

Development of Wound Management Products for the US: An Anomaly for Global Product Development Model

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Wound care products are primarily aimed at ensuring timely wound healing and effective infection control. There are hundreds of wound care products available on the market, from over-the-counter (OTC) to prescription products. Most wound care products are topical and are approved as medical devices; but a few drugs and biologics have been approved for the treatment of wounds as well.

The wound care market is very centralized at present, with the US, Europe and Japan collectively accounting for more than 80% of global wound care product sales; the worldwide market value is estimated to be about \$12–15 billion (US). The biggest variables, however, are the regulatory pathways required for marketing approval of wound management products, with the US regulatory requirements being very different from most other countries.

In addition, the standard of care differs greatly between developed and developing countries, making it harder to conduct adequately controlled clinical trials in a truly global setting. For these reasons, a global product development paradigm, which is standard for most medical products, is hard to implement for wound care products, particularly those intended for chronic wounds.

Types of Wounds and Wound Care Products

The types of wounds can be organized into four broad categories. The assemblage contains anything from minor scrapes to severe burns and wounds caused by chronic illnesses.

Table 1 summarizes the major wound categories, with most common representative indications in the US alone. The distribution of types of wounds is similar in most regions of the world.

More than 90% of wounds come from surgical processes or traumatic injuries. Most of these wounds can either be treated with traditional wound management and closure products such as adhesive bandages, topical ointments, gauzes and sutures. Treatment of these wounds is fairly similar the world over and most remedies in this category are either available as OTC products or lower-risk prescription products.

In the US, most traditional wound management and closure products are considered low-risk Class I medical devices that do not require much preclinical and clinical evidence for marketing approval.

Treatment of burns or wounds caused by underlying illnesses usually require more specialized treatments such as moist or active wound healing products. These include diabetic foot ulcers (DFU), pressure ulcers (PU) and venous leg ulcers (VLU). It is in management of these wounds where significant differences exist between the US and the rest of the world in regulatory requirements for marketing approval.

Not only is the standard of care available to patients very different between developed and

developing countries, but major differences exist even between the US, Europe, Canada, Japan and Australia. In the US, many products for the treatment of skin ulcers and burns are considered high-risk Class II or III medical devices, and some could even be classified as combination products to be regulated as drugs or biologics.

Such products usually require a significant number of complex animal and clinical studies to support marketing approval applications. **Table 2** lists the major categories of wound care products, with representative products and the most common regulatory pathway needed in each category.

Almost all the new developments in the field of wound care are concerned with innovative and advanced products in the moist and active categories, primarily in response to the increasing incidence of DFU, PU and VLU (collectively called chronic skin ulcers or CSU) in the aging population in the US, Europe and Japan. Adoption of pathbreaking technology in the skin replacement segment coupled with Medicare reimbursement in the hydrogel-dressing segment has resulted in a change in the treatment of chronic wounds.

Considering the high costs associated with probable complications, including lengthy hospital stays, extended physician care and infection, wound care expenses are expected to escalate. The growing elderly population, rising incidence of hospital-acquired infections and rapid increase of modern epidemics such as obesity and diabetes (both principal triggers of chronic wounds) are aggravating the healthcare cost scenario.

In light of an increasing number of requests for advice for development of wound healing products for CSU and burn wounds, the US Food and Drug Administration (FDA) released a guidance document specific to them in 2006 that provides insight into the complex expectations FDA has for these products.¹

Preclinical Studies Needed for CSU and Burn Wound Products

The preclinical studies needed for wound healing products are not as well-defined as those for traditional drugs or biologics. While most wound care products are classified as medical devices by FDA, several products for treatment of chronic wounds may be considered combination products that are reviewed as drugs or biologics.

For products classified as medical devices, most typical toxicity animal studies may not even be needed. However, for combination products or products classified as drugs or biologics, preclinical studies usually are required primarily to establish the safety of the product.

Animal wound models based on the best science available, using the most relevant species are required for assessing potential toxicities of wound-treatment products. Although animal models can be useful for establishing proof of concept for some types of products, in general,

Table 1. Prevalence of Different Types of Wounds

Medical Condition	Wound Type	No. of Patients/Year (millions)
Underlying Illness	Venous ulcers	1.60
	Arterial ulcers	1.70
	Diabetic foot ulcers	1.30
Long-term Immobility	Pressure ulcers	2.50
Surgical Processes	Surgical wounds (major)	36.00
	Surgical wounds (minor/moderate)	31.00
Trauma	Burn injuries	1.30
	Amputations	0.15
	Traumatic wounds/lacerations	16.30
Total		92.00

they can be inadequate predictors of efficacy in clinical trials.

