
Guidance for Industry Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)**

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Clinical/Medical**

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Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment

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Guidance for Industry¹

Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to sponsors for the development of drugs, biological products, and devices² to treat chronic cutaneous ulcer and burn wounds (i.e., *wound-treatment products*). The first part of this guidance addresses specific preclinical considerations. The guidance then addresses important considerations in clinical study design, including endpoint selection and manufacturing.

This guidance specifically refers to venous stasis ulcers, diabetic foot ulcers, pressure ulcers, and burn wounds. For the purposes of this guidance, a *chronic cutaneous ulcer* is defined as a wound that has failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure. A *burn wound* is defined as a cutaneous wound induced by thermal, chemical, or electrical injury.

In the Food and Drug Administration (FDA), the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) all regulate products to treat cutaneous wounds. This guidance contains recommendations applicable to the development of products regulated by any of the three Centers. Center-specific issues and advice are noted where appropriate.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

² This guidance applies only to those medical devices for which clinical trials are required.

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cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. INDICATION FOR USE CONSIDERATIONS

A product's labeled *indication for use* is based on substantial evidence and is reflective of the safety and efficacy of the product as determined in clinical investigations. In the case of wound-treatment products, the stated indication should include the types of wounds for which a product is intended (e.g., venous stasis ulcer, diabetic foot ulcer, pressure ulcer, burn sites, and donor sites) as well as the product's benefits, risks, and limitations. Because wounds differ in their pathophysiology, it is difficult to generalize results obtained from a trial conducted in subjects with one wound type to patients with another wound type. Therefore, separate clinical trials should be considered for each type of wound indication sought. However, if a scientific rationale and clinical data support clinical activity of a product in more than one wound type, it may be possible for studies performed in one wound type to support another in establishing substantial evidence of efficacy and safety.

III. PRECLINICAL CONSIDERATIONS

This section consists of specific points to consider for wound indications (including wound healing and wound care) for drugs and biological products. It is not intended as a general guidance for preclinical testing.³

A. Animal Wound Models

Animal wound models can be helpful in establishing pharmacological responses, as well as assessing potential toxicities of wound-treatment products. The choice of an animal wound model should be based on the best science available, as well as its applicability to the scientific questions that one is attempting to answer. The animal species selected should exhibit a biological responsiveness to the test product (i.e., should be a relevant species). Although animal models can be useful for establishing proof of concept for some types of products, in general they can be inadequate predictors of efficacy in clinical trials. Since currently there are no ideal animal models for chronic wounds or extensive burns, multiple animal models typically should be used to assess activity of wound-treatment products. 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

³ General guidance for preclinical testing of drugs and biologics can be found in International Conference on Harmonisation (ICH) documents, including *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* and *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

For medical devices, general guidance for assessing preclinical safety can be found in Blue Book Memorandum #G95-1 *Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing*.

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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.

In impaired-healing models, the window of time for measuring treatment effects is extended. Impaired-healing models include infection, necrotizing trauma, irradiation, administration of corticosteroids or chemotherapeutic drugs, or drug-induced or genetic diabetes mellitus in mice, rats, hamsters, guinea pigs, and young pigs. Each model has one or more of the characteristics that can be useful for evaluating a product's activity. For example, the rabbit ear dermal ulcer model is useful for evaluating re-epithelialization because it lacks the vigorous wound contraction seen in other rodent models and, in addition, allows for the induction of ischemia in the wound. There is extensive scientific literature that can be consulted for a more comprehensive discussion of the advantages and disadvantages of the models previously cited, in addition to other available wound models.

B. Biodistribution and Pharmacokinetic Studies

Although there are no ideal animal models for chronic wounds, in vivo biodistribution and pharmacokinetic (BD/PK) studies generally provide helpful data for the design of toxicology studies. Preferably, the pharmacokinetic (PK) profile can be determined in the same animal species that will be used in the toxicology assessment. 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 a chronic wound indication might be better approximated by subcutaneous injection. 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 of the wound-treatment product.

C. Toxicology Studies

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. It is important to assess any exaggerated pharmacological responses and potential toxicities of wound-treatment products. Administration of the wound-treatment product at multiples higher than the anticipated therapeutic dose (potentially determined from wound models) can provide an estimate of the therapeutic index (toxic dose/effective dose) to aid in the selection of the initial clinical starting dose. 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. The vehicle control animals should receive the same excipients and formulation as are in the intended clinical product, without the active agent. The sham control animals should be manipulated in the same manner as the vehicle control animals, but should not receive the vehicle or the active agent.

