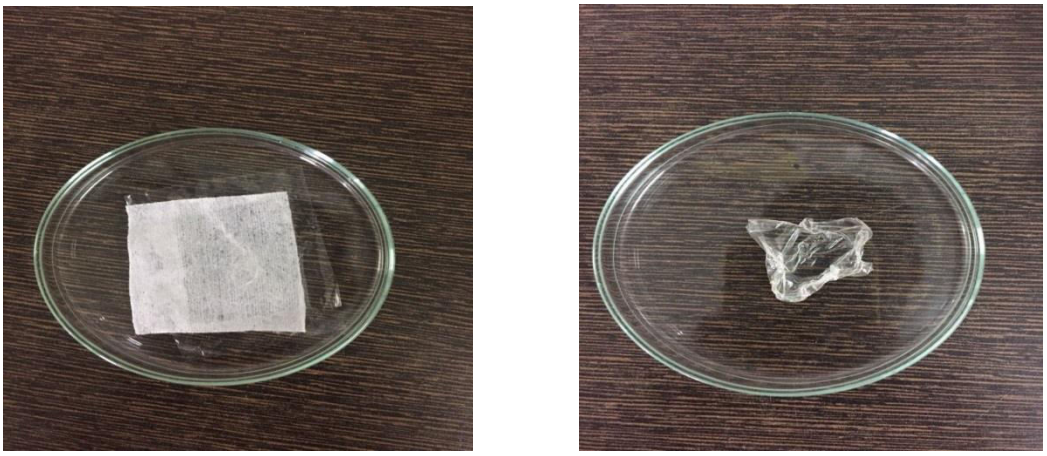
Sr. No	Weight of empty petri dish (gm)	Weight test sample with petri dish (gm)	Weight of sample (gm)	Weight of sample after drainage (gm) (W)	Weight of sample after drainage (24hr) (gm) (D)	After drying sample weight with petri dish (gm)
1	45.5883	45.6500	0.0617	46.7837	45.5624	45.6340
2	45.5669	45.6182	0.0513	46.6932	45.5591	45.5899
3	45.5591	45.6303	0.0712	46.7145	45.5167	45.4978
Average				46.7304	45.5460	45.5739

Where, W is the wet mass of specimens, D is the dry mass of specimen and T is the time.

Dehydration rate (g/min) = (W-D) / T

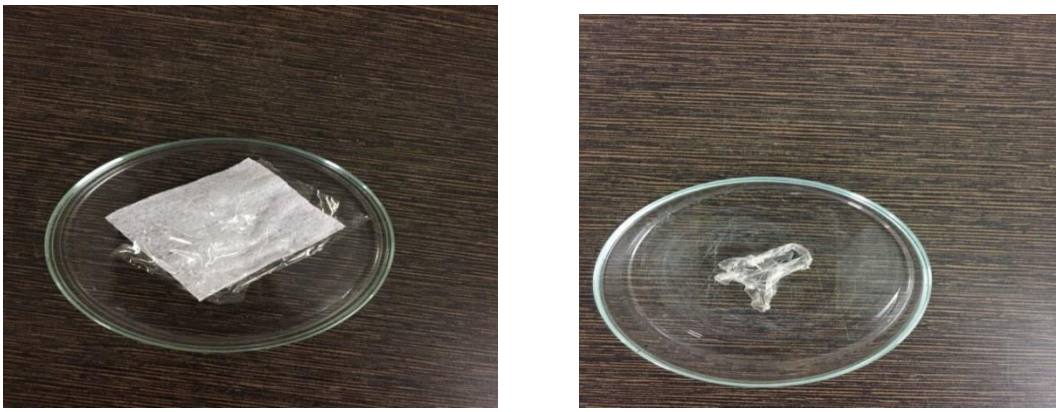
Dehydration rate (g/min) = (46.7304- 45.5460) / 1440

= 0.000822 g/min



A: Sample B: Standard

Fig.62. Drainage (A) Sample (B) Standard



A: Sample B: Standard

Fig.63. After drying (A) Sample (B) Standard

7.2.4 Fluid handling capacity

Dressing sheets of sample and standard (2x2 cm) were dried to a constant weight (M_0) in an oven at 105°C. After that they were incubated in 10 ml of pseudo-extracellular fluid (PECF) buffer at 37°C for 3 hrs. PECF buffer simulates the wound fluids and was prepared by dissolving 0.68g of sodium chloride (NaCl), 0.22g of potassium chloride (KCl), 2.5g of sodium hydrogen carbonate ($NaHCO_3$) and 0.35g of sodium dihydrogen phosphate (NaH_2PO_4) in 100 ml of distilled water. The pH of PECF was adjusted to 8±0.2. The swollen weights of the sample and standard were determined by draining the surface and weight (M_t) was noted. The weight of the sample and standard was recorded every 30 min. The PECF absorption was calculated from the equation.[189, 192]

Table 39: Fluid handling capacity

Sample	Initial Weight (gm)	Swollen Weight M_t (gm)	Weight After Drying M_0 (gm)
Sample	0.0456±0.00165	0.0558±0.000781	0.0436±0.00198
Standard	0.0182±0.00115	0.0188±0.00107	0.0179±0.00201

Fluid handling capacity (S_A) = $[(M_t - M_0) / M_0] \times 100$

% Fluid handling capacity of test sample = [(0.0558-0.0436) / 0.0436] X 100 %

= 27.981%

% Fluid handling capacity of marketed sample = [(0.0188-0.0179) / 0.0179] X100%

= 5.027%

7.2.5 Moisture vapour transmission rate (MVTR) testing

The MVTR test is important for wound and burn dressings as it is a key parameter that affects the healing process of a wound. Liquid formed inside the wound layer changes to vapour and evaporate to atmosphere. That provides a moist environment at the wound site. The sample size of 40 mm in diameter is fixed in a container having inner diameter 35.7 mm. The container is filled with 20 ml distilled water. The container with sample weighed at 0^{th} hour and reading taken as W1. The testing condition of MVTR was kept at 37±1°C at RH 20%. The sample was kept for 24hrs and then again container was weighed with sample at 24^{th} hour. The reading was taken as W2. Now, the difference was calculated between 0^{th} hour and 24^{th} hour and the result was calculated using formula as mentioned below.[70, 191]

7.2.5.1 MVTR of sample

Initial weight of sample with liquid and container = 50.7355 gm

After 24hr incubation weight of sample with liquid and container = 42.0677 gm

$$X= [(W1-W2) / T] X 1000X 24$$

Where, W1 is the mass of the container, sample and liquid in grams, W2 is the mass of the container, sample and liquid in grams after test period and T is the test period in hours.

X= [(50.7355-42.0677)/24] X 1000 X 24

=8667.8 g/m2/24 hour

7.2.5.2 MVTR of standard

Initial weight of the standard with liquid and container = 51.4395 gm

After 24 hours of incubation, weight of standard with liquid and container = 40.0737 gm

X= [(W1-W2)/T] X 1000 X 24

Where, W1 is the mass of the container, sample and liquid in grams. W2 is the mass of the container, sample and liquid in grams after test period and T is the test period in hours.

X= [(51.4395 - 40.0737) / 24] X1000X24

= 11365.8 g/m^2/24 hour

7.2.6 Stickiness test

The stickiness of the film formed is determined by pressing cotton wool on the dry film with low pressure. Depending upon the quantity of the cotton fibres that are retained by the film, the stickiness is rated high if there is dense accumulation of fibers on the film. Medium, if there is a thin fiber layer on the film and low if there is an occasional or no adherence of fibres. This evolution parameter is essential, as the formulation should be non-sticky to avoid adherence to the patients' clothes. [70, 190-191]

Standard- Occasional or no adherence of fibers on film, but glue available at the side of the dressing can get stick to the hairs of the skin which further causes pain while removing or changing the dressing.

Sample- Occasional or no adherence of fibers on film.

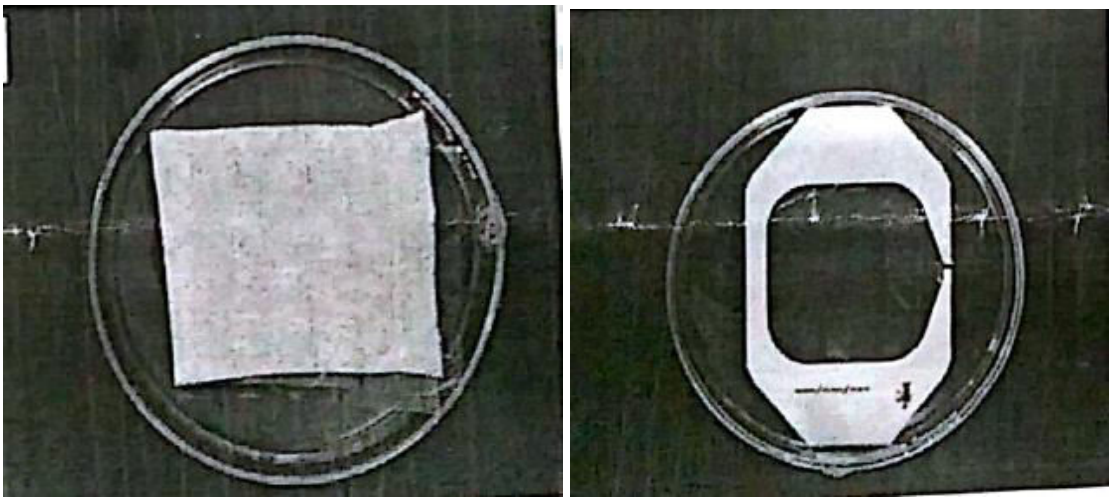
7.3 Comparison of results

From the results obtained, it was found that sample drying rate (0.000527g/min) was lower than the standard (0.000822 g/min) as it is a good property of dressing that it should not dry at the wound site.

