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Regulatory consideration for the commercialization of topical products for wound healing in India.

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ABSTRACT
Topical medications, like all other pharmaceuticals, are subject to restrictions to guarantee the consistency, purity, and effectiveness of the medication both at the time of delivery and during its shelf life. There is some scientific evidence that topical products are safe and effective treatment choice for the control of various skin-related diseases such as burns, eczema, psoriasis, skin infections, skin ulcers, and so on, and that it is used for local intervention. Topical formulations are a good choice for drug distribution because of their various unique characteristics and they can be quickly separated from the skin.. Different countries must adhere to different legal standards in order to approve a new drug on their market. Until a drug substance can be approved for manufacture, production, or selling in the region, it must first be tested for safety and effectiveness in humans. The government has established a number of regulatory bodies to oversee the production and sale of drug products in order to ensure their safety and effectiveness.
Topical, Skin, regulation, wound healing, and so on are some of the key words.

I. INTRODUCTION

Wound and healing of wounds

Wound healing is a natural mechanism that entails a series of complex cellular and bio molecular processes that help to return injured wound tissue to its pre-injury state.[1]

Hemostasis, inflammation, proliferation, and remodeling are the four stages of the operation, which are traditionally separated into four steps that overlap. Alarm signals, chemokine, and growth factors are released by wounded tissue cells, which attract immune cells from the bloodstream and promote the replication of tissue resident populations, resulting in immune cell aggregation at the wound site.[2]

The majority of wounds recover on their own, but the only care given to them is to keep them safe from the world. Burn wounds are graded according to the depth of the burn, while acute and nonhealing wounds are differentiated based on the time to heal. For example-

- Cleaning and debridement of the wound, as well as antibiotics if required, are common treatments for superficial burns.
- Topical antimicrobials are mostly used to treat deep partial-thickness and full-thickness burn wounds, but if a wider area has to be covered, skin replacements or skin grafts like autologous split thickness graft are the gold standard around the world.[4]

CLASS	EXAMPLE
Product which enhance epithelialization	• Collagen dressings • Hydrogels • Hydro foams • Hydrocolloid • Growth factors
Product which prevent infection	• Antimicrobials like silver

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	impregnated dressings • Mupirocin • Retapamulin
Desloughing and debriding agents	• Maggots • Debridace • Enzymatic agents (collagenase, papaya extracts
Product which enhance granulation issue formation	• Hydrocolloids • Hydrogels • Alginates • Collagen granules

Repeated dressing adjustments, wound debridement, antibiotics to cure bacteria, and prevention of increased strain at the injury site are all part of the existing standard of treatment for nonhealing wounds. Just four wound-healing pharmaceuticals have been approved by the Food and Drug Administration (FDA) as active medicinal products[3]. Since nonhealing wounds have such a large systemic effect, researchers are working hard to find ways to enhance wound healing.

Topical therapeutics are promising because they exert local effects while minimizing systemic side effects, but they are inhibited by the proteolysis wound environment, which limits medication bioavailability.[2]

CLASS	EXAMPLE
Product which enhance epithelialization	• Collagen dressings • Hydrogels • Hydro foams • Hydrocolloid • Growth factors
Product which prevent infection	• Antimicrobials like silver impregnated dressings • Mupirocin • Retapamulin
Desloughing and debriding agents	• Maggots • Debridace • Enzymatic agents (collagenase, papaya extracts
Product which enhance granulation issue formation	• Hydrocolloids • Hydrogels • Alginates • Collagen granules

TABLE 1-Classification of newer wound care products

CATEGORY	ACTIVE WOUNDS	CHRONIC WOUNDS	BURNS
BASIC WOUND CARE (cover and protect wounds)	• Topical antibiotics • antiseptics	• topical antibiotics • topical antifungal	• topical silver nitrate • anti-microbial
ADVANCED WOUND CARE (promote moist environment)	• film dressing • foam dressing • hydrogel dressing • alginate	• film dressing • foam dressing • hydrogel dressing • alginate dressing • hydrocolloid dressing	• foam dressing • hydrogel dressing