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Cutaneous irritation and sensitization testing should be generally indicated for all topically applied wound-treatment products, since these adverse reactions can seriously complicate human wounds. Products that will be delivered in an aerosol formulation should be evaluated for pulmonary toxicity, and possibly ocular toxicity (products known to be cutaneous irritants are assumed to be ocular irritants, and testing is generally waived).

The immunogenic potential of biotechnology-derived wound-treatment products can be a confounding factor in repeat-dose toxicology studies because antibodies to the administered product may affect the PK profile, the pharmacodynamic response, and the toxicity of the product. Although the development of antibodies to antigenic products generally has not been predictive of the clinical response, data on antibody formation should be collected to provide a complete preclinical safety assessment of the wound-treatment product. Sponsors are encouraged to seek FDA input during development to ensure collection of adequate immunogenicity information.

Carcinogenicity studies generally should be conducted for drugs intended to treat chronic ulcers.⁴ For biological products, the 2-year chronic bioassay and carcinogenicity study currently used for drugs is generally inappropriate because of species specificity and immunogenicity of the product. However, data in rodent initiation-promotion carcinogenesis models support the potential of various growth factors to act as tumor promoters. Current unresolved issues regarding the carcinogenic and tumorigenic potential of wound-treatment products include the likelihood of tumor promotion in the proposed patient populations and the additional susceptibility of patients exposed to environmental or other potential carcinogens (e.g., systemic chemotherapy) as well as the possibility of inducing *scar carcinomas* in chronic wounds. Sponsors are encouraged to address this issue by referencing the existing scientific literature, and evaluating the potential of the test product to stimulate the growth of normal and malignant cells that express the receptor for the product. Sponsors are encouraged to seek FDA input for product-specific questions that can affect the carcinogenicity evaluation.

Reproductive and developmental toxicology studies are recommended for wound-treatment products that might be administered to women of childbearing potential.⁵

Genotoxicity studies should be performed for all nonbiological drug products. These studies are indicated for a biotechnology-derived product only when supported by appropriate scientific rationale.⁶

⁴ Guidance for drug carcinogenicity studies can be found in the ICH documents *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*, *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals*, and *S1C(R) Addendum to Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addition of a Limit Dose and Related Notes*.

⁵ General guidance on preclinical study designs can be found in the ICH document *S5A Detection of Toxicity to Reproduction for Medicinal Products*.

⁶ Further guidance is available in the ICH documents *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals*. The ICH document *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* provides further discussion regarding biological products.

IV. CLINICAL TRIAL DESIGN

This section consists of specific points to consider for wound indication trial design. It is not intended as general guidance on trial design.⁷

A. Randomization and Stratification

Randomization is particularly important for reducing bias in wound indication trials because standard wound care procedures and baseline wound characteristics generally have a profound effect on outcome. If variation in standard wound care procedures among clinical study sites is unavoidable, stratification by study center is recommended to minimize any imbalances among study arms. In some cases, it may be appropriate to prospectively stratify 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 (see section IV.I., Statistical Considerations Specific for Wound-Treatment Product Trials).

B. Comparator Arms

A comparator arm is recommended for many wound-treatment product trials involving drugs, biologics, devices, and combination products (i.e., drug delivery studies or cellular wound dressings). This is usually a vehicle control arm. The vehicle control should contain the same formulation and excipients as the study product, without the active agent. Such trials should be performed with identical standard-of-care procedures in both the control and investigational product arms. If the effect of a product's vehicle is not established, product development should also include a study arm treated with standard of care alone, usually in exploratory studies. In the selection of comparator groups, careful consideration to optimizing the dosage, frequency of administration, and method of use is important.

Trial designs in which subjects serve as their own control 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.

C. Blinding

In general, blinding of subjects and investigators to the assigned treatment reduces bias and should be employed when feasible. Early trials of topical wound-treatment products often include a treatment group that receives only standard care (see section IV.B., Comparator Arms) to establish whether the vehicle has an effect on healing. Often the standard care only 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.

⁷ General guidance on this topic can be found in the ICH documents *E8 General Considerations for Clinical Trials*, *E9 Statistical Principles for Clinical Trials*, and *E10 Choice of Control Group and Related Issues in Clinical Trials*.

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D. Wound Assessment and Quantification

For most ulcer types, we encourage the selection of a single target lesion for efficacy determination before subject randomization. In some cases, it may be appropriate to treat other lesions with the investigational product to obtain additional safety information, which is still reported as *per patient*. An alternative approach, that may be appropriate, is complete healing of all lesions reported as *per patient*.

The tools to assess clinical trial endpoints should be both prespecified 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.

Regardless of the methodology, the following variables should be addressed in all clinical trials for wound-treatment products.