All preclinical studies must be conducted under Good Laboratory Practice (GLP) regulations described in 21 CFR 58. Although preclinical studies needed for wound healing products can be done anywhere in the world provided they meet GLP requirements, they are feasible only in the US and a few locations in Europe and Canada due to the need for complex study design and special expertise available only in these regions.

Since there are no FDA-recognized animal models for chronic wounds or extensive burns, multiple animal models may be used to assess product activity. Fibroplasia and stroma formation can be evaluated by subcutaneous injection of some products in various animal models. Contraction and re-epithelialization can be evaluated by topical application on full-thickness excisional wounds or in a pig graft donor site model.

Pigs can be useful models because their cutaneous architecture is most similar to that of human skin. Induction of angiogenesis can be evaluated in chick chorioallantoic membrane or rabbit cornea. Breaking strength can be tested in a rat linear incision model.

For topical wound treatment products, application of the product to a wound site on the animal's skin may provide more relevant information than application to intact animal skin. When technically feasible, the potential for regional and systemic exposure to a product for chronic wound use might be better approximated by subcutaneous injection. FDA expects sponsors to cite available scientific literature to justify usability and relevance of the chosen animal models.

Additionally, *in vivo* biodistribution and pharmacokinetic (BD/PK) information is usually requested. Consideration should also be given to alterations of the BD/PK profile and the potential for product accumulation with repeated dosing.

Information regarding the stability of the product at the target site (target receptor levels for biological products) contributes to a better understanding of the activity and potential toxicity. The design of nonclinical toxicology studies for wound treatment products should reflect, as

much as possible, the intended clinical use of the product with respect to route, dosing regimen and duration of exposure.

Vehicle and sham controls should be employed, where appropriate, to evaluate any adverse or beneficial effects of product formulation ingredients on wound healing and adverse events. Cutaneous irritation and sensitization testing should be done for all topically applied wound treatment products, since these adverse reactions can seriously complicate human wounds.

The sponsor may also be asked to evaluate the immunogenic potential of biotechnology-derived products, carcinogenicity potential for products containing drugs intended to treat chronic ulcers, reproductive and developmental toxicity potential for products that might be administered to women of childbearing potential, and genotoxicity for all products containing drug components.

Characteristics of the Wound Indication Clinical Trials

Wound indication clinical trials need to take into consideration several specific issues in addition to issues common to all clinical trials. Typical elements such as placebo- or sham-controlled randomization and blinding are required in pivotal studies. In cases where placebo or sham control might not be clinically feasible or ethical, standard of care may be used as the control arm. Often, the standard of care arm cannot be blinded.

In other cases, especially for trials of some medical devices, it is impractical or unethical to implement a control treatment that mimics the test product for the purposes of blinding. In these situations, blinded assessment by a third-party evaluator should be considered.

For multi-site trials, a primary concern is the variation in standard wound care procedures among clinical study sites, which is unavoidable but must be minimized. Parameters defining the standard of care must be described in the clinical protocol. It is best if all participating centers agree to use the same procedures as described within the clinical protocol. It is also important that the sample size within study centers and

Table 2: Wound Care Product Categories

Category of Products	Examples	Most Common Applicable Regulatory Pathway
Traditional Wound Management Products	Adhesive bandages, topical ointments, gauzes	510k or monographs
Wound Closure Products	Internal staplers, skin staplers, surgical/ligature clips, sutures	510k
Advanced Moist Wound Healing Products	Alginate dressing, film dressing, foam dressing, hydrocolloid dressing, hydrogel dressing	510k or Premarket Approval (PMA) application
Active Wound Healing Products	Skin replacements, cell-based replacement, collagen dressings, growth factors	PMA, New Drug Application (NDA) or Biologics License Application (BLA)
Debriding Products	Cleansers and sealants	510k
Antimicrobial Dressings	Silver antimicrobial dressing, non-silver antimicrobial dressing	510k or PMA

wound care records be adequate to assess the effect of wound care variation.

Stratification by study center is recommended to minimize any imbalances among study arms. In some cases, it may be appropriate to establish randomization by other important covariates, such as wound size or duration. Variables thought to significantly affect outcome should be incorporated into the planned efficacy analyses, even if these variables are not used for stratification in randomization.

Trial designs in which subjects serve as their own controls have been used to study topical products intended for serious burns in an attempt to minimize the heterogeneity characteristic of this patient population. However, this approach compromises the evaluation of systemic toxicity, necessitating additional controls or studies to collect adequate safety data. Due to extreme variability in standards of care in a multi-national setting, global trials with wound healing indications generally are not practically feasible.

Additional considerations for clinical trials for wound indications include wound assessment and quantification parameters such as single or multiple lesions, wound classification, size and severity of infection. The tools to assess clinical trial endpoints should be both pre-specified and, for multicenter trials, standardized across clinical sites.