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	dressing • hydrocolloid dressing		
ACTIVE WOUND CARE (stimulate healing)	• cell based therapy • growth factors	• cell based therapy • growth factors	• Skin replacement

Table2 - Different Level of Wound Care Applied For Distinct Wound Category

RECENT ADVANCES IN TOPICAL PRODUCT RELATED TO WOUND HEALING

Topical semisolid medication preparations are one of the oldest medical dosage forms known to human civilization, and they're frequently utilised to treat a wide range of skin disorders. Despite their relevance and long history of usage, semisolid medicines lag behind other pharmaceutical product categories in terms of innovation. Because topical treatments often generate smaller revenues, predicted return on investment-related risks stymie the development of both innovative and generic medicines.[16]To be specific, the pharmaceutical business must devote substantial resources to demonstrating the quality, effectiveness, and safety of any product before it can be approved for sale by the authorities.[17]

Semisolid formulations, such as ointments, creams, and gels, have a more complicated, interdependent microstructure (i.e., the micro scale arrangement of matter and state of aggregation) than solid and injectable dosage forms, which increases the potential for heterogeneity in performance[18, 19]. Furthermore, as compared to other medication products for which standard pharmacokinetic techniques may be used to determine bioequivalence, topical medicinal products confront distinct challenges in the creation of generics.[16, 20]

For the treatment of both acute and chronic non-healing wounds, a wide range of dressing procedures, topical products are available.[12]

The area of wound care appears to have as many treatment methods and modalities as the number of wound care practitioners. Although many clinicians rely on and have good results with older “tried and true” therapies, new products and innovations are constantly being added to the wound care arsenal.Silver dressings have long been used to treat wounds, but modern delivery methods seek to improve effectiveness while reducing side effects. Negative pressure wound devices are a relatively new treatment choice in wound care, and their indications are steadily expanding to include areas of wound management where there were previously few options.

Advanced wound dressings can help optimise wound healing by changing the wound climate. Skin replacements are being developed as a result of biosynthetics and tissue engineering, and they are not only providing novel efficient temporary wound coverage, but they are also changing the wound care paradigm.Finally, hyperbaric oxygen therapy can supplement the above wound-healing modalities, particularly in chronic wounds that haven't responded to other treatments.[13]

PRODUCT	INDICATION	EXAMPLES
Antimicrobials Mupirocin	Wounds infected with gram positive organisms.	• T-bact ,Bactroban(Glaxosmithkline pharmaceuticals ltd)
Retapamulin	Effective against staphylococcus aureus and pyogenes.	• Retarel(Ajanta Pharma ltd.)
Silver impregnated dressings	Deep burns skin sloughing disorders	• Acticoat (Smith & Nephew) • Silvel(dattMediproductspvt.ltd.) • actisorb(Johnson and Johnson)
Foams	Prrssure ulcers and lower limb ulcers wit min to mod exudates	• Allevyn(smith & nephew) • Biatain foam dressing(coloplast)