Further, fluid handling capacity was determined. It was found that the layer present between the sandwich type sample dressing was acting as a good absorbent. Analytical result shows that sample was good in fluid handling (27.981%) that was quite good as compared to standard (5.027%).

One of the main factor responsible for wound healing is a moisture vapour transmission rate. It was found that the sample was having MVTR value 8667.8 g/m^2/24 hour and standard was 11365.8g/m^2/24hour which was quite high. Higher the MVTR value more will be drying rate.

The stickiness is one of the major factor in wound healing as more will be the stickiness more will be peel off skin during change of dressing. When stickiness was tested, it was found that none of the dressings were found to have sticky property.



Sample A Sample B

Fig.64. Stickiness (A) Sample (B) Standard

7.4 Trend analysis of the results

The results obtained during analysis were compared with published data and results are compiled in Table 40. The results for pore size, MVTR, FHC, absorbency, adhesiveness, mass, pH, drying rate, vertical wicking and swelling ratio were studied. The trends of results given in different research papers gives us a conclusion that results are being reported in a wide range that further effects the quality of the product.[70,192-196] Only the research papers which followed the same testing procedure were included. The trend of results obtained during the study is given in Table 40.

7.5 Limits of test parameters

The justification of limit was prepared to compare all analytical data available for branded dressings in literature as well the comparative results obtained during analysis of sample and standard. Based on the applicable test on the particular dressings, manufacturers can develop their products. Different type of tests applicable on different types of dressings with standard test procedures, limits and their justification are given in Table 41.

Table 40: Trend analysis of results reported in different studies of dressings

Pore size (µm)	Thickness (mm)	Adhesiveness (N/cm)	Mass (g^{m-2})	Density (g/cm^3)	Air permeability (cm^3s)	FHC (g/cm)	Absorbency rate(g/g)	pH	Drying rate (g/min)	MVTR (g/m2)	Tensile strength (kgf/mm)	Vertical wicking	Swelling ratio
25-75	1.6	0.34	108±1.2	0.19	1380	19.07±2.1	19	6.4	0.028	812	0.033	35	2.88
52-154	2.0	0.63	148±4.2	0.14	1104	18.44±2.1	18	7.3	0.037	641	0.020	28	0.54
53-158	3.9	0.42	447±5.9	0.18	280	11.11±2.1	11	7.2	0.036	698	0.020	35	1.74
32-214	3.4	0.05	268±3.3	0.09	288	13.56±2.1	14	7.2	0.037	586	0117	5	0.15
22-88	1.2	0.06	260±2.0	0.06	345	3.54±2.1	4	7.9	0.028	0	0.011	15	0.09
112-423	2.5	0.03	1040±12.2	0.14	1100	4.16±2.1	4	6.2	0.032	1912	0.018	13	2.82
75-255	4.2	0.57	828±7.2	0.21	700	7.71±2.1	8	6.9	0.080	724	0.025	16	2.73
334-899	4.2	0.04	723±3.2	0.14	300	7.85±2.1	8	6.9	0.040	1658	0.0248	23	0.31
123-426	5.9	0.07	696±1.1	0.09	1030	11.87±2.1	13	7.9	0.030	1513	0.018	17	1.62
573-832	1.6	0.02	384±0.9	0.12	478	4.08±2.1	4	7.9	0.034	914	0.041	23	0.06
35-89	4.2	0.08	1128±3.5	0.26	-	3.82±2.1	4	6.2	0.028	550	0.018	11	2.81
67-112	1.8	0.63	633±2.1	-	-	6.80±2.1	7	6.5	0.037	220	-	26	0.53
1000	3.4	-	988±2.2	-	-	7.42±2.1	7	5.3	0.057	700	-	-	1.73
62-232	5.14	-	-	-	-	11.7	3.34	5.0	0.047	192	-	-	-
88-453	6.15	-	-	-	-	8.2	5.43	5.2	0.032	221	-	-	-
55-243	4.43	-	-	-	-	6.3	4.20	6.3	0.090	220	-	-	-
-	3.32	-	-	-	-	7.0	0.7	7.1	-	180	-	-	-
-	8.15	-	-	-	-	1.2	3.34	-	-	110	-	-	-
-	5.33	-	-	-	-	14.1	5.30	-	-	90	-	-	-
-	4.82	-	-	-	-	11	4.51	-	-	14980	-	-	-
-	4.53	-	-	-	-	5	4.44	-	-	4892	-	-	-
-	6.77	-	-	-	-	3.24	23.33	-	-	23935	-	-	-
-	5.29	-	-	-		4.83	22.72	-	-	5022	-	-	-
	2.74	-			-	2.41	24.43	-	-	21146			

Note: This table has been compiled using data reported in various research papers.[70, 192-196]

7.6 Significance of test parameters, their limits and justification

Table 41: Significance of analytical tests, limits and their justification

Parameters	Significance of test	Standard test procedure	Limits	Justification	Applicable on dressings
Dressing mass and thickness[70]	Thickness and mass of dressing effects the absorption capacity, MVTR and dehydration rate. More is the thickness more is bulkiness and cost of dressing	BS EN 12127:1998 and BS EN ISO 9073-2:1997'	Thickness:1.5mm-3.5mm For single layer: 1.0mm to 2.0mm For multilayer layer: 2.0mm to 3.5mm Mass:100 -1000gm^{-2} For single layer: 100gm^{-2} to 500 gm^{-2} For Multilayer: 500gm^{-2}m to 1000 gm^{-2}	Thickness and mass of the dressing generally depend upon the number of layers associated with the dressing. Single layer dressing should have thickness and mass in the range as given in column "Limit"	All dressings
Pore size [197]	Smaller the pore, the less likely new skin on a healing wound will migrate into the foam. Small pore size results in the dressing's–ultra-soft and satiny smooth. The pore size of the wound contact layer is essential to exclude fibroblast and keratin, thus contributing to reduced secondary damage upon dressing change	In -house test	Should have pore size of skin. Big size will allow bacteria and virus to pass thorough and pore size smaller than skin will decrease ventilation to skin *e.g.* 25 ~ 75μm on the wound contact layer and 100 ~ 350μm in the cross-section	Will have more capillary action. Can effectively exclude tissue formed and better absorb. Exudation and maintain moist condition.	Foam dressings
Adhesiveness stickiness[70, 193,197]	To check pain, peel off	BP 1993, Vol 2, App XX H	3.5-5N/cm	More is the adhesives, more will be skin peel off and more will be pain	Gauze

Tensile strength [70]	To check the strength of the dressing until it ruptures. This test is mandatory to check the flexibility of the dressings. The force needed to rupture the films (N) and distance to burst (mm) is calculated	In -house test available	Should be higher than 1.8 (N/mm^2)	The tensile strength of a human skin is reported to be in the region of 1.8(N/mm^2) otherwise, even with slight stress at the near vicinity of the wound, the dressing is likely to get ruptured	
Absorbency [199-200]	Absorbency capacity determines the exudate handling capacity. This test determines the dressings that can be used for higher exudating wounds.To form moist gel on wound surface to regulate moisture at wound bed	BS EN 13726-1:2002	1.25g/cm^2	It should not too much high and not too much low because higher value leads to leakage of the dressing and lower value will leads to frequent change of dressing	Alginates, Foam and Cellulose based dressings
Dehydration rate [70,190-191]	Measuring the difference between the mass of wet and dry specimens	In -house test	Incubate 24hrs and check drying	The dehydration rate has inverse dependency to the thickness of wound dressings. Increasing the thickness of the wound dressing causes a decrease in the fraction of water released from it at a specific time	All dressings
pH determination [192,199-201]	This increase in the pH value can also adversely affect the wound healing process. The pH value within the wound influences indirectly and directly, all biochemical reactions taking place in the healing process	In -house test	After 3 hours of dressing:5-6 After 24 hours of dressing :6-8 Common range :7.15-8.9	The acidification of the dressings decreases, as the application period of the dressings increases. It is not advisable to keep these dressings in situ for long periods of time as this will affect the pH balance	All dressings

Air permeability [189-191]	Quantitative measurement of how well a material allows the passage of air through it. It measures the maceration rate and further comfort to patient Effects the healing process at early stage	ASTM D737-96	NA	NA	All dressings
Fluid handling capacity [70,190-191]	To indicate the ability of dressing to manage exudate important Parameter for maintaining a moist environment over the wound. Absorptive capacity and the ability to retain the absorbed fluid under application of external pressure	BS EN 13726-1	NA	Unless otherwise specified, the test should be performed at temperature (T) 37±1°C and relative humidity (RH) <20%, using the artificial exudate test solution A (containing 142mmol/l Na+ and 2.5mmol/l Ca^2+) for 24 hours or at T 23±2 °C and RH of 50±5%, maintaining test solution A at 37°C for 24 hours. More than 100% buffer should be absorbed	Water proof foams, Alginates, hydrocolloids, Cellulosic dressing
Free swell test [199-200]	To indicate absorptive capacity	BS EN 13726-1:2002 Section 3.2	NA	NA	Waterproof and non-waterproof foams, Alginate dressings, Chemically modified cellulose fibres (CMC carboxymethyl cellulose fibres and other fibres) like Hydrocolloids
Moisture vapour	The MVTR test is	BS EN 13726-	Permeability shall be	As per BIS	Non-

