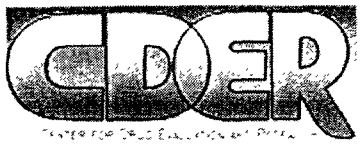

Guidance Document

Guidance for Industry

Chronic Cutaneous Ulcer and Burn Wounds
Developing Products for Treatment

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DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Mary Jane Walling, 301-827-2268, (CBER) Bette Goldman, 301-827-5098, or (CDRH) Charles Durf 301-594-3090.

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Center for Biologics Evaluation And Research (CBER)
Center for Devices and Radiologic Health (CDRH)
Center for Drug Evaluation and Research (CDER)
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Chronic Cutaneous Ulcer and Burn Wounds - Developing Products for Treatment

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Guidance for Industry[1]

Chronic Cutaneous Ulcer and Burn Wounds - Developing Products for Treatment

I. INTRODUCTION

This document is intended to provide guidance to sponsors on the development o drugs, biological products, and devices[2] to treat chronic cutaneous ulcer and burr wounds. The guidance contains recommendations about labeling claims, outcom measures, and trial design, as well as special considerations for preclinical development.

For the purposes of this guidance, a *chronic cutaneous ulcer* is defined as a wour that has failed to proceed through an orderly and timely series of events to produ durable structural, functional, and cosmetic closure. This document specifically addresses venous stasis ulcers, diabetic foot ulcers, pressure ulcers, and burn wou

The Center for Biologics Evaluation and Research (CBER), the Center for Devic and Radiologic Health (CDRH), and the Center for Drug Evaluation and Researc (CDER) within the FDA regulate products to treat cutaneous wounds. This docur contains guidance applicable to the development of products regulated by any of three Centers. Center-specific issues and advice are noted where appropriate.

II. CLAIMS

A. General Considerations

The claim (also referred to as the *indication*) refers not only to the beneficial effe of a product, as determined through clinical investigations, but also to the type of wound for which a product is intended (e.g., venous stasis ulcer, diabetic foot ulc pressure ulcer, burn sites, donor sites). Wounds differ pathophysiologically, mak difficult - if not impossible - to generalize results obtained from a trial conducted patients with one type of wound to those with another wound type. Separate safet and efficacy data should be submitted for each wound type for which an indicatic sought.

Claims sought for the use of wound products should be prespecified before trials performed and amenable to study using outcomes that are direct measures of clin benefit or validated surrogates. The primary efficacy outcome is key to demonstr the effectiveness of a product. In selecting endpoints, it is important to consider whether reliable means of assessing the endpoint exist, or can be developed.

Outcome measures for chronic cutaneous ulcers and burns are in evolution, as understanding of pathophysiology and techniques for wound treatment and assessment advance. Suggestions for possible outcome measures are based on the principles noted above and on the natural history and current management of bur and ulcers. Comments regarding other appropriate wound claims, endpoints, and assessment tools are invited.

Two broad categories of wound product claims include (1) claims related to improved wound healing and (2) claims related to improved wound care other th healing.

B. Claims Related to Improved Wound Healing

1. Incidence of Complete Wound Closure

A claim of *complete wound closure* for chronic, non-healing wounds is considere the most clinically meaningful of the claims related to improved wound healing. *Complete closure* is defined as skin closure without drainage or dressing requirements. Generally, studies to support such a claim would be designed to measure incidence of complete wound closure in the treatment vs. the control gr by a specified time (landmark analysis). Efficacy *success* would be defined as a statistically significantly greater proportion of patients assigned active product achieving closure compared to the proportion in the control arm. The prespecifie time for endpoint measurement should be based on the natural history of the dise process and the expected response to standard care.

The clinical benefit of wound closure that lasts for a very brief time is at best, hig limited. In general, trials should be designed such that subjects remain on study a continue to be evaluated at least 3 months following complete closure. The purp for this follow-up period is to measure durability of the effect and to ensure that t product does not adversely affect durability of closure relative to standard care. F some products, durability of closure is also important for distinguishing wound healing from transient wound coverage.

Measurement of partial healing, if prospectively defined, may demonstrate relev biological activity and be supportive of the determination of efficacy, but cannot used as primary evidence of clinical efficacy. Partial healing, per se, is not consi an acceptable wound healing claim because the clinical benefit of statistically significant differences in wound size has not been established. Validated method measuring degrees of change in wound size also present difficulty. As described below, however, *partial healing that facilitates surgical closure* can be an accept claim.