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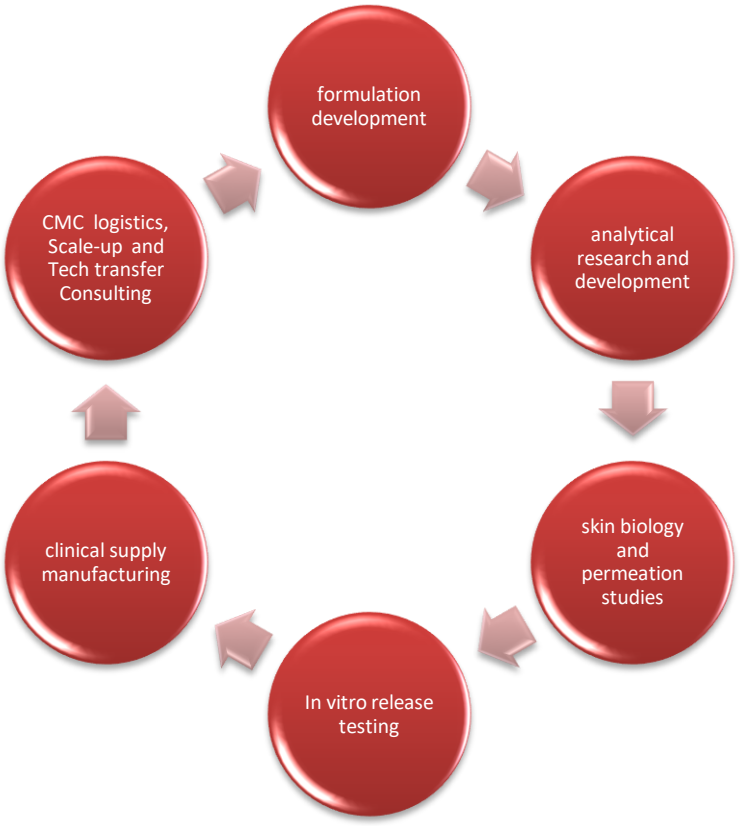
Films	Partial thickness wounds with minimal exudates,pressureulcers,grafts	• 3M Tegaderm (Health Care) • Biocclusive (Johnson amd Johnson medical Ltd.) • Dermasite (Derma Sciences)
Hydrogels	Dry wounds, painful wounds mainly pressure sores, lower limb ulcers, skin tears and surgical wounds	• Intrasite gel (smith &Nephew) • Solosite(smith &nephew)
Hydrocolloids	Wounds with min. to mod exudates like pressure ulcers and venous stasis ulcers.	• DuoDerm (convatec) • Comfeel (coloplast India Pvt.Ltd.)
Alginates	Pressure sores, diabetic ulcers, infected wounds,lower extremity ulcers with moderate to heavy exudates	• Kaltostat (ConvaTec) • Algiderm(Bard) • Kalginate(DeRoyal)
Enzymatic debridement	For necrotic sloughy wounds	• Collagenase santyl (Smith & Nephew) • Salutyl (Elder pharmaceuticals Ltd)
Growth factors	In small non healing wounds	• Plermin (Dr. Reddy's laboratories ltd) • Regen -D 150 (bharat biotech)

TABLE3- examples of topical products related to wound healing

STAGES IN FORMULATION DEVELOPMENT



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QC FOR TOPICAL PRODUCTS

❖ PRODUCT QUALITY TEST-GENERAL

Specifications (tests, methods, and acceptance criteria) to guarantee that marketed drug products are safe and effective at release and during shelf life are recommended by the International Conference on Harmonization (ICH) Guidance Q6A (available at www.ich.org). Description, identification, assay, and impurities are tests that are widely used to verify safety and efficacy.[15]

- Qualitative description
- Identification
- Assay
- Impurities
- Physicochemical properties
- Uniformity of dosage units
- Water content
- Microbial limits
- Antimicrobial preservative content

❖ PRODUCT QUALITY TESTS FOR TOPICAL DRUG PRODUCTS

For topical medication products, general product quality tests should be conducted, including identification, assay, content uniformity (uniformity of dosage units), contaminants, pH, water content, microbiological limits, antimicrobial preservative content, antioxidant preservative content, and sterility. Specific testing for topical dosage forms should also be carried out.[15]

- Viscosity
- Tube/content uniformity
- pH
- particle size
- sterility

PATENT AND CLINICAL TRIALS RELATED TO WOUND HEALING TOPICAL PRODUCTS

Treatment	Condition	Administration route	Ongoing clinical trial
ABSOLVE	Diabetic foot ulcers	Collagen dressing	NCT03037970
Masenchymal stem cells	Diabetic foot ulcers	Single-dose topical application seeded into collagen scaffold	NCT03509870
ABCB5-positive MSCs	Chronic venous ulcers	Topical application	NCT03257098 NCT02742844
Masenchymal stem cells	Second degree burn wounds	Topical application	NCT02104713
Stromal vascular fraction	Chronic leg ulcers	Local injection	NCT02987101
MRG-110	Wound healing in healthy participants	Local injection	NCT03603431
TotaSure topical gel	Punch biopsy wounds in healthy	Topical gel	NCT03620175
Granexin	Diabetic foot ulcers	Topical gel	NCT02667327 NCT02666131

Table4 Ongoing clinical trials assessing the effect of different medicinal products in wound healing.