1. Ulcer Classification

The type of chronic ulcer (venous stasis, diabetic, pressure, arterial insufficiency) usually can be determined by considering the subject's history and performing a physical examination. Objective tools to confirm the diagnosis can include the following:

- Doppler sonography to qualify and quantify vascular insufficiency: arterial or venous (deep, superficial, or mixed)
- Transcutaneous oxygen tension ($t_c pO_2$) measurements
- Ankle/brachial index
- Filament testing to quantify sensory neuropathy
- Measurement of laboratory markers for diabetes mellitus
- Histopathology of ulcer biopsies to exclude neoplastic, immune-mediated, or primary infectious disease

2. Wound Size

Quantitative measurements of wound size are routinely used to assess initial wound size before and after debridement, as well as progress toward closure. For ulcers that are more superficial, such as venous stasis ulcers, the area of the wound opening should be measured. For ulcers that extend deeply into tissue, volume or surface area should be measured when feasible. The extent of tissue undermining and sinus tracts is an important part of the evaluation. In the case of diabetic ulcers, qualitative assessment by determining the maximal depth is a frequently used method. For other ulcers, such as pressure ulcers, molds can be used to provide precise measurement of volume and surface area. Alternatively, semiquantitative measurements can be achieved using the maximal width/length/depth and shape coefficient. There are also widely accepted criteria used to classify the stages of ulcers (e.g., National Pressure Ulcer Advisory Panel (NPUAP) for Pressure Ulcers: NPUAP Classification, Wagner's Classification for foot ulcers).

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For acute burns, it is important to attempt a determination of the burn depth as this parameter affects both the choice of standard-of-care regimen and the expected time to healing. The distinction between partial, full-thickness, and indeterminate wounds is currently based on clinical judgment; biopsy and Doppler measurement of blood flow are sometimes used as well. Clinical parameters include appearance of the tissue, sensation, and bleeding upon debridement. Wound depth heterogeneity is often an impediment to quantitative measurement, and burn depth extension in the first 24 to 48 hours post-injury frequently necessitates reassessment. Because burn wound depth often becomes better defined following the initial evaluation, the initial clinical assessment of the body surface area affected by deep partial full-thickness (2nd degree) and full-thickness (3rd degree) wounds can be compared with the total body surface area ultimately grafted.

When the target wound is an autograft donor site, the protocol should clearly delineate the method for harvest, and the size, thickness, and anatomic location of the donor site.

3. Infection

Infection should be assessed clinically by symptoms and signs that include purulent drainage, erythema, warmth, exudation, odor, pain, fever, and leukocytosis as well as wound size and time to wound healing. Fever, pain, and leukocytosis may be absent, however, especially in subjects with diabetic foot ulcers. Quantitative and qualitative culture of a tissue biopsy can be used at baseline to help determine if the wound is infected or merely colonized, and to guide appropriate antimicrobial therapy. This method is generally preferred to quantitative and qualitative culture of swab specimens.⁸

E. Study Population

The patient population to be included in clinical trials should be appropriate for the type of wounds to be studied. In general, the patient population chosen should be one that optimizes the study's ability to detect a treatment effect, but should also be a population that reflects the population for which the product will be indicated and used.

1. Chronic Cutaneous Ulcers

Three of the major categories of chronic cutaneous ulcers are diabetic ulcers, venous stasis ulcers, and pressure ulcers. As previously stated, separate trials generally are appropriate for each type of chronic ulcer because these ulcers have different etiologies and potentially different responses to therapy. If demonstration of efficacy is restricted to ulcers with a limited range of size or duration, and the ability to extrapolate to larger or more recalcitrant ulcers is unclear, then the labeled indication can be limited to ulcers with similar parameters to those studied.

⁸ In 1998, the Agency published a series of draft guidances on drugs to treat antimicrobials, including uncomplicated and complicated skin infections. These guidances currently are being finalized. Once finalized, these guidances will reflect the Agency's views on developing antimicrobial drug products.

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Healing of chronic ulcers can occur as subject compliance with standard treatment improves during the initial involvement in a clinical trial. Variability in aspects of care that affect outcome can interfere with a study's ability to demonstrate the treatment effect of the investigational product. Approaches for minimizing this variability can include the use of: a) a study design with an initial phase (e.g., 1 to 2 weeks) when subjects receive only standard of care, and b) an entry criterion that excludes subjects whose study ulcer size decreases by a stated amount (e.g., 30 percent to 50 percent) during this initial *standard-of-care* phase. Thus, the randomized study population would exclude subjects demonstrating substantial healing resulting solely from improved compliance with standard care.