transmission rate [70,190-193]	important for wound dressings that are used on wound in which liquid formed inside the wound layer are changes to vapour and transport to atmosphere. This moisture vapour transmission helps to heal the wound	1:2002 BS EN 13726-2:2002 BS EN 13726-4:2003	not less than 500 g m-z per 24 h		waterproof foams, Hydrocolloid, foam, Hydrocolloid fibrous, Collagens
Retention under pressure[70,201]	To assess the retention ability of a dressing	No standard test available however in-house testis available in published articles	Should be optimum	Affect wound healing	Waterproof and non-waterproof foams, Alginate dressings, Hydrocolloids, chemically modified cellulose fibres
Volumetric strain [70,201]	Volumetric strain is important for the choice of the size of the dressing in relation to the surface and volume of the lesion	Currently there is no standard test for this parameter is available	Should be optimum	Affect absorption capacity of exudate	Waterproof and Non-waterproof Foams, Alginate dressings, Hydrocolloids, Chemically modified cellulose fibres
Lateral spread [70,200]	The lateral spread of exudate with possible re-contamination of the area around the wound is a negative parameter of the performance of a dressing	Since there is no standard test is available to evaluate lateral spread	Should be optimum	Affect absorption of exudate	Polyurethane foams
Vertical spread [70,200]	The property to absorb	In -house test	Should be optimum	Higher is the absorbance	Foam dressing

	and remove the exudate internally and towards the outer surface favours partially the evaporation of excess exudate and most of all protects the surrounding skin from damage and irritation			lesser will be the vertical wicking. Because absorption of fluid resulting in a large increase in the fibre diameter decreases the vertical wicking		
Dispersion characteristics [200]	High dispersion is therefore seen as a negative factor when evaluating the quality of a dressing. Determines how the physical characteristic of the dressings change when they interact with fluid	BS EN 13726-1	Should be optimum	Pain free removal of dressing dispersion characteristic should be tested. Dressing should be completely dispersed		Polyurethane foams, Alginate dressings and chemically modified cellulose fibres
Waterproofness[200]	Waterproofness resistance is defined as the ability to withstand a hydrostatic head of 500 mm of water for 5 minutes. This parameter must guarantee the absolute protection of injured area and surrounding skin from external contaminants	BS EN 13726-1	No water shall pass through	As per BIS Limits		Waterproof foams, Hydrocolloids
Resilience	Resilience may be relevant when choosing polyurethane dressings in compression therapy and for treating pressure ulcers	BS EN ISO 8307:2007	Should be optimum	Dressings of high resilience are more resistant to deformation under pressure, and favour an even distribution of pressure on the wound bed		Polyurethane foams, Foam dressings

Viscosity [201]	Viscosity of a fluid may also be defined as flow resistance, and can be quantified by measuring the space covered by the sample (migration) from the point of application for a given period of time	In -house test	Should be optimum	Hydrogels with optimum viscosity stick quickly to the wound bed and remain in the right position even against gravity	Hydrogels
Hydration capacity	A gel with high fluid affinity facilitates rehydration of necrotic tissue by encouraging autolytic debridement	BS EN 13726-1	No specific limits yet available	Hydration capacity is related to the supply of water, and greater the loss in weight of the hydrogel is, greater its ability to hydrate	Hydrogels
Odour control [201]	Objective of the test is to assess the resistance of wound dressing to penetration by odour. Specially in case of cancer wounds	BS EN 13726-6:2003	Do not allow odour to penetrate	Bad odour led to patient discomfort and non-society acceptance	Charcoal, Foam
Sterility[200]	To test dressings free from microbes	As per ISO	Irradiation with gamma rays 5-50 kGy at room temperature. Sterility assurance level should be 10^{-3}	Above dose will affect tensile strength and lead to degradation of polymer, decreases its flexibility	All dressings that are in direct contact with wound exudate and burn site

CHAPTER-8

8. DEVELOPMENT OF REGULATORY GUIDELINES

Deaths due to burns and wound infections are abnormally high in India. Innovators and manufacturers of wound and burn dressings need to keep themselves abreast of the new Medical Device Rules, 2017. The concept of advanced dressings is now emerging in India; however, indigenous manufacturing is hindered due to absence of clear regulatory guidelines. The lack of availability of advanced wound and burn dressings in the market critically affects patient survival rate. Imports from other countries make dressings unaffordable for middle class patients.

After critical analysis of all the key points in chapter 4 to 7 *i.e.* market availability of advanced dressings, physician's acceptability, cost, import needed, lack of manufacturers and many others; it is concluded that there is a strong need of regulatory guidelines that can provide clear picture to the innovators and manufacturers.

8.1 Identification of gaps

From the study carried out in Chapter 4 in respect of India, various gaps have been identified in the existing regulations (Medical Device Rules, 2017 as applicable since 01 Jan 2018) as tabulated below.

Table 42: Identification of gaps in the existing regulations

Present	Proposed	Reason for inclusion of particular section
Surgical dressings covered under Medical Device Rule, 2017	Definition of surgical dressing should be included in the rules	Applicant/Innovator can better classify their dressing category and rules applicable
Surgical dressings can be classified as class A, B, C, D category as applicable	Definition of invasive and non-invasive surgical dressing like antimicrobial bio-patch used with catheters used to be defined	Applicant/Innovator can better classify their dressing category and rules applicable
For class B one of the most imp. requirement is "Essential principles checklist for demonstrating conformity to the Essential principles of safety and performance of the product should be submitted"	Essential principles of safety and performance should be explained in the rules. How it is to be determined should be explained	Brief details about essential principles will leads to applicant better understanding in development of their product
Conformity assessment	Procedure for conformity assessment should be explained	Proper conformity evaluation procedure or check list will provide better understanding

Document as specified in the clause b of paragraph (i) of this part page 35 of the act	The list of documents required should be explained as clause b is not explained in the rules	The line mentioned in the rules, applicant is not able to trace what exactly documents required to be submitted to Health Authority of India
Information on product development not asked	Information on product development should be one of the requirement	Product development is one of the crucial step and it should be included in the guidelines or rules
Information on process validation is missing	Information on process validation should be required	Process validation parameter provides the information about consistency of the product
No quality control on raw material used for preparation of dressing	Requirement on the control of raw material used in the manufacturing of dressing should be discussed	The quality of the product can be achieved only if the quality is maintained at the initial step
Specification of dressings tests required not explained	Specification – list of tests given in annexure should be referenced	Applicant/ manufacturer is unaware about the list of tests required for dressings
Analytical procedure standard not defined	Analytical procedure should be referenced from Indian standard or British pharmacopoeia	Applicant/ manufacturer is unaware about the list of tests required for dressings
Analytical validation parameters explained only for in-vitro products	Analytical validation should also be mandatory for dressings	Analytical validation provides consistency and suitability of analytical test. Therefore, it should be mandatory requirement
Requirement of COAs not defined	Requirement of COAs, justification of specification should be one of the necessary requirement	At least three batches COA's should be one of the requirements. This ensure quality of product reaching market

8.2 Development of regulatory guidelines

After critical evaluation of gaps identified in the existing regulations in India and also regulatory formats existing in other countries, a regulatory framework is developed and named as **"COMMON SUBMISSION DOSSIER FOR ADVANCED WOUND AND BURN DRESSINGS"**.

The same are presented in the form of a PRACTICAL DOSSIER DOCUMENT which can be filled by a manufacturer seeking approval of advanced wound care and burn dressings in India. The format can also be utilized by regulatory agencies to ensure that the regulatory framework is robust and in harmony with international framework as followed in nearly 13 countries, whose dossier formats were reviewed to arrive at the present format.

Methodology adopted

A. Identification of gaps in existing guidelines as approved for medical devices under the new Medical Devices Rules, 2017 released by India's Ministry of Health and Family Welfare in Gazette of India, Extraordinary Part II, section

3, sub section (i), vide notification no G.S.R. 983(E), implemented since 01 January 2018.

B. Review of the regulatory approval framework in 13 countries covering major continents viz. Europe, Asia, Africa, Middle-East and Latin America. The 13 countries viz. United States, Europe, Japan, Canada, Australia, Brazil, China, Singapore, Malaysia, Mexico, India, Israel and Russia were studied, compiled and analyzed.

C. Review of technical parameters compiled from published sources relating to wound care and burn dressings (Table 41 page no 112).

The PRACTICAL DOSSIER DOCUMENT [202-208] is presented in Annexure -3.

CHAPTER-9

9. RESULTS AND DISCUSSION

The market value of the advance dressing is reaching new peaks in developed countries since they are associated with benefits like the simplicity of use, reduced recovery time and optimum results. The various types of advanced dressings like collagen dressing, alginate dressing, hydrogel dressing, hydrocolloid dressing, foam dressing and other biologics dressings like skin implants *etc.* are available across the globe. From the list of available dressings, collagen dressings hold the largest demand in the market due to its tenacity to control wound and burn infection. In near future biologics, biomembrane and other advanced dressings will grow at the rapid rate because they possess many advantages like higher absorbency and reduces the frequency of dressing change as compared to old dressings.

Unlike developed countries like the EU and US, not all developing countries can manage the production of such dressings in their own countries even if they are associated with reduced healing time and further reduces hospital expenses. Therefore, imports of such products dominate in these countries. It has been observed from the study that dressing market in India is majorly dominated by Smith & Nephew plc (U.K).

There are a high prevalence and death rate due to wound injury. The reasons for the high death rate were analyzed using WHY- Five concept. It was found that the available dressings are in patches and therefore, cannot cover the entire infected area of burn and wound patient, also there is lack of availability of advanced dressings, non-maintenance of hygiene to prevent infection. It is found that there is very less number of manufacturers available and that's why advanced dressings are imported in India. Due to lack of government support, lack of clarity in guidelines further de-motivates the manufacturers and innovators as they are not able to showcase their products/inventions in the market. Unaffordable prices further reduce the availability of dressings to patients. In the view of the above, it is concluded that there is a strong requirement of clear regulatory guidelines for advanced dressings.