Treatment	Condition	phase	Administration route	Completed clinical trial (reference)
Epidermal growth factor	Diabetic foot ulcers	III	Topical spray	NCT01629199(7)
Recombinant human GM-CSF hydrogel	Deep partial thickness burn	IV	Topical gel	NCT01785784(8)
BioChaperone™ PDGF-BB	Diabetic foot ulcers	III	Topical spray	NCT02236793
APOSEC™	Healthy volunteers	I	Topical gel	NCT02284360(9)
ALLO-ASC-	Second degree	I	Hydrogel sheet	NCT02394873

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DFU	burn			
HPβCD-I	Pressure ulcers	I,II	Topical gel	NCT02418676(10)
SANTYL	Diabetic foot ulcers	IV	Ointment	NCT01143714 NCT01143727 NCT01408277 NCT01056198(11)

Table 5-Completed clinical trial assessing the effect of different medicinal products in wound healing

REGULATORY PERSPECTIVE

CURRENT SCENARIO AND NEED FOR EFFECTIVE DRUG REGULATION

Optimal modern wound dressings should assure a moisture wound bed, help drainage, remove debris of the wound surface, provide optimal thermal stability, might be removed without trauma of the wound bed and wound edge, and be antiallergenic and without immunogenicity. But wound dressings have experienced continuous and significant changes over the years which emanate from a more detailed understanding of wound healing and improved technological, clinical, and scientific research in the field of wound healing. Now, wound dressings are getting more and more functionalized to a targeted therapy by including different pharmaceutical compounds (e.g., antiseptics, analgetics, or growth factors). Those interactive additives might help optimize the healing process[14]

There have been a variety of regulatory issues in the process of improving drug regulation.

REGULATORY BODIES INVOLVED IN APPROVAL PROCESS

At the moment, there is no single body in charge of ensuring the overall efficacy of the Indian drug regulatory system. There are many regulatory bodies involved in the complete commercialization procedure for the topical products.

- **CDSCO-**the Ministry of Health & Family Welfare's Central Drugs standard Control Organization (CDSCO) provides general information on drug regulatory criteria; CDSCO is in charge of approving clinical trials, experimental medicines, specialized medical products as well as import and export authorizations.
- **NPPA-**It promotes and supports the Central Drugs Standard Control Organization in the testing of drugs.
- **D & C ACT,1940-** In India, the Drugs and Cosmetics Act of 1940 governs the import, manufacture, delivery, and selling of drugs.
- **GCP GUIDELINES**-the Ministry of Health, in collaboration with the Drug Controller General of India (DCGI) and the Indian Council for Medical Research (ICMR), has published draught research guidelines for human subjects.
- **SCHEDULE M OF THE D & C ACT-** It defines the general and precise specifications for factory premises, supplies, plant, and facilities, as well as the minimum recommended areas for standard installation .

VARIOUS FORMS OF APPLICATION REQUIRED FOR THE COMMERCIALIZATION OF TOPICAL PRODUCTS

S.no.	Purpose	Application for grant of permission	Grant of permission (permission issued in form)
1	To conduct clinical trial	CT-04	CT-06
2	For the Manufacturing of new drug for clinical trial or for examination, test and analysis	CT-10	CT-11
3	New drug imported for clinical study or review, research and study	CT-16	CT-17
4	To Import or manufacture of new	CT-18	CT-19 for API and CT-20 for pharmaceutical formulation