2. *Burns*

The population for burn trials is usually characterized by the depth, surface area, and location of the burn injury, as well as subject characteristics. Important characteristics of a burn wound include its cause (thermal, chemical, electrical), anatomic location, depth (full or partial thickness), duration, and extent (percent total body surface area). Subject characteristics that affect burn wound healing include age, nutritional status, underlying medical conditions, concomitant injury (e.g., head trauma, inhalation injury, bone fractures), and scores that represent an overall severity of illness or injury (e.g., the American Society of Anesthesiologists (ASA) Classification, the Trauma-Injury Severity Score (TRISS), or the Acute Physiology and Chronic Health Evaluation (APACHE) III score). Patients with serious burns commonly receive multiple concomitant treatments, making it sometimes difficult to detect a treatment effect. For this reason, stratification by injury severity and other potentially confounding factors that are clinically significant should be considered to minimize imbalances among treatment groups. In early clinical development, to protect subject safety, generally it is not advisable to include investigational treatment of burns in anatomic locations such as the face and hands as well as sites deemed high risk for developing compartment syndrome; similarly, the body surface area treated with the investigational product should be limited.

In clinical trials of subjects with full-thickness burn wounds, donor sites for autografts are sometimes selected as the target wound for study. However, the demonstration of safety and efficacy of a product for a donor site wound does not support the safety and efficacy of the product for burn wounds, because burn wounds differ in clinically significant ways from surgical wounds.

F. Standard Care

Standard care refers to generally accepted wound care procedures, other than the investigational product, that will be used in the clinical trial. Good standard care procedures in a wound-treatment product trial are a prerequisite for assessing safety and efficacy of a product. Since varying standard care procedures can confound the outcome of a clinical trial, it is generally advisable that all participating centers agree to use the same procedures and these procedures are described within the clinical protocol. If it is not practical to apply uniform standard care procedures across study centers, randomization stratified by study center should be considered. It is also important that the sample size within study centers and wound care records be adequate to assess the effect of wound care variation.

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A number of standard procedures for ulcer and burn care are widely accepted. Several professional groups have initiated development of care guidelines for ulcers and burns. The Agency does not require adherence to any specific guidelines, the basic principle being that standard care regimens in wound-treatment product trials should optimize conditions for healing and be prospectively defined in the protocol. The rationale for the standard care chosen should be included in the protocol, and the study plan should be of sufficient detail for consistent and uniform application across study centers. Case report forms (CRFs) should be designed such that, at each visit, investigators describe the type of ulcer or burn care actually delivered (e.g., extent of debridement, use of concomitant medications). For outpatients, the CRF should also capture compliance with standard care measures, including wound dressing, off-loading, and appropriate supportive factors, such as dietary intake.

The value of study site consistency in standard care regimens within a trial cannot be over-emphasized because of the profound effects these procedures have on clinical outcome for burns and chronic wounds. Consistency in standard care regimens is important for minimizing variability and allowing assessment of treatment effect. It may be reasonable to evaluate a single standard care regimen in early trials to minimize this variability. If comparison of an investigational product to more than one commonly used standard care option is desired, the overall development plan should include specific assessment of the effect of these standard care options on the experimental treatment. These common options should be identified and addressed prospectively in clinical trial design including being clearly described in the clinical protocol and compliance captured via the CRFs; criteria for data poolability should be defined prospectively. Every attempt should be made to minimize deviations from the procedures described in the protocol and subject compliance recorded in CRFs. If more than one standard care regimen is used in the same clinical trial, then randomized treatment allocation within strata defined by these options in standard care is important.

1. Standard Care Considerations for Chronic Cutaneous Ulcers

Parameters for consideration in choosing standard care procedures for chronic cutaneous ulcer trials include the following:

- Removal of necrotic or infected tissue
- Off-loading
- Compression therapy for venous stasis ulcers
- Establishment of adequate blood circulation
- Maintenance of a moist wound environment
- Management of wound infection
- Wound cleansing
- Nutritional support, including blood glucose control for subjects with diabetic ulcers
- Bowel and bladder care for subjects with pressure ulcers at risk for contamination

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a. Debridement

The presence of necrotic tissue, sinus tracts, exudation or transudation, and infection of soft and hard tissues can interfere with ulcer healing. Appropriate debridement procedures for the indicated ulcer should be specifically defined in the protocol. To avoid bias and confounding of potential treatment effects, ulcer debridement should generally precede evaluation of ulcer extent and infection. Enzymatic debriding products, like other concomitant topical products, can confound results in topical wound-treatment product trials and generally should be avoided.