From the literature review, it has been concluded that certain types of advanced dressings are in the innovation phase. It is expected that the dressing under clinical

trials will be able to provide a better treatment to the burn and wound patients. It has come out from the shreds of evidence and earlier studies that a dressing should have the following properties:

i. Pore size that allows oxygen to pass through but not the bacteria and viruses
ii. It should maintain a moist environment at the wound site
iii. It should not stick to the skin
iv. It should be transparent

A comprehensive study on global regulatory aspects of wound care and burn dressings reveals that reveals that such dressings are categorized under the medical device and not the drug. Dressings are removed from The Drug and Cosmetic Act, 1940 and Rules, 1945 thereunder. A new Medical Device Rules, 2017 implemented since 01 Jan 2018. From the study, it has been concluded that most of the countries have very well-defined guidelines for manufacturing and development, approval and renewal procedure. The well-defined guidelines promote manufacturing in their own country and thus the quality product with low cost reaches to the bedside of the patient. To maintain the quality standards many countries are following the GHTF, ISO, BSEN, US standards to develop their products and some having their own quality manual/ quality confirmation system. It was noticed that India is missing for own quality regulatory guidelines although having new Medical Device Rules, 2017 is in place. The following are the good observations of the new Rules:

i. Dressings have been removed from the drug category and introduced as a medical device.
ii. The proper classification system has been well defined as Class A, B, C and D with their respective examples.
iii. Documents have been properly listed for the application filing.
iv. Role of central and state government has been well defined and thus facilitates application filing.

Despite above mentioned favoured points this act is lacking behind in defining the quality parameters, test procedures for advanced dressings.

Market availability of advanced dressings in India

The innovators and manufacturers are facing issues in the development and marketing of their product. The regulatory hurdles and unclear pictures of regulatory guidelines

further de-motivate the manufacturers to set up their business in the Indian market and exporters to India are taking advantages of a monopoly. The study in chapter-5 shows that India needs import for advanced dressings. The market import-export analysis report shows that demand growth of such imported products in India. It shows country-level analysis of the market with respect to the market size from import and export perspective. In addition to the above, this report also provides profiling of key products in demand in India, their usage patterns attract global suppliers of such products.

The high import shows that India is having very less in-house production and innovators; manufacturers have very fewer interests in this area that need to be boosted. Innovators need to be motivated to bring better products on medical parameters. The approval process should take minimum time for certification. Industrialists should be able to produce the product at the lower cost so that the product reaches to patient bedside economically.

To analyze the trends on expenditure on the wound and burn dressing the raw data of the year 2008-2017 were collected from various market research analysis sites and import-export analysis is done on the same. The detailed analysis reveals that India is a growing market for wound and burn dressings and spending a lot of exchequer on importing the subject commodity.

Wound dressing export is averaged to same from 2013 to 2017 India has seen a continuous rise in wound dressing export since 2013. It averaged approx. INR 2791 lac from 2008 to 2017 and it attained its all-time high of INR 3514 lac in 2016 and record low of INR 1642 lac in 2010 (Fig 22).

According to the statistical data, the import of wound dressing fell in 2017 as compared to 2016. It is decreased by about INR1814, however, in last eight years; it follows the tendency to increase. Overall, India saw a rise of wound dressing import over the past 10 years. It averaged INR 50271 lac from 2008 to 2017 and it reached its all-time high of INR 7656 lac in 2016 and record low of about INR 2177 lac in 2008. The import value was found high as compared to export as shown in Fig 22.

Further study of major advanced dressings in-use in India from 2014 to 2016 was studied and it was found that the overall yearly import never came down below INR 980 lac that itself reveals that there is a huge import of the subject commodity (wound

and burn dressing) and relatively higher consumption over the production within the country. The import has touched the peak of INR 1718 Lac in 2014 and INR 1533 Lac in 2016. The average import comes out to be INR 1410 Lac which anyhow attracts the exporters of the commodity to expand their business in India. But for Indian self-reliance point of view, this trend needs to be encountered with the local production which can compete for the subject commodity in the international market. For that India needs to have advanced dressing which should be of a better quality on all surgical parameters and of low cost.

From the study of imports-exports trends of the burn and wound care dressing in Chapter-5, it is very much clear that import of the dressing is dominating over the exports and producing the deficit in Balance of Payments (BOP). Exports are not touching even a crore value which means there is no export per say for the commodity. That directly states that the country does not stand anywhere in the market of the commodity. It is a matter of concern for economics.

The report of import and export analysis very clearly highlights that there is a strong demand of dressings in the country and due to lack of own manufacturers of such dressing in India and therefore, they are imported. Since these products are expensive and there is a large outflow of Indian currency due to imports. It is imperative that such products get government attention and should be manufactured within the country.

Referring to the above import value, the reason for import and physician interest in selecting such advanced dressings were identified.

Critical analysis of survey with physicians:

Ten different categorical set of data based on different variables were interpreted. The percentage distribution in the form of pie charts or graphs was prepared, in order to emphasize the importance of a particular area or subject based on the response. Another test involves the Chi-square test which does not take into account the percentage responses of the respondents. Further, Chi-square testing is done to prove whether any statement is accepted or rejected based on the value of ‘p’ and the significance level. From the data analysis report it can be summarized that among the three hypothesis, only the first two hypothesis which is the association between the most cause of death due to burn and the common challenge to treat patient with open

wound treatment is accepted and rejected the third one. From the survey study of physicians, it was found that infection is the most common cause of death in burn and wound injury. The equal percentage (46%) reported both reasons *i.e.* "non-availability of advanced dressings" and "infection" as the major cause of death. After that current practice to treat burn and wound patients were analyzed on a scale of 1 to 5 and it was found that 42% physicians reported the current practice used is moderate, 40% reported it as difficult and 6% reported it is very difficult to treat patients with the current practice followed in hospitals. To calculate the overall cost of the treatment, patient hospitalization was determined. 66% of physicians reported that generally, 1 month is the most likely duration for hospitalization in burn case. Further, common frequency to change the dressings were reported as 18-24hrs (60%), 8-10 hrs and 4-6 hrs by 10% and 20% physicians respectively. The problem is using advanced dressings were analyzed. It was found that 60% of physicians reported that due to high cost these are not affordable by common patients and 30% reported they are not easily available. In a study about the most common challenge to treat these patients, 70% of physicians reported that infection control is the most common challenge. Finally, 98% of physicians reported yes advanced dressings can prevent infection caused during post burn and wound injury. Currently from the list of advanced dressings "Bactigras" is the most preferred advanced dressings as reported by 46% physicians and 34%, 10%, 2% for cellulosic dressings, Alginate dressings, Primapore respectively. It was reported that 50% of physicians are still using traditional dressings like paraffin gauze and silver sulfadiazine and 24 % are using advanced dressings and rest 10% are still use ointment and creams in the treatment. To provide better treatment and to reduce the death rate several possible expectations were reported by physicians. 30% reported that the cost of the advanced dressings should be reduced and 14% reported for better sterilization of dressings and maintenance of the aseptic area. Further, 12%, 10%, 8% reported to improve hygiene, increase burn units, prevent indiscriminate use of antibiotics respectively.

From the interpretation of physicians survey study, the value of the chi-square test is 15.041 with df = 4 having $p = 0.005 < 0.05$ of significance level. It was found to have an association in the most cause of death due to burn and the common challenge to treat patient with open wound treatment. In hypothesis-2 the value comes out to be

1.198 with df = 2 and have p =0.043 < 0.05, significance level. From the values, it could be interpreted that there is an association between the most cause of death due to burn and advance dressing can prevent death due to infection. In third hypothesis the value of chi-square test is 7.257 with df = 6 having p-value = 0.298 > 0.05, significance level. It means there is no any association between the most cause of death due to burn and the most preferred advanced dressings.

The survey study of pharmacists shows that in India 74% advanced dressings are EU regulatory body approved and only 24% available dressings are Indian approved and most of them are traditional only. Currently, foreign companies regulatory bodies have a complete hold on advanced dressings market. From the survey study, major products were of Smith and Nephew Health Care ltd., followed by Convatec and 3M Health Care, Molnlycke Health Care, Coloplast and Insense. In case of cost-effectiveness the Acticoat advanced dressings having the highest cost followed by Allevyl, Comfeel plus and then Tegaderm and Mepilex

Quality parameters evaluation:

To check the quality of dressings, their evaluation parameters, limits and the significance of test parameters; an in-house study was carried out on an in-house test sample and marketed standard dressings. It was found that the various factors affect the quality of the product and further limits its use for wound healing. Cellophane dressing has found to have better quality results and having well known efficacious in advancing the wound healing process. From the results obtained, it was found that sample drying rate was 0.000527g/min and for standard it was 0.000822 g/min that was lower than the standard as it is a good property of dressing that it should not dry at the wound site.

Further, FHC was determined. Analytical result shows that sample was good in fluid handling *i.e.* 27.981% as compared to standard 5.027%. One of the main factor responsible for wound healing is a moisture vapour transmission rate. It was found that the sample was having MVTR value 8667.8g/m^2/24hour and standard was 11365.8g/m^2/24hour which was quite high. The stickiness is one of the major factor in wound healing as more will be the stickiness more will be peel off skin during change of dressing. When stickiness was tested, it was found that none of the dressings were found to have sticky property.

Development of guidelines

Based on key points identified in chapter 4 to 6, the regulatory guidelines have been developed into the form of a "Practical dossier" which can be filled by a user who seeks approval of any type of dressings for wound care and burns in India. Same is enclosed as Annexure-3.