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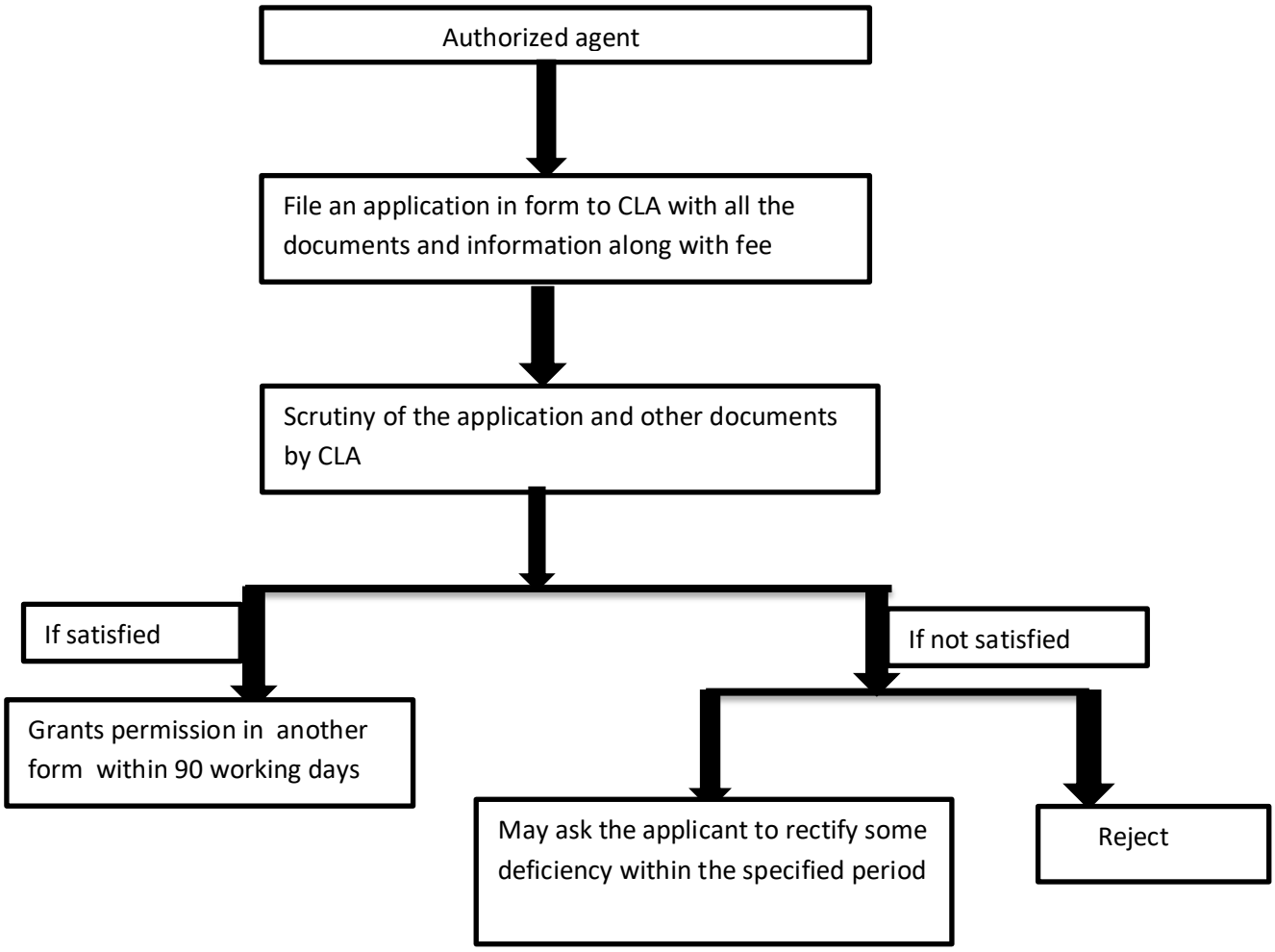
	drug for sale or for distribution		
5	To manufacture a new drug formulation for sale or distribution	CT-21	CT-22 for API and CT-23 for pharmaceutical formulation