The need for additional sharp surgical debridement, performed after study treatment has started, may indicate product-induced wound deterioration. Any surgical debridement should be documented on CRFs and included in analysis of product safety and efficacy. In general, the study protocol should specify that investigators discontinue study treatment if repeat debridement is needed to address wound deterioration. For example, ongoing removal of callus as part of standard diabetic ulcer care would not require discontinuation of study treatment, but deep debridement for new onset osteomyelitis would.

b. Off-loading and compression

Relief of pressure is critical in determining the outcome for certain chronic ulcers. Off-loading is often difficult to standardize because equipment (e.g., type of bed) may not be available at all sites, and compliance with study procedures is labor intensive (e.g., turning). If these critical aspects of effective therapeutic intervention cannot be standardized across all sites, it is important to specify the actual care delivered in CRFs and to consider concomitant care in the efficacy analyses. For diabetic foot ulcers, compliance with off-loading is a strong factor associated with wound closure and should be monitored throughout the clinical trial. Off-loading approaches (e.g., some form of casting and elevation) should be weighed against the need to apply study treatments and monitor outcome. Similar considerations are important in choosing compression methods for venous stasis ulcers.

c. Maintenance of a moist wound environment

Maintenance of a moist wound environment generally is accepted as a component of standard care for all chronic cutaneous ulcers. Methods of maintaining a moist wound environment should be identified in the clinical protocol and optimized for the specific patient population, the wound type to be studied, and the type of product being tested. If there is a sound rationale for the expected benefit of a test product that cannot be used with established standard care dressings, alterations in standard care might be safely implemented. This can be done by including in the protocol adequate criteria for discontinuing subjects from study treatment or through the appropriate implementation of an independent data safety monitoring board to oversee trial safety.

d. Management of wound infection

Effective control and management of infection is critical for treatment success of all wound-treatment products, regardless of the claim. For this reason, wound-treatment products that are

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not intended for use as an anti-infective generally should be studied in subjects in whom the target ulcer is uninfected. To this end, it is often appropriate to include in the trial design a run-in period with standard therapies to control infection.

In specific cases, such as the case of diabetic foot ulcers, wound-treatment products that are not anti-infective can be studied in wounds where infection is limited and responding to standard systemic antimicrobial therapy. In trials involving infected ulcers it is especially important that the protocol clearly delineate adequate criteria for discontinuing subjects from study treatment because of wound deterioration during the treatment period (see section IV.H.3., Discontinuation of Treatment).

If a subject's ulcer becomes infected during a study for a topical wound-treatment product, and the investigator prescribes topical antimicrobial treatment, the subject generally should be discontinued from study treatment. (As for all discontinued subjects, safety assessment should continue throughout the trial and these subjects should be included in efficacy analysis). However, if sponsors anticipate that post-approval clinical use would likely entail concomitant topical products, the trial should be designed to address this variable.

Systemic antimicrobial therapy for target wound infection may become necessary during the treatment period of the study. Whether or not study treatment should be discontinued in this situation should be discussed prospectively and the plan included in the protocol. For example, treatment discontinuation might be indicated in early trials, where little is known about product safety and where infection may signal test product-induced deterioration of the wound, but not in later trials in subjects for whom systemic antimicrobial therapy would be considered a component of standard care.

e. Nutritional support

Nutrition is important to healing and immune competence, and should be tracked to allow assessment of this aspect of a subject's ability to heal. Caloric intake and metabolic status should be captured in the CRFs if the product is known to have metabolic effects (e.g., anabolic steroids). For products not known to have metabolic effects, these data may be useful if the inclusion criteria encompass subjects significantly above or below ideal body weight (e.g., cachectic subjects with pressure ulcers). In studies of subjects with diabetic ulcers, it is important to record blood sugar levels because nutritional support with adequate blood sugar control is considered standard care for wound healing in these subjects.

2. *Standard Care Considerations for Burns*

Standard care for serious burns includes careful attention to the following parameters:

- Hemodynamic resuscitation
- Management of co-morbidities
- Timely burn debridement and excision
- Wound closure
- Management of wound infection

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- Pain control
- Nutritional support
- Measures to inhibit excessive scar formation
- Rehabilitation, including passive range of motion when burns overlie joints

Because large burn centers tend to have well-established, distinct standard care regimens, randomization within multicenter burn trials may require stratification by center. Since standard care procedures have profound effects on clinical outcome, every effort should be made to reach agreement among site investigators and to capture actual care delivered in the CRFs.