Suggestions:

1. Government should run more dedicated awareness programmes for burn and wounded patients. Existing programmes should be revamped and new should be initiated in the support.
2. The education system (M. Pharmacy or Ph.D in regulatory affairs) should be directly linked with the govt. regulatory bodies which are responsible for registrations and renewals.
3. There should be certified regulatory agents whom an innovator and manufacturer can vouch upon for a legal guidance.
4. India should endeavour for self-reliance and try to curb the high rising graphs of imports of advanced dressings. On the other hand, to give subsidies on the imports can be an economic tool to bring an affordable advanced dressing at the bedside.
5. There must be proper guidelines that states which type of dressing is to be used for which type of wound. As on date such guidelines/ procedure are not yet available.
6. The government should have own manufacturing units as it is not there till date and should release funds to motivate innovators and manufacturers of the advanced dressing.
7. India should boost the in-house manufacturing and why not to divert the "Make-in-India" programme towards the manufacturing of medical devices like advanced dressings.
8. Due to long approval procedures of Indian regulatory authority, manufacturers and innovators in India seek for their approval in other countries and leads to loss of exchequer/ Indian currency. To maintain other country's regulatory standards, manufacturers need to pay a hefty amount for the audits and infrastructures charges. Therefore, a clear picture of the regulatory guidelines is required that

attracts manufacturers to seek approval from Indian regulatory and carry out the production on the same. These products should be at par with international standards which can compete with foreign products in the market.

9. There should be proper wound and burn care regulatory guidelines like in EU, US and Canada.
10. The guidelines should be compatible and harmonized with regulatory bodies of other developed countries.
11. There should be an application based information system to make clarity on application filing, registrations, renewals, audits *etc.*
12. The clear picture of quality regulatory guidelines that are still missing with following points:
    a. There are no standardization/validation guidelines for the instruments used in the assessment of wound size and its type.
    b. Unavailability of quality testing monographs for testing of advanced dressings.
    c. The absence of proper guidelines on clinical trials. There is no ideal animal model available to carry out clinical study.
    d. Non-availability of the standard sterilization procedure.
13. There is a confirm requirement of strict adherence to the audit regulations by the audit teams like ISO, BIS *etc.*
14. There should be an electronic system for the filing of the application and registrations dossiers.

CHAPTER-10

10. SUMMARY, CONCLUSION AND FUTURE PERSPECTIVE

Innovations are the key to technological advancements and improved healthcare. In case of burn and wound care, several groups worldwide are working on improved dressings to enable better care for patients and enhance survival rates of burn and wound patients.

Apart from technology, a very critical aspect influencing availability of advanced dressings is economy *i.e.* cost of such dressing? Despite the availability of technologies, advanced dressings which can take care of wounds, burns and help to save patients, are available mainly in developed countries and patients in third world countries like India, have no access to such dressings owing to high cost.

Indigenous manufacturing can drastically cut down the cost of advanced wound and burn dressings. However, the lack of knowledge of regulatory approvals becomes a major barrier to indigenous manufacturing and "Make-in-India" efforts. In absence of quality regulatory guidelines Indian manufacturers are forced to take approval from foreign regulatory authorities. This creates lots of hurdles for small scale manufacturers and enhances the cost of dressings.

Hence, there is a dire need to address the issue and develop suitable guidelines for approval of such dressings in India. Accordingly, the study was carried out and involved data collection at field level from Pharmacists (to understand which type of dressings are currently in use in India for burns and wounds, costing and also whether indigenous or imported) and also interaction with doctors (to understand the reasons for preferences and also knowledge and availability of dressings and advances in wound care and burn treatment in India). Data collection and analysis was also carried out with respect to imports of dressings in India and exports also.

Thereafter, data relating to various technical parameters as reported in literature, for burn and wound dressings were compiled and compared to understand the range of variation for various parameters. Quality parameters concerning the type of material, pore size, MVTR, FHC, shape, dehydration rate, size and other test parameters applicable to such dressings were compiled and analyzed. A novel dressing consisting of regenerated cellulose membranes with a central absorbent pad of non-woven

cellulose developed in India as an advanced wound and burn dressing was compared with internationally approved dressing.

To understand and develop the regulatory guidelines for advanced dressings, the regulatory process and guidelines from 13 countries worldwide viz. United States, Europe, Japan, Canada, Australia, Brazil, China, Singapore, Malaysia, Mexico, India, Israel and Russia were studied, compiled and analyzed.

The results of the study revealed that there are well-defined technical parameters and ranges relating to desirable properties of advanced dressings which if put into place and notified by the Indian Regulatory Authorities can greatly facilitate the approval of new and innovative burn and wound dressings. They can also help in indigenous manufacturing of dressings already approved in developed countries.

An outcome of the present work is a well-defined framework in the form of 'guidelines' which can help regulatory agencies in India in the approval of advanced wound care and burn dressings. The framework is based on an extensive review of the regulatory framework in 13 countries and harmonizes the administrative and technical requirements which must be fulfilled to grant approval to a wound care or burn dressings.

The 'Regulatory Guidelines' have been organized into the form of a 'Practical Dossier' [202-207] which can be filled by a user who seeks approval of any type of dressing for wound care/burns in India (Annexure-3).

In future this document can be converted to e-form which will be flagged on health authority website and hence, will be an arm of "Digital India". This e-database will help in the post lifecycle management of the innovative dressings and also can be used as benchmark/standard for the next innovator/manufacturer. The guidance document will help in future for better understanding of regulatory requirements of advanced dressings to innovators and manufacturers in India. This will give a ray of hope for all pipelined products to reach bedside of the patient with low cost. Further it will give a boost to the production of the advanced dressings in India and hence will counter the import of the commodity. Availability of low cost advanced dressings will lower down the threat of deaths due to infection caused during burn and wound injury. It will not only reduce the exchequer outflow but also will give a support to good health vision of Government of India.

CHAPTER-11

11. REFERENCES

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DEVELOPMENT OF REGULATORY GUIDELINES FOR ADVANCED WOUND CARE AND BURN DRESSINGS

Chapter 1 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 3,00,000 deaths occur each year as a consequence of fire-induced burns.[2-3] The burden of such injuries generally fall on poor patients as they cannot afford costly treatment. A primary contributing factor that leads to infection and finally to death in this population, is poor hygiene.[4-5] Burn injury management is challenging, due to significant fluid loss, tissue damage and deep wounds, thus contributing to death.[6]

It is estimated that there are about 7 million burn injuries in India annually, of which 7,00,000 require hospitalisation and 1,40,000 are estimated to be fatal. According to the National Burns Programme data 91,000 of these deaths are of women.[7] In cases of surgical site infection, the mortality rate resulted in 70-80%, where deep and extensive infection takes place during surgery. The high prevalence and death rate due to burn mandates the need for guidelines.

1.1 Major cause of death in burn injury

- Burn shock
- Low blood volume
- Respiratory failure
- Infection at the site

1.2 Treatment for wounds and burns

Wide range of traditional and advanced dressings are available for the treatment. Despite availability of advanced dressings, the death rate is still high. Therefore, the "WHY-5" (Fig1) concept was designed and applied to check the most common cause of death due to burn and wound injury and necessity of regulatory guidelines in India was identified.[8]

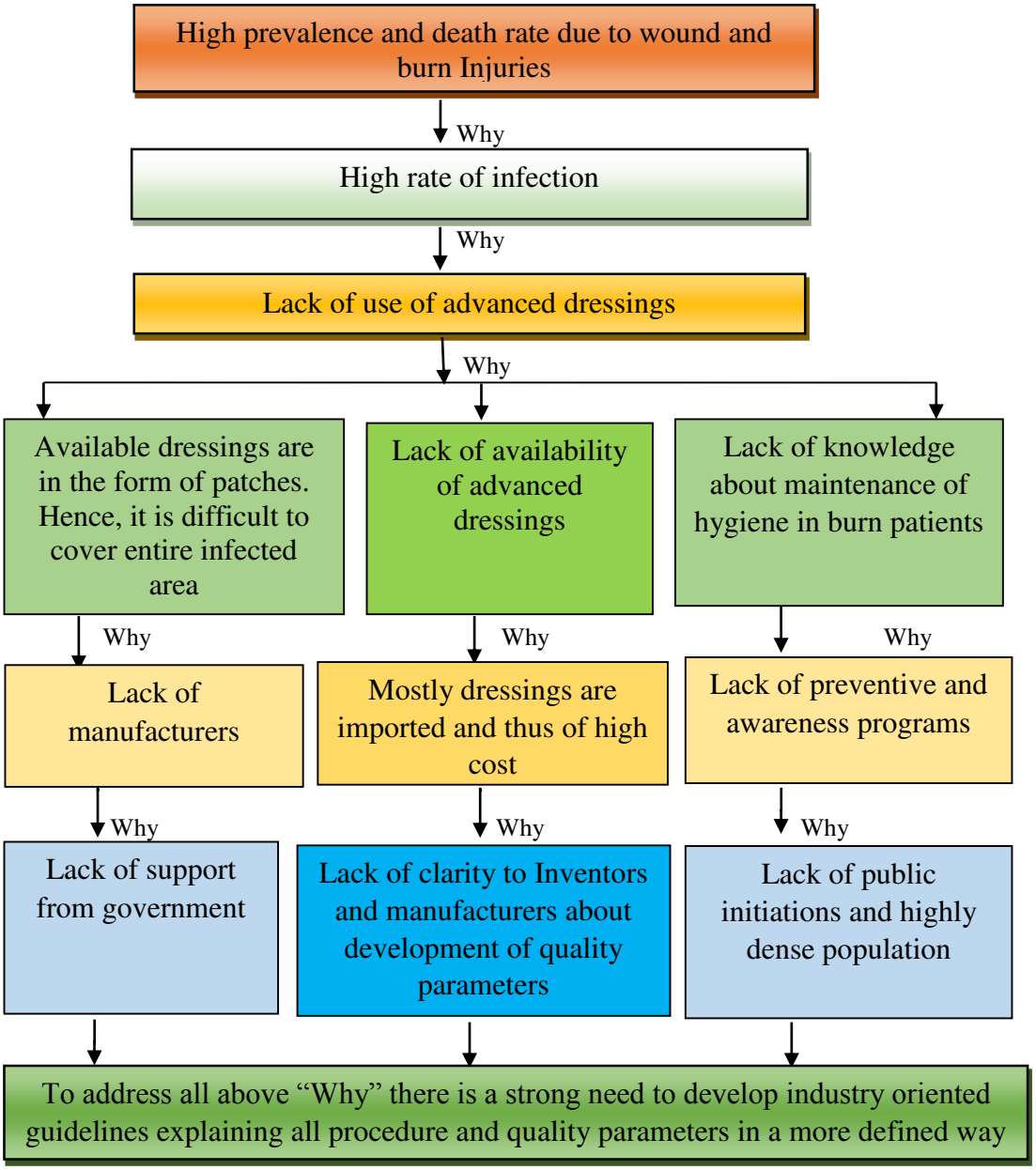

Fig.1. Need of guidelines for wound care and burn dressings

Chapter 2 Literature review

This chapter aim to offer a critical investigation on the work carried out so far on advanced wound care and burn dressings. It is important to explore the advancement in the study and to know the regulatory status of such products. The study details about the infection causing microorganisms and recent development been done so far to curb this critical care issue. Discussion on need of harmonisation of quality regulatory guidelines has been discussed. The need of standardisation of quality test parameters

and significance of upper and lower limits affecting the wound healing have been identified.