PROCEDURE FOLLOWED BY THE AUTHORIZED AGENT FOR THE APPROVAL



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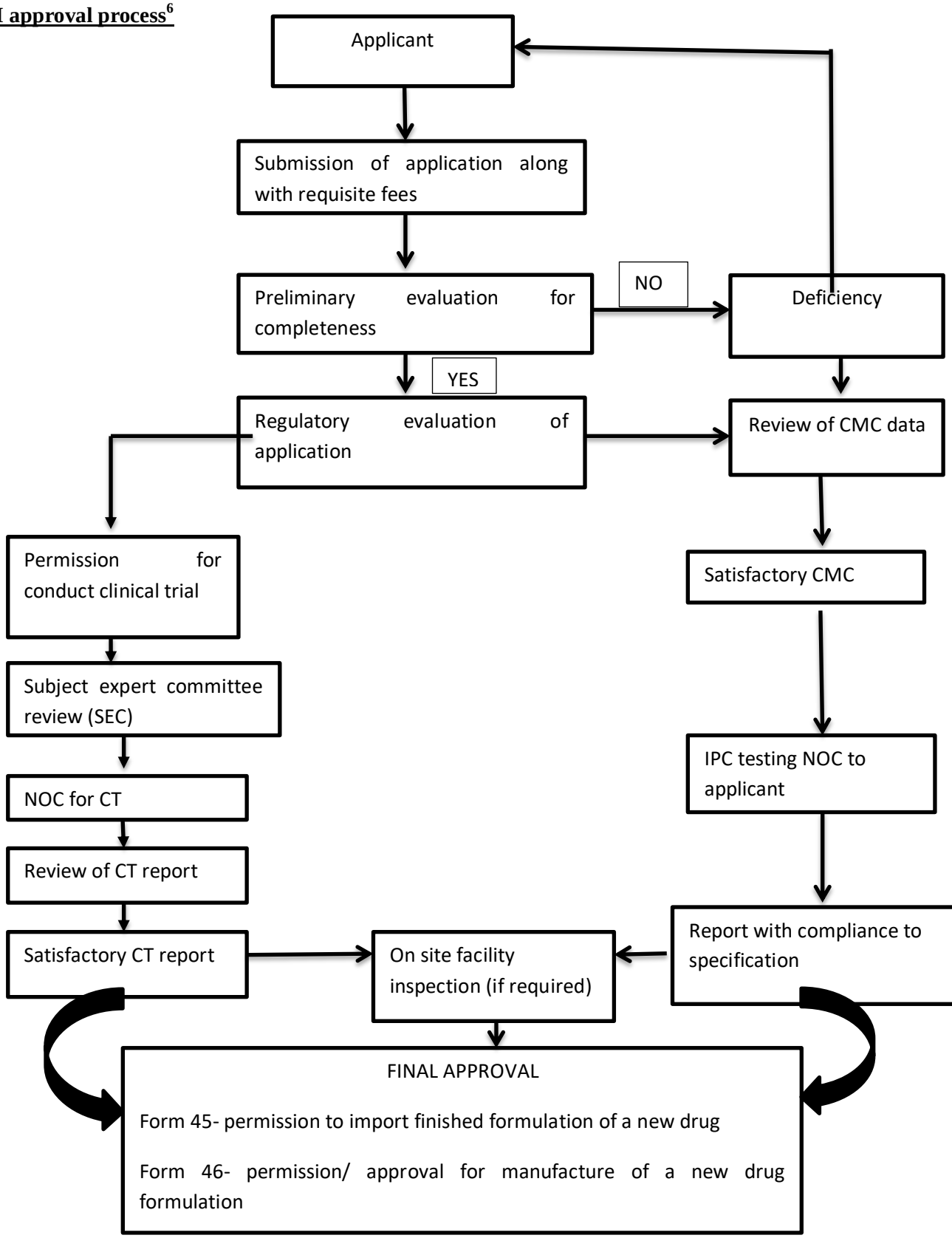
DCGI approval process[6]