G. Efficacy Endpoints

In general, clinical outcomes associated with the use of a wound-treatment product can be broadly grouped into two categories: improved wound healing and improved wound care. Each outcome category includes a variety of potential endpoints for clinical trials. Suggestions for possible outcome measures and clinical trial endpoints offered in this guidance are based on current knowledge of the natural history and management of burns and ulcers.

1. Improved Wound Healing

a. Incidence of complete wound closure

Complete wound closure of a chronic, nonhealing wound is one of the most objective and clinically meaningful wound healing endpoints. *Complete wound closure* is defined as skin re-epithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart. Generally, trials to support an indication of complete wound closure measure incidence of complete wound closure in the treatment group and the control groups by a specified time (landmark analysis). In the simplest case, a treatment effect would be established if a clinically and statistically significant greater proportion of subjects in the treatment group achieved complete wound closure compared to the control arm. Timing of the endpoint measurements should be based on the natural history of the disease process, the anticipated time course for the treatment effect, and the expected response to standard care in the control arm.

Trial subjects generally should remain in the study for follow-up evaluation at least 3 months following complete wound closure. The purpose for this follow-up period is to help distinguish actual wound healing from transient wound coverage, determine if the product affects the strength of wound closure relative to standard care, and monitor for adverse effects on surrounding tissue (e.g., skin, bones, supporting structures).

Measurement of partial wound healing in early phase clinical trials, if prospectively defined, may indicate relevant biological activity and help guide subsequent trial design. Partial healing would not, however, suffice as a primary endpoint in phase 3 studies because the clinical benefit of incremental wound size changes has not been established. However, *partial healing that facilitates surgical wound closure* can be a measurable trial endpoint of clinical benefit.

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b. Accelerated wound closure

An indication of *accelerated wound closure* should reflect clinically meaningful reduction in the time to healing using a time-to-event analysis (the *event* being complete closure). Assessments should be performed at intervals sufficiently frequent to detect a meaningful difference in time-to-closure between treatment groups. If claims are sought for *both* increased incidence of wound closure *and* accelerated healing, the study should be designed to detect both effects.

Because partial thickness donor sites generally heal in 2 to 3 weeks with standard care regimens, when considering clinical endpoints for a product that accelerates closure of donor sites, the anticipated clinical benefit should be taken into account. For example, a product that accelerated donor site healing by only 1 or 2 days might provide clinical benefit if it could be safely used in extensively burned patients requiring repeated re-harvesting of donor sites. In studies where donor site wounds are chosen as the primary target for efficacy determinations, it is important to also assess the engraftment of tissue obtained by re-harvesting as a safety evaluation, because graft take should not be worsened by a product that accelerates healing of donor sites.

c. Facilitation of surgical wound closure

If the claim sought is facilitation of surgical wound closure by partial healing, studies should be designed to measure the incidence of complete wound closure following the needed surgical procedure (such as flap closure of an extensive chronic pressure ulcer). The durability and quality of the surgical wound closure should be assessed over time to ensure that the product does not have a deleterious effect.

d. Quality of healing (cosmesis and function)

Studies evaluating the cosmetic aspects of quality of healing (*cosmesis*) can be designed to demonstrate a clinically significant effect on outcomes such as scarring, the contour and feel of the healed skin, or normalization of skin markings or pigmentation. In choosing clinically relevant endpoints for an improved cosmesis claim, it is important to consider the type and location of wound (e.g., facial versus plantar surface of the foot) and whether a reliable assessment tool exists, or can be developed.

Wound healing resulting in hypertrophic scar formation can be a source of long-term morbidity by inhibiting function (e.g., inhibition of range of motion across joints). As such, wound-treatment products that reduce hypertrophic scarring may also lead to improved function. Studies designed to evaluate the outcome of improved function through clinically relevant endpoints can be useful in supporting a labeling claim for *function*.

2. *Improved Wound Care*

We recognize that products intended for wound management may provide important patient benefit without improving the incidence or timing of wound closure relative to standard care. However, it is important to demonstrate that such products do not significantly impede healing.

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Thus, wound closure should be evaluated as a safety outcome for all products with a wound care claim.

a. Treatment of wound infection

Infection at the wound site impairs healing. Primary efficacy outcomes for topical antimicrobial wound-treatment products can thus be *healing, prevention of, or cure of* infection. Such antimicrobial products generally should have an established and appropriate spectrum of antimicrobial activity.⁹

b. Debridement

Debridement of necrotic tissue generally is considered part of standard care for most ulcers and burns. Although there is debate about the optimal design of trials to assess the efficacy of debriding products, examples of clinically relevant endpoints include improved wound healing (increased incidence or acceleration of complete closure), reduced pain associated with the debridement process, or decreased blood loss during or immediately following debridement. When wound closure is not the chosen primary efficacy endpoint, the study should evaluate whether the debriding product impairs healing relative to standard of care.

c. Wound pain control

Wound pain amelioration endpoints should be accompanied by assessment instruments that are prospectively defined and appropriate to measure the type of pain for which an indication will be sought.¹⁰ These studies should include, as a safety endpoint, an assessment of product effects on the healing process itself.