Chapter 3 Rationale of study

Burn and wound injuries are recognised as a serious health problem.[9] Various reported study details that burn and wound injuries have a major contribution in death occurring each year.[10] According to the WHO every year more than 3, 00,000 individuals died of fire-related burns and 95% of these deaths occurred in low and middle-income countries.[2] Despite having recent advancement in medical sciences the infection caused during the injury is still uncontrolled. For the successful management of burn injuries and to prevent death and deformity following burns, the systemic study of death reasons following burns and wounds has not yet been carried out so far. Therefore, an attempt has been undertaken with a view to fill up the lacuna in regard to knowledge about burns and associated problems.

The present study offers an overview of the significance of regulatory guidelines for marketing authorization of advanced dressings for wound and burn care in India. It is important to note that burn is a serious hazard and prone to infections that can finally lead to the death of the patient. Deaths due to burn are a major public health problem in a developing country like India.[3-4] Moreover, poor sanitation of burn care centers further aggravates the situation.

One of the major causes behind this is the quality and cost of advanced dressings that are being marketed in India. These are either imported or manufacturers trying to get it approved in EU/US. Further maintaining their standards related to infrastructure, approval fee, renewals finally led to increased cost of the product. India is lacking behind of their own quality regulatory standards for advanced dressings.

Hence, the treatment becomes further very costly as the dressings need to be changed regularly. This makes the purchase of such dressings non-affordable. Ultimately, this may lead to serious infection or death of the patient. Despite such alarming situation that occurs not due to the burn but due to the costly therapy. So, there is an urgent need for the development of advanced dressings without compromising its quality which is totally ignored by the Indian regulatory bodies.

Keeping all the facts, the aim of the present study is to develop quality regulatory guidelines for advanced wound care and burn dressings.

In order to achieve this aim, the following objectives have been proposed:

3.1 Brief objective of the research

1. Systematic analysis of regulatory requirements for surgical dressings in regulated and semi-regulated countries.
2. Survey of market availability of surgical dressings in India and their regulatory status.
3. Identification of gaps associated with existing regulatory guidelines for successful positioning of dressings in India.
4. Addition of parameters those are required for regulatory approval of surgical dressings.
5. Comparative study of physicians based acceptability of in-house surgical dressing and quality testing with respect to its established brand.
6. Statistical analysis of survey reports and preparation of guidance document.

3.2 Plan of work

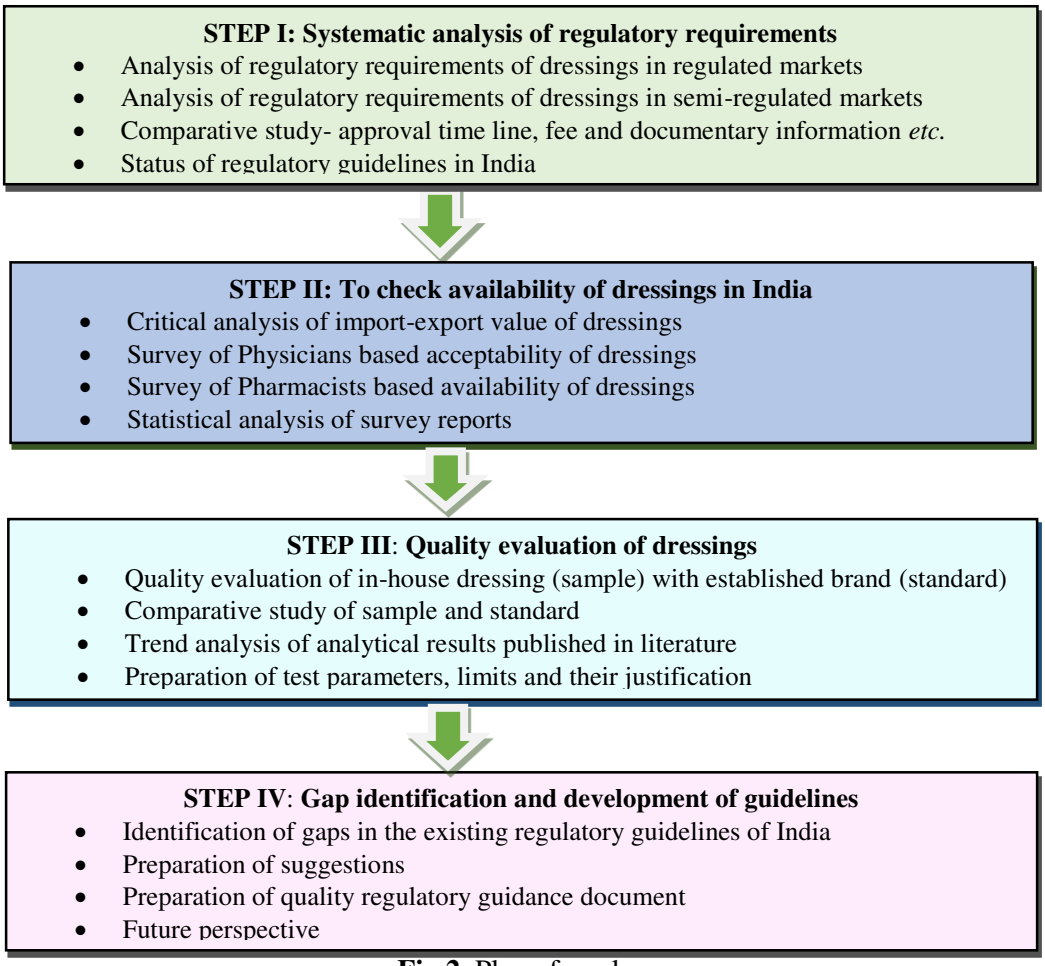

Fig.2. Plan of work

Chapter 4 Global regulatory aspects of wound care and burn dressings

Global regulatory study on dressings 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. 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.

Chapter 5 Import-export market of dressings in India

The Indian wound care market is growing at a CAGR of 7.4% which is quite higher in comparison to rest of the world.[11-12] Currently, dressings market is dominated by international companies, the major players are Molnlycke Health Care, Convatec Inc., B. Braun, Melsung AG, Medline Industries Inc., Kinetic Concept Inc., Systagenix Wound Management Ltd., Smith and Nephew, 3M Health Care, Coloplast A/S, Derma Science Inc., Paul Hertman AG. The market entry trends of Indian wound care dressings are given in Fig 3 and Fig 4 details different type of dressings and their contribution in Indian market segment. [13-14]

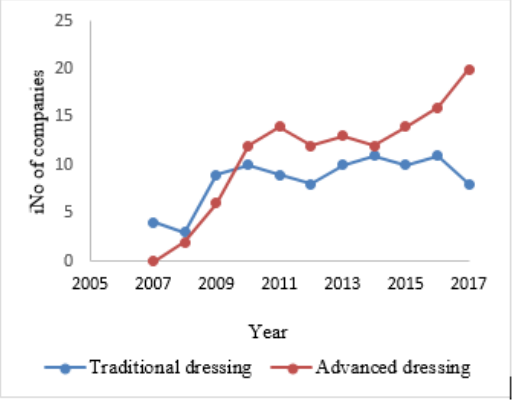

Fig.3. Market trends of wound care dressings

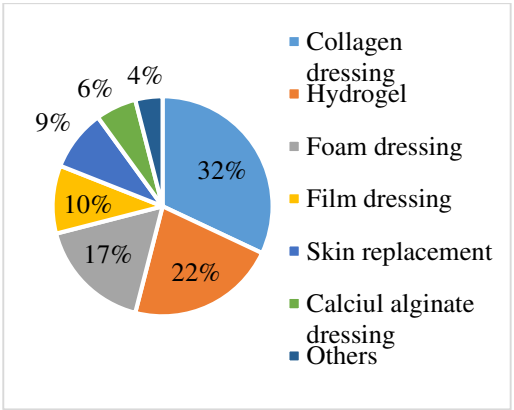

Fig.4. Wound care segments

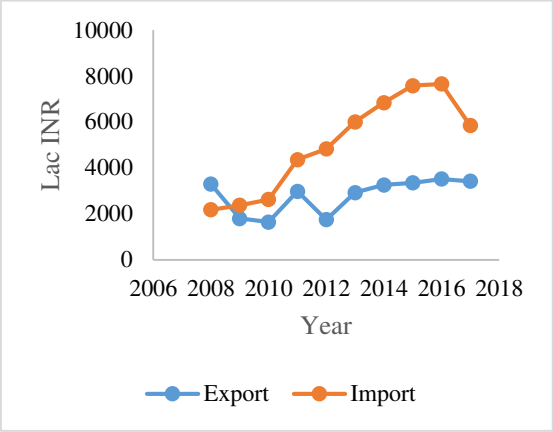

Fig.5. Import-export value 2008-2017

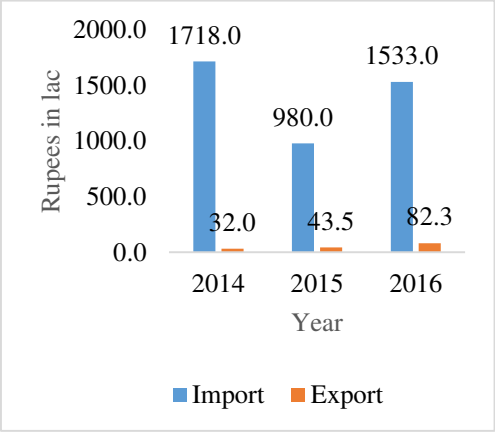

Fig.6. Import-export of major dressings

This chapter provides a complete analysis of import-export value of wound care and burn dressings in India. It helps in preparing growth strategies, knowledge about leading players, recent developments, business strategies and manufacturing status of the wound care and burn dressings in India. From the study, import need of dressings has been identified for India (Fig 5 and Fig 6).