2. Accelerated Wound Closure

A claim of *accelerated closure* reflects a clinically meaningful diminishing of th time until complete closure occurs. Time to event analysis (time to complete 100 percent closure) is recommended for this type of claim. A claim of *accelerated closure* should be supported by a finding of faster reduction in the size of the wo during the treatment period. Therefore, for this claim, accurate measuring of wou size over time should be conducted.

For products that significantly increase the incidence of closure over the course o clinical study, the increased incidence of closure per se is likely to result in a sup outcome in rank analyses of time to healing, because even very slow healing cou as *faster* healing in such analyses than does failure to heal. Thus, the time to wou closure is most meaningfully compared when the incidence of complete closure i same in both arms. As a result, given a finding of increased incidence of closure, additional finding of superiority in time to complete closure may reflect little or r

additional information about the product. When an improvement in time to closu results from an improvement in the incidence of closure, a claim of *improved incidence of closure* suffices to explain the clinical benefit and should not be supplemented by an additional claim of *accelerated wound closure.*

Accelerated healing claims for burns should distinguish between partial thickness burns, full thickness burns, or donor site wounds. *Accelerated closure* of the donc site produced during harvest of autologous grafts is a claim for which it is especi important to prespecify the clinical benefit expected because these partial thickne wounds heal well in 2 to 3 weeks with standard care regimens. For example, a product that accelerated healing of donor sites by only 1 or 2 days might provide clinical benefit if it could be safely used in extensively burned patients requiring repeated reharvesting of donor sites. If time to reharvest is used as the primary efficacy outcome to support this type of claim, careful attention to masking is important to prevent bias, since reharvest is generally undertaken before the donc site reaches 100 percent re-epithelialization.

Accelerated healing claims based on study of donor sites cannot be generalized t burns and chronic cutaneous ulcers because burns and ulcers do not share the clir characteristics of uniform, partial thickness donor sites. However, for systemicall administered test products, healing of both the donor sites and the ulcer or burn a important safety outcomes. For example, a product that accelerates the healing of donor sites should not worsen graft take.

3. Facilitation of Surgical Closure

The Agency does not consider partial healing per se to be an appropriate claim fc wound healing agents because the clinical benefit of statistically significant decre in wound size has not been established. However, agents that heal wounds to the point that surgical closure is more feasible, safer, or more effective may lead to tl claim of *facilitates surgical closure.* Studies should be designed to measure the incidence of complete wound closure following application of the surgical graft. durability and quality of surgical wound closure should be assessed over time to ensure that the product does not have a deleterious effect on these outcomes.

Timely excision and grafting have greatly reduced morbidity and mortality in pat with full thickness burns. The clinical benefits of engraftment in burn injury incl reduced wound sepsis rates, improved hemodynamic status, and decreased requirement for donor site harvest. Since engraftment rates are high with good standard care, studies of surgical closure of burn wounds may take large numbers patients to detect a difference between the test product and standard care. It is important to evaluate healing outcomes such as durability, functionality, and cosmetic appearance, including scarring.

4. Improved Quality of Healing

Trials for *improved cosmesis* claims should demonstrate a significant effect on outcomes such as scarring, the contour and feel of the healed skin, or normalizati of skin markings or pigmentation. The appropriateness of an improved cosmesis claim depends on the type and location of the wound. For example, normalizatio skin markings or pigmentation would clearly benefit patients who require graftin full thickness burns on the face, whereas this outcome would be a less convincin measure of benefit for patients with plantar ulcers. In choosing endpoints to supp

improved cosmesis claims, it is important to consider whether a reliable assessm tool exists, or can be developed.

Products that reduce scarring may also improve function, for example, range of motion. Standardization across treatment arms of the use of concomitant therapie such as pressure garments and rehabilitative therapies (e.g., passive range-of-mot exercises), is important for adequate assessment of this outcome.

C. Other Considerations Related to Improved Wound Care

FDA recognizes that products intended for wound management may provide important patient benefit without improving the incidence or timing of closure relative to standard care. However, it is important to demonstrate that such produ do not significantly impede healing. Thus, wound healing should be evaluated as safety outcome for all products with a wound care claim.