3. *Temporary Dressings*

Temporary dressings, including interactive temporary dressings, are intended to provide supportive care until definitive closure can be accomplished. Temporary dressings are expected to function as a barrier, much like human skin. Trial endpoints other than healing should reflect one or more clinically relevant barrier functions, such as retardation of fluid loss or reduced infection rates. If healing is not the primary efficacy endpoint, it should be evaluated as a safety endpoint.

⁹ In 1998, the Agency published a series of draft guidances on developing antimicrobial drug products. Two of those guidances may be of interest: *Developing Antimicrobial Drugs — General Considerations for Clinical Trials and Uncomplicated and Complicated Skin and Skin Structure Infections — Developing Antimicrobial Drugs for Treatment*. Once finalized, these guidances will reflect the Agency's views on developing antimicrobial drug products.

¹⁰ For more information regarding endpoints, see the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Once finalized, this guidance will reflect the Agency's views on patient-reported outcome measures.

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4. *Other Wound Care Claims*

Wounds can negatively affect many aspects of patients' lives. Clinically significant improvement in certain aspects of daily living (e.g., improvements in functional abilities) might support a labeling claim if appropriate trial endpoints measure a direct clinical benefit or if the endpoints are assessed with a clinically relevant validated instrument.¹¹

H. Safety Considerations

1. *Immune Reactions*

For biological products and some drugs, immunogenicity generally is addressed by measuring antibody titers before and after the treatment. Further immunological characterization with measures of the effect of antibody formation upon bioactivity, safety, and efficacy may be appropriate, since the development of an immune response can render the product inactive (neutralizing antibodies), and induce acute or chronic immune reactions (e.g., anaphylaxis, contact sensitization, autoimmune disease).

2. *Trial Stopping Rules*

Because the patient populations in burn and chronic ulcer trials often have a high background incidence of serious adverse events, it is recommended that a safety data monitoring board be used for blinded trials when the known or suspected risk is significant, and the study population is critically ill (e.g., seriously burned patients). Early in clinical development, sponsors may need to incorporate specific trial stopping rules based upon the occurrence of certain important adverse events, such as death or respiratory failure.

3. *Discontinuation of Treatment*

Since the active ingredients or the vehicle of a topical wound-treatment product may have a deleterious effect on healing, subjects participating in early stage clinical trials generally should be discontinued from study treatment if signs or symptoms suggest wound deterioration. Wound deterioration can manifest as erythema, pain, discharge, infection, tissue necrosis, requirement for repeat debridement or other surgical intervention (i.e., amputation), and increase in ulcer size. Undesirable alterations of soft tissues, ligaments, periosteum, or joint capsules underlying deep wounds also should be evaluated. Once reasonable assurance has been achieved that the product does not harm the wound, it may be appropriate to continue study treatment in later trials, depending on the type of wound and patient population. Subjects who are discontinued from study treatment should remain in the study for safety assessment and efficacy analysis.

¹¹ For more information regarding endpoints, see the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Once finalized, this guidance will reflect the Agency's views on patient-reported outcome measures.

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4. Absorption Studies

For topical drug, biological, and combination products, early clinical evaluations should include quantitation of absorption through the wound. Systemic bioavailability of topically applied products is generally assessed using standard pharmacokinetic measurements with serial serum sampling. Systemic uptake is influenced by wound factors such as size and vascularity, as well as product characteristics such as molecular weight, chemical composition, and the presence of excipients. Systemic availability of a topical product may be profoundly influenced by wound bed preparation. Thus, such studies should be performed when possible on a well-debrided wound as long as the debridement process is consistent with the methods of applying the investigational product and standard methods of wound care. In the case of growth factors, relatively little (less than 1 percent) absorption typically occur from chronic ulcer sites, but these amounts might be clinically significant because some growth factors are active in vitro at nanogram concentrations. For this reason, it is important to perform sensitive assays against serum background of the endogenous growth factor.

For products that are absorbed from the wound bed, the systemic dose depends on several factors including the concentration of the active ingredient, the total body surface area treated, the volume applied, frequency of application, and duration of contact with the wound. Safety and pharmacokinetic studies for topical wound-treatment products usually should be conducted in subjects with the indication sought, since absorption through intact skin of a healthy volunteer would not predict absorption in a wound.