Chapter 6 Survey of physicians and pharmacists

From the import-export study of burn and wound care dressings (Chapter-5), it is very much clear that import of the dressing is dominating over the exports and producing the deficit in Balance of Payments (BOP). Exports are not touching even a one crore value which means there is no export per say for the commodity. That directly states that the country does not stand anywhere in the market of the concern commodity. It is a matter of concern for all. Apart from this, to know the ground reality of the requirement of our subject commodity (burn and wound care dressings), there are many questions which need to be answered, which will lead to the actual requirement of the advanced dressing. To know the answers of most of the dressing related questions, a questionnaire was made and the answers were requested form 50 physicians and 100 pharmacists. The entire survey data is endorsed in this chapter.

Chapter 7 Quality evaluation and significance of different test parameters

Quality evaluation of in-house dressing (sample) was carried out and test results were compared with the imported dressing (standard). Significance of each test parameter that finally affect the wound healing was analysed.[15-18]

The sample (NANOKIN) was arranged which is having properties similar to the dressings that are currently imported to India.[17] Various samples of standard like BACTIGRASS and PRIMAPORE (Smith and Nephew), MEPORE (Molnlycke Health Care), TEGADERM™ (3M) were purchased from Kumar and Company drug store near PGI Chandigarh. It was found that TEGADERM film dressing was best suited to be selected as standard because it was having all the properties that the innovator's sample designed to claim for. The dressing was tested for parameters like appearance, dehydration rate or drying rate, fluid handling capacity, moisture vapour transmission rate and stickiness.[18-19]

Chapter 8 Development of regulatory guidelines

From the study in chapter 4,5,6 and 7 it was analysed that the concept of advanced dressings is emerging in India; however, indigenous manufacturing is hindered due to absence of clear regulatory guidelines. The lack of availability of advanced wound and burn dressings in the market critically affects patient survival rate. Imports from other countries make dressings unaffordable for middle class patients.

8.1 Gap analysis

Various gaps have been identified in the existing regulations (Medical Device Rules, 2017 as applicable since 01 Jan 2018) and tabulated below.

Table 1: Identification of gaps in the existing regulations

Present	Proposed	Reason for inclusion of particular section
Surgical dressings covered under Medical Device Rule, 2017	Definition of surgical dressing should be included in the rules	Applicant/Innovator can better classify their dressing category and rules applicable
Surgical dressings can be classified as class A, B, C, D category as applicable	Definition of invasive and non-invasive surgical dressing like antimicrobial bio-patch used with catheters used to be defined	Applicant/Innovator can better classify their dressing category and rules applicable
For class B one of the most imp. requirement is "Essential principles checklist for demonstrating conformity to the Essential principles of safety and performance of the product should be submitted"	Essential principles of safety and performance should be explained in the rules. How it is to be determined should be explained	Brief details about essential principles will leads to applicant better understanding in development of their product
Conformity assessment	Procedure for conformity assessment should be explained	Proper conformity evaluation procedure or check list will provide better understanding

Document as specified in the clause b of paragraph (i) of this part page 35 of the act	The list of documents required should be explained as clause b is not explained in the rules	The line mentioned in the rules, applicant is not able to trace what exactly documents required to be submitted to Health Authority of India
Information on product development not asked	Information on product development should be one of the requirement	Product development is one of the crucial step and it should be included in the guidelines or rules
Information on process validation is missing	Information on process validation should be required	Process validation parameter provides the information about consistency of the product
No quality control on raw material used for preparation of dressing	Requirement on the control of raw material used in the manufacturing of dressing should be discussed	The quality of the product can be achieved only if the quality is maintained at the initial step
Specification of dressings tests required not explained	Specification – list of tests given in annexure should be referenced	Applicant/ manufacturer is unaware about the list of tests required for dressings
Analytical procedure standard not defined	Analytical procedure should be referenced from Indian standard or British pharmacopoeia	Applicant/ manufacturer is unaware about the list of tests required for dressings
Analytical validation parameters explained only for in-vitro products	Analytical validation should also be mandatory for dressings	Analytical validation provides consistency and suitability of analytical test. Therefore, it should be mandatory requirement
Requirement of COAs not defined	Requirement of COAs, justification of specification should be one of the necessary requirement	At least three batches COA's should be one of the requirements. This ensure quality of product reaching market

8.2 Development of regulatory guidelines

After critical evaluation of gaps identified in the existing regulations in India and also regulatory formats existing in other countries, a regulatory framework is developed and named as **"COMMON SUBMISSION DOSSIER FOR ADVANCED WOUND AND BURN DRESSINGS"**.

Methodology adopted

A. Identification of gaps in existing guidelines as approved for medical devices under the new Medical Devices Rules, 2017 released by India's Ministry of Health and Family Welfare in Gazette of India, Extraordinary Part II, section 3, sub section (i), vide notification no G.S.R. 983(E), implemented since 01 January 2018.

B. Review of the regulatory approval framework in 13 countries covering major continents viz. Europe, Asia, Africa, Middle-East and Latin America. The 13 countries viz. United States, Europe, Japan, Canada, Australia, Brazil, China, Singapore, Malaysia, Mexico, India, Israel and Russia were studied, compiled and analyzed.

C. Review of technical parameters compiled from published sources relating to wound care and burn dressings.

Chapter 9 Results and discussion

The market value of the advance dressing is reaching new peaks in developed countries since they are associated with benefits like the simplicity of use, reduced recovery time and optimum results. Unlike developed countries like the EU and US, not all developing countries can manage the production of such dressings in their own countries even if they are associated with reduced healing time and further reduces hospital expenses. Therefore, imports of such products dominate in these countries. It has been observed from the study that dressing market in India is majorly dominated by Smith & Nephew plc. (U.K).

During literature review it has been found that certain types of advanced dressings are in the innovation phase. It is expected that the dressing under clinical trials will be able to provide a better treatment to the burn and wound patients. Various types of materials or combination of materials have been used to prepare such innovative dressings.

Results of comprehensive study of global regulatory guidelines for wound care and burn dressings reveals that these dressings are categorized under the medical device and not the drug. Dressings are removed from The Drug and Cosmetic Act, 1940 and Rules, 1945 thereunder. A new Medical Device Rules, 2017 implemented since 01 Jan 2018. The critical analysis of regulatory guidelines of 13 countries shows that most of the countries have very well-defined guidelines for manufacturing and development, approval and renewal procedure. The well-defined guidelines promote manufacturing in their own country and thus the quality product with low cost reaches to the bedside of the patient. To maintain the quality standards many countries are following the GHTF, ISO, BSEN and US standards to develop their products and some having their own quality manual / quality confirmation system. It was noticed that India is missing for own quality regulatory guidelines although having new Medical Device Rules, 2017 is in place. The ISO or BIS has not been revised yet for such advanced dressings and their no monographs available for testing of such dressings and no quality control is available on raw materials used in manufacturing of these advanced dressings.

Therefore, due to unclear regulatory guidelines for quality parameters, the export import market study was done to know the exact status of these dressings in India.

To analyze the trends on expenditure on the wound and burn dressing the raw data of the year 2008-2017 were collected from various market research analysis sites and import-export analysis is done on the same. The detailed analysis reveals that India is a growing market for wound and burn dressings and spending a lot of exchequer on importing the subject commodity.

Further, study of major dressings in-use in India from 2014 to 2016 was studied and it was found that the overall yearly import never came down below INR 980 lac that itself reveals that there is a huge import of the subject commodity (wound and burn dressing) and relatively higher consumption over the production within the country. The import has touched the peak of INR 1718 Lac in 2014 and INR 1533 Lac in 2016. The average import comes out to be INR 1410 Lac which anyhow attracts the exporters of the commodity to expand their business in India. Exports are not touching even a crore value which means there is no export per say for the commodity. That directly states that the country does not stand anywhere in the market of the commodity. It is a matter of concern for economics.