For example, if photographs will be used for measurement and documentation of wound changes, the lighting, distance, exposure and camera type should be specified and consistent at all clinical centers. The patient population to be included in clinical trials should be appropriate for the type of wounds to be studied; in general, one that optimizes the study’s ability to detect a treatment effect. It should also be a population that reflects the one for which the product will be indicated and used.

In general, the efficacy endpoints used in a wound-treatment product can be broadly grouped into two categories: improved wound healing and improved wound care. Improved wound healing can be measured by incidence of complete wound closure, accelerated wound

closure and quality of healing, while improved wound care is measured by prevention or treatment of infection, reduced pain and reduced blood loss during debridement.

The trial must also contain all relevant safety endpoints such as local irritation and contact sensitization, immune reactions and absorption of the product. Obviously, the trial must be adequately statistically powered, and the data must be analyzed by criteria pre-specified in the clinical protocol.

Regulatory Requirements

Clinical trials can only be initiated after appropriate regulatory approvals such as an Investigational Device Exemption (IDE) for products classified as medical devices, or Investigational New Drug (IND) for those classified as drugs or biologics. Most wound healing products are classified as medical devices, although an increasing number of combination products whose major mode of action involves a drug or a biologic component are being assigned to FDA’s Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) instead of the Center for Devices and Radiological Health (CDRH).

In the case of a combination product, one FDA center—CDER, CBER or CDRH—takes on the role of the lead regulatory review center. The sponsor has to follow the regulatory pathways of the lead center, which means that if CDRH is in the lead role, the sponsor would file an IDE, 510k and/or PMA application, and if the CDER or CBER is in the lead role, the sponsor will need to follow the IND, New Drug Approval (NDA) and/or Biologics License Application (BLA) regulatory requirements.

For combination products, the sponsor is required to request a product classification designation from the Office of Combination Products (OCP) at FDA. The process for requesting a designation from OCP is described in a recent FDA guidance document.²

A wide range of regulatory approval conditions is applied to cell-based therapy products.

Many of the technical challenges associated with creating a new tissue-engineered product are focused on the clinical proof phase, the regulatory requirements associated with manufacturing, proving product effectiveness and safety and a number of controls on product claims and usage.

Often, the approach to achieving regulatory approval seems to be arduous, inconsistent and arbitrary. This is best illustrated by the complexity of approval for new tissue engineered products described below:

- Autologous tissue and cells transplanted during surgery do not have any regulatory requirements placed upon them by FDA. However, the devices used to carry out the surgical procedure are regulated as Class I medical devices. These products are required to be manufactured under Good Manufacturing Practices (GMPs). They are regulated as devices and require 510(k)s.
- Donated cadaveric tissue products produced to aid surgical construction must be manufactured under GMPs and require a Premarket Application (PMA), if extensively processed between removal from the donor and transplantation to the recipient. They require extensive infectious disease screening and testing, with procedures that closely control good handling practices. They require premarket approval as they represent a substantial risk due to the risk of spreading infectious agents. The PMA for these products is reviewed by the Center for Biologics Evaluation and Research (CBER), as they contain biologically derived materials.
- Tissue engineered implants represent a broad category of materials, from those that are substantially donated allogeneic tissue with cells removed, to those products that are completely biologically based such as follicle and placental cell infusions. These products mostly require a BLA with significant nonclinical and clinical data.

Global Development is Not Practical for Wound Healing Products

With continuous developments in the wound care market, companies are devising new procedures and therapies for reducing the time associated with the healing process and for enhancing cost savings. The advent of novel biological techniques is expected to accelerate the pace of recovery and reduce the hospitalization period for patients undergoing surgical procedures.

Biological dressings are also capable of improving patient care and reducing the overall costs of hospitalization. This is attributed to the fact that products or treatments that help

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lower hospital costs are likely to find increased demand, particularly during current adverse economic conditions. Several new wound care devices and products are rapidly being introduced to market as part of efforts to enhance clinical outcomes.

The wound management products market is predominated by developed countries, owing to the presence of sophisticated medical delivery infrastructures as well as extensive insurance coverage for various primary healthcare procedures.

The demand in developing countries is expected to increase, as a result of the increased accessibility and availability of basic healthcare services, but is still expected to be a small fraction of what it is in the US, EU, Canada and Japan. This is reflected in more than three-quarters of all wound healing product companies in the world being located in the US.

Since most of the developments in the field are focused on developed countries, most clinical and preclinical resources are available only in these regions. Along with the fact that the standard of care for wound management is extremely different between developed and developing countries, this is one of the few medical product development fields where truly global development pathways are not practical. And, this is not expected to change in the near future.

Although treatment and product development are currently focused on a few major markets in the world, these indications are equally prevalent in most countries. It is prudent for developers to look at the current market for immediate returns on their investment but not to forget that other markets in the developing countries may open up in the future.

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