5. Irritation and Contact Sensitization

When preclinical studies or previous clinical experience suggest that a topical product might induce clinically significant dermatitis, irritation, or sensitization, we recommend that testing be done on intact skin before conducting clinical trials in chronic ulcers, wounds, or burns. The testing is recommended because superimposed dermatitis can be deleterious to wounds. The inclusion of routine testing of the final formulation depends on the product, and sponsors are encouraged to discuss dermal toxicity testing with the appropriate center before initiating the trials.

I. Statistical Considerations Specific for Wound-Treatment Product Trials

This section addresses issues that present special considerations for wound-treatment product trials.¹²

1. Significance Tests

Analysis should be prespecified in the protocol. For *incidence of closure* endpoints, categorical techniques are recommended (e.g., Chi-square, tests of homogeneity, or logistic regression). For *time-to-closure* endpoints, outcome survival analyses should be performed.

¹² General guidance about data analyses also is available (e.g., ICH guidance for industry *E9 Statistical Principles for Clinical Trials*).

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For wound-treatment product trials, the center or investigator is frequently included as a factor in the analysis, because of variations in standard of care. Some analytical tests (e.g., Mantel-Haenszel statistic and the Cox Proportional Hazards Model) allow for covariate adjustment.

2. Data Transformation and Covariate Analyses

In the clinical trial design, prospective stratification in randomization should attempt to balance the trial arms for the one or two most important variables that are highly likely to affect the trial's primary endpoint. Covariate analyses can be employed to adjust for variables that affect the outcome. If covariate analyses are used, the covariates and the analyses should be prespecified to avoid concerns about interpretability of significance tests.

When analyzing covariates, experience suggests that it is generally not useful to transform continuous variables into dichotomous variables (e.g., baseline ulcer size greater than or equal to 5 cm² and duration of the ulcer more than 1 year). The covariate should be used as a continuous variable. Exploratory analyses can examine subgroups defined by various cut points, but when a particular cut point is deemed to be important in guiding the use of the product (e.g., ulcers greater than 10 cm² do not respond), this cut point should be prospectively identified and studied in a clinical trial.

V. WOUND-TREATMENT PRODUCT QUALITY MICROBIOLOGY

A wound represents a breach in the body's natural barrier to microbial invasion; therefore, the final formulation of topical products used for the treatment of chronic ulcers, wounds, or burns should be sterile to avoid introducing exogenous microorganisms. Guidance on validation of the manufacture of sterile products can be found in the guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. Methods for performing sterility tests on drug products can be found in USP <71> *Sterility Tests*.

To avoid contamination of a sterile product, it is preferable for wound-treatment products to be packaged in single-use containers. However, if packaged in multi-use containers, wound-treatment products should either include a preservative system or possess innate antimicrobial activity. Antimicrobial preservatives should not be used as a substitute for good manufacturing practices. The antimicrobial activity of the product, with (or without) a preservative system, should be demonstrated by performing a microbial challenge test such as USP <51> *Antimicrobial Effectiveness Test*. The minimum acceptable limit for the content of preservatives (or other antimicrobial material, as in the case of an innately antimicrobial API) in a product should be demonstrated as microbiologically effective by performing a microbial challenge test of the formulation with an amount of preservative less than or equal to the minimum amount specified as acceptable. For the purpose of application approval, stability data on pilot-scale batches should include results from microbial challenge studies performed on the product at appropriate intervals. Typically, microbial challenge studies should be conducted initially, annually, and at expiration. Chemical assays of preservative content also should be performed at all test points. Upon demonstration of the antimicrobial effectiveness of the minimum specified

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preservative concentration, chemical assays of the preservative may be sufficient to demonstrate the maintenance of adequate antimicrobial activity for annual batches placed into stability testing. For biological products, testing should be done to ensure that the preservative does not compromise biological activity.

Some products cannot withstand sterilization processes because they degrade when heated or irradiated, and they are not filterable. If a wound-treatment product cannot be manufactured to be sterile, it should have a low bioburden. Bioburden testing should be performed according to a validated test procedure such as in USP <61> *Microbial Limit Tests* and <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* (when implemented) at appropriate, defined time points during stability studies. Additionally, bioburden testing should include identification of recovered microorganisms to exclude potentially deleterious organisms.

Refer to the following standards for validation of sterilization of medical devices:

- ISO 11137:1995 Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization
- ISO 11135:1994 Medical devices — Validation and routine control of ethylene oxide sterilization
- ISO 11134:1994 Sterilization of health care products — Requirements for validation and routine control — Industrial moist heat sterilization (available in English only)