Ten different categorical set of data based on different variables were interpreted. The percentage distribution in the form of pie charts or graphs was prepared, in order to emphasize the importance of a particular area or subject based on the response. Another test involves the Chi-square test which does not take into account the percentage responses of the respondents. From the survey study of physicians, it was found that infection is the most common cause of death in burn and wound injury. The equal percentage (46%) reported both reasons *i.e.* "non-availability of advanced dressings" and "infection" as the major cause of death. After that current practice to treat burn and wound patients were analyzed on a scale of 1 to 5 and it was found that 42% physicians reported the current practice used is moderate, 40% reported it as difficult and 6% reported it is very difficult to treat patients with the current practice followed in hospitals. To calculate the overall cost of the treatment, patient hospitalization was determined. 66% of physicians reported that generally, 1 month is the most likely duration for hospitalization in burn case. Further, common frequency to change the dressings were reported as 18-24hrs (60%), 8-10 hrs and 4-6 hrs by 10% and 20% physicians respectively. The problem is using advanced dressings were analyzed. It was found that 60% of physicians reported that due to high cost these are

not affordable by common patients and 30% reported they are not easily available. In a study about the most common challenge to treat these patients, 70% of physicians reported that infection control is the most common challenge. Finally, 98% of physicians reported yes advanced dressings can prevent infection caused during post burn and wound injury. Currently from the list of advanced dressings "Bactigras" is the most preferred advanced dressings as reported by 46% physicians and 34%, 10%, 2% for cellulosic dressings, Alginate dressings, Primapore respectively. It was reported that 50% of physicians are still using traditional dressings like paraffin gauze and silver sulfadiazine and 24 % are using advanced dressings and rest 10% are still use ointment and creams in the treatment. To provide better treatment and to reduce the death rate several possible expectations were reported by physicians. 30% reported that the cost of the advanced dressings should be reduced and 14% reported for better sterilization of dressings and maintenance of the aseptic area. Further, 12%, 10%, 8% reported to improve hygiene, increase burn units, prevent indiscriminate use of antibiotics respectively.

From the interpretation of physicians survey study, the value of the chi-square test is 15.041 with df = 4 having $p = 0.005 < 0.05$ of significance level. It was found to have an association in the most cause of death due to burn and the common challenge to treat patient with open wound treatment. In hypothesis-2 the value comes out to be 1.198 with df = 2 and have $p = 0.043 < 0.05$, significance level. From the values, it could be interpreted that there is an association between the most cause of death due to burn and advance dressing can prevent death due to infection. In third hypothesis the value of chi-square test is 7.257 with df = 6 having p-value = $0.298 > 0.05$, significance level. It means there is no any association between the most cause of death due to burn and the most preferred advanced dressings.

The survey study of pharmacists shows that in India 74% advanced dressings are EU regulatory body approved and only 24% available dressings are Indian approved and most of them are traditional only. Currently, foreign companies regulatory bodies have a complete hold on advanced dressings market. From the survey study, major products were of Smith and Nephew Health Care ltd., followed by Convatec and 3M Health Care, Molnlycke Health Care, Coloplast and Insense. In case of cost-effectiveness the

Acticoat advanced dressings having the highest cost followed by Allevyl, Comfeel plus and then Tegaderm and Mepilex.

Quality Evaluation of Dressings

To check the quality of dressings, their evaluation parameters, limits and the significance of test parameters; an in-house study was carried out on an in-house test sample and marketed standard dressings. It was found that the various factors affect the quality of the product and further limits its use for wound healing. Cellophane dressing has found to have better quality results and having well known efficacious in advancing the wound healing process. From the results obtained, it was found that sample drying rate was 0.000527g/min and for standard it was 0.000822 g/min that was lower than the standard as it is a good property of dressing that it should not dry at the wound site.

Further, FHC was determined. Analytical result shows that sample was good in fluid handling *i.e.* 27.981% as compared to standard 5.027%. One of the main factor responsible for wound healing is a moisture vapour transmission rate. It was found that the sample was having MVTR value 8667.8g/m^2/24hour and standard was 11365.8g/m^2/24hour which was quite high. The stickiness is one of the major factor in wound healing as more will be the stickiness more will be peel off skin during change of dressing. When stickiness was tested, it was found that none of the dressings were found to have sticky property.

Based on key points identified, the regulatory guidelines have been developed and following suggestions have been showcased:

Suggestions:

1. Government should run more dedicated awareness programmes for burn and wounded patients. Existing programmes should be revamped and new should be initiated in the support.
2. The education system (M. Pharmacy or Ph.D in regulatory affairs) should be directly linked with the govt. regulatory bodies which are responsible for registrations and renewals.
3. There should be certified regulatory agents whom an innovator and manufacturer can vouch upon for a legal guidance.

4. India should endeavour for self-reliance and try to curb the high rising graphs of imports of advanced dressings. On the other hand, to give subsidies on the imports can be an economic tool to bring an affordable advanced dressing at the bedside.
5. There must be proper guidelines that states which type of dressing is to be used for which type of wound. As on date such guidelines / procedure are not yet available.
6. The government should have own manufacturing units as it is not there till date and should release funds to motivate innovators and manufacturers of the advanced dressings.
7. India should boost the in-house manufacturing and why not to divert the "Make-in-India" programme towards the manufacturing of medical devices like advanced dressings.
8. Due to long approval procedures of Indian regulatory authority, manufacturers and innovators in India seek for their approval in other countries and leads to loss of exchequer / Indian currency. To maintain other country's regulatory standards, manufacturers need to pay a hefty amount for the audits and infrastructures charges. Therefore, a clear picture of the regulatory guidelines is required that attracts manufacturers to seek approval from Indian regulatory and carry out the production on the same. These products should be at par with international standards which can compete with foreign products in the market.
9. There should be proper wound and burn care regulatory guidelines like in EU, US and Canada.
10. The guidelines should be compatible and harmonized with regulatory bodies of other developed countries.
11. There should be an application based information system to make clarity on application filing, registrations, renewals and audits *etc.*
12. The clear picture of quality regulatory guidelines that are still missing with following points:
    a. There are no standardization/validation guidelines for the instruments used in the assessment of wound size and its type.
    b. Unavailability of quality testing monographs for testing of advanced dressings.
    c. The absence of proper guidelines on clinical trials. There is no ideal animal model available to carry out clinical study.

d. Non-availability of the standard sterilization procedure.

13. There is a confirm requirement of strict adherence to the audit regulations by the audit teams like ISO, BIS *etc.*
14. There should be an electronic system for the filing of the application and registrations dossiers.

Chapter-10 Summary, conclusion and future perspective

Innovations are the key to technological advancements and improved healthcare. In case of burn and wound care, worldwide several groups are working on improved dressings to enable better care for patients and enhance survival rates of burn and wound patients.

Apart from technology, a very critical aspect influencing availability of advanced dressings is economy *i.e.* cost of such dressing? Despite the availability of technologies, advanced dressings which can take care of wounds, burns and help to save patients, are available mainly in developed countries and patients in third world countries like India, have no access to such dressings owing to its high cost.

Indigenous manufacturing can drastically cut down the cost of advanced wound and burn dressings. However, the lack of knowledge of regulatory approvals becomes a major barrier to indigenous manufacturing and "Make-in-India" efforts. In absence of quality regulatory guidelines Indian manufacturers are forced to take approval from foreign regulatory authorities. This creates lots of hurdles for small scale manufacturers and enhances the cost of dressings.

Hence, there is a dire need to address the issue and develop suitable guidelines for approval of such dressings in India. Accordingly, the study was carried out and involved data collection at field level from Pharmacists (to understand which type of dressings are currently in use in India for burns and wounds, costing and also whether indigenous or imported) and also interaction with doctors (to understand the reasons for preferences and also knowledge and availability of dressings and advances in wound care and burn treatment in India). Data collection and analysis was also carried out with respect to imports of dressings in India and exports also.

Thereafter, data relating to various technical parameters as reported in literature, for burn and wound dressings were compiled and compared to understand the range of variation for various parameters. Quality parameters concerning the type of material,

pore size, MVTR (Moisture Vapour Transmission Rate), FHC (Fluid Handling Capacity), shape, density, size and other test parameters applicable to such dressings were compiled and analyzed. A novel dressing consisting of regenerated cellulose membranes with a central absorbent pad of non-woven cellulose developed in India as an advanced wound and burn dressing was compared with internationally approved dressing.

To understand and develop the regulatory guidelines for advanced dressings, the regulatory process and guidelines from 13 countries worldwide viz. United States, Europe, Japan, Canada, Australia, Brazil, China, Singapore, Malaysia, Mexico, India, Israel and Russia were studied, compiled and analyzed.

The results of the study revealed that there are well-defined technical parameters and ranges relating to desirable properties of advanced dressings which if put into place and notified by the Indian Regulatory Authorities can greatly facilitate the approval of new and innovative burn and wound dressings. They can also help in indigenous manufacturing of dressings already approved in developed countries.

An outcome of the present work is a well-defined framework in the form of 'guidelines' which can help regulatory agencies in India in the approval of advanced wound care and burn dressings. The framework is based on an extensive review of the regulatory framework in 13 countries and harmonizes the administrative and technical requirements which must be fulfilled to grant approval to a wound care or burn dressings.

In future this document can be converted to e-form which will be flagged on health authority website and hence, will be an arm of "Digital India". This e-database will help in the post lifecycle management of the innovative dressings and also can be used as benchmark/standard for the next innovator/manufacturer. The guidance document will help in future for better understanding of regulatory requirements of advanced dressings to innovators and manufacturers in India. This will give a ray of hope for all pipelined products to reach bedside of the patient with low cost. Further it will give a boost to the production of the advanced dressings in India and hence will counter the import of the commodity. Availability of low cost advanced dressings will lower down the threat of deaths due to infection caused during burn and wound injury. It will not only reduce

the exchequer outflow but also will give a support to good health vision of Government of India.

Chapter 11

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Publication and conferences

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4. Attended conference on "Design of Experiments" jointly organised by Qsutra and School of Pharmaceutical Sciences, Lovely Professional University.
5. Published paper in Regulatory Focus. A new regulatory paradigm for medical device in India Nov.2017. Available at regulatoryfocus.org.
6. Submitted article on Regulatory approval process for advanced dressings in India – an overview of new rules in Journal of Wound Care.
7. Submitted article on Quality evaluation of cellulosic dressing and physician perception about its use in Journal of Wound Care.
8. Submitted article on Import need of wound care and burn dressings in India: a bio economic challenge in International Wound Journal.
9. Submitted article on Role of advanced dressings in burn and wound injury- an Indian perspective in Wounds Asia.