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DATA TO BE SUBMITTED WITH THE APPLICATION

Documents that must be handed in

1. The object of the application for (permission to manufacture/import/clinical trial) should be explicitly stated.
2. The applicant's name
3. The new drug's name
4. Application in Form 44, properly signed and approved by an authorized representative of the company in all respects
5. INR 50,000 (phase I) or INR 25,000 (phase II/III) Treasury challan
6. A copy of a current production license (Form 25/28)
7. Bulk pharmacy supplier
8. An outline of the drug and the treatment community to which it belongs.
9. Information on chemicals and pharmaceuticals
10. Drug specifics (Generic Name, Chemical Name, or International Nonproprietary Names (INN))
11. Pharmacology of animals
12. Toxicology of animals
13. Pharmacology in humans or in clinical trials (Phase I)
14. Therapeutic exploratory trials (Phase II)
15. Therapeutic confirmatory trials (Phase III)
16. Research programs
17. Other countries' regulatory position
• **Promoted**
• **Accepted**
• **Approved as an IND (Investigative New Drug).**
• **Any withdrawals, if any, of justifications**
18. Information for prescribing
19. Testing protocol/s and samples
20. Global drug trial and new chemical entity:
21. A copy of the State Licensing Authority's license to import any substance for sale (in case the application is for manufacture for sale of new drug)

FEE PAYABLE FOR LICENSE, PERMISSION AND REGISTRATION CERTIFICATE

SERIAL NO.	SUBJECT	IN RUPEES (INR)
1.	Application for permission to conduct clinical trial	
	i. Phase I	3,00,000
	i. Phase II	2,00,000
	i. Phase III	2,00,000
	v. Phase IV	2,00,000
2.	Application for permission to manufacture new drugs for clinical trial.	5000 per product
3.	Application for import of new drugs for clinical trial or for examination, test and analysis.	5000 per product
4.	Application for permission to import new drug (Finished formulation) for marketing	5,00,000
5.	Application for permission to import new	5,00,000

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	drug (Active pharmaceutical ingredient) for marketing	
6.	Application for permission to manufacture new drug (Active pharmaceutical ingredient or finished formulation) for sale or distribution	5,00,000
7.	Application for permission to manufacture fixed dose combination already approved for sale or distribution.	3,00,000
8.	Application for permission to manufacture unapproved new drug but under clinical trial for treatment of patient of life threatening disease	5000
9.	Pre- submission meeting	5,00,000
10.	Post- submission meeting	50000

Topical drug delivery challenges and drawbacks for speeding wound healing

There are many challenges to address when developing topical drugs for wound healing. In addition to accelerating wound healing, such a treatment must be able to withstand the proteolytic wound environment in order to ensure the active substance's bioavailability. Furthermore, dressing changes disrupt the healing process, so the best treatment includes extended release and/or consequences. In order to get into the market, the procedure must also be cost-effective. Combining both of these attributes is a difficult task.New-generation biological drugs in the form of growth factors and chemokines are integrated into wound dressings and/or co-administered with protease inhibitors to resolve the proteolytic environment and provide extended drug release. Furthermore, since cell and gene therapy provide continuous release of growth factors or chemokines, there is a greater need for limiting dispersion beyond the wound region to avoid systemic effects. However, these promising recombinant proteins, gene, and cell therapies are currently prohibitively costly, limiting clinical availability.[2]

II. CONCLUSION

Wound care has come a long way from its inception, thanks to increased knowledge of wound healing's physical properties and the use of smart wound dressing products. Wound dressings should no longer only function as exudate controllers or absorbents; they should also interact on a cellular basis to correct wound milieu imbalances and aid wound healing.

New physical procedures and dressing fabrics, such as cold argon plasma or silk fibres, have also made their way into wound care as groundbreaking recovery alternatives.

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