1. Wound Infection Control

Infected wounds do not heal, and the primary efficacy outcome for topical anti-infective wound products can be either *healing* or *control of infection*. Both outc should be assessed, and reasonable concordance would be expected. Products for treatment or prophylaxis of infection in serious wounds (e.g., burns, diabetic foot ulcers) should have a well-established and appropriate spectrum of activity.[3]

2. Debridement

It is generally accepted that necrotic tissue inhibits healing by interfering with tis repair and promoting microbial growth. Thorough debridement of wounds is therefore considered standard care essential to healing. *Partial debridement* is no acceptable endpoint because the clinical benefit of partial debridement is unclear methods for measuring extent of debridement have not been validated. Although there is debate about the optimal design of trials to assess the efficacy of debridir agents, a reasonable endpoint for a debridement claim might be *thorough* remova necrotic tissue (e.g., produces a wound bed suitable for grafting). Other clinically relevant endpoints, such as pain or blood loss during or immediately following debridement, could provide supportive evidence for clinical benefit when the pri efficacy endpoint is debridement equivalent to that produced by standard mechanical/surgical procedures. For burn wounds, ***timeliness*** of thorough debridement is an especially important consideration. Note that all studies should assess the debriding product's effects on wound closure to ensure that the product does not impair healing or cosmetic outcome.

3. Wound Pain Control

Studies of topical products that reduce wound site pain should distinguish betwe chronic wound pain and acute pain associated with wound care procedures. Appropriate instruments to measure pain should be prospectively defined and properly validated. The effect of topical pain control products on healing is an important safety outcome.

4. Other Wound Care Claims

Serious wounds may negatively affect many aspects of patients' lives. Clinically significant improvement in certain aspects of daily living not already captured by of the previously described outcome measures (e.g., decreased drainage when experienced by the patient as an important improvement in ability to function) m support a labeling claim if demonstrated with a validated instrument.

III. PRECLINICAL CONSIDERATIONS

This section consists of specific points to consider for wound indication drugs an biological products. It is not intended as a general guidance for preclinical testing

A. Animal Models for Wounds

Wound models may be helpful in establishing pharmacological responses, as wel assessing potential toxicities of wound products. The animal species selected sho exhibit a biological responsiveness to the test agent (i.e., should be a relevant species), where appropriate. Although animal models have been useful to establi proof of concept for some types of products, in general they have been poor predictors of efficacy in clinical trials. Because currently there are no ideal anima models for chronic wounds or extensive burns, multiple animal models are typica used to assess activity of wound healing agents. Fibroplasia and stroma formatio be evaluated by subcutaneous injection of some products. Contraction and re-epithelization can be evaluated by topical application on full thickness excisional wounds or in a pig graft donor site model. (Pigs are often useful models since the cutaneous architecture is most similar to that of human skin.) Induction of angiogenesis can be evaluated in chick chorioallantoic membrane or rabbit corne 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. Impaire healing models include infection, necrotizing trauma, irradiation, administration corticosteroids or chemotherapeutic drugs, or drug-induced or genetic diabetes mellitus in mice, rats, hamsters, guinea pigs, and young pigs. Each model has on more of the characteristics that can be useful for evaluating a product's activity. F example, the rabbit ear dermal ulcer model lacks the vigorous wound contraction seen in rodent models and allows for the induction of ischemia in the wound.

B. Biodistribution and Pharmacokinetic Studies

In vivo biodistribution/pharmacokinetic studies are helpful in the design of toxicology studies. Preferably, the pharmacokinetic (PK) profile can be determin the same animal species that will be used in the toxicity assessment. For topical wound products, animal wound models may provide more relevant information t application to intact animal skin. Since currently there are no chronic ulcer mode regional and/or systemic exposure after topical applications of a product for a chr indication might be better approximated by subcutaneous injection (when technic feasible). Consideration should also be given to alterations of the PK profile and potential for product accumulation with repeated dosing. Where feasible, informa regarding the stability of the product at the target site, and for biological products target receptor levels, contribute to a better understanding of the activity and pote toxicity of the wound product.

C. Toxicity Studies

The design of nonclinical toxicology studies for wound products should reflect, a 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 exaggerat pharmacological responses and potential toxicities of wound products. Administration of the wound product at multiples higher than the intended therapeutic dose (determined from wound models) may provide an estimate of th 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 effects of product formulation components o wound healing.

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

The immunogenic potential of biotechnology-derived wound 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/or the toxicity of the agent. Although the development of antibodies to antige products has generally not been predictive of the clinical response, data on this should be collected to provide a complete preclinical safety assessment of the wo product.

Carcinogenicity studies generally should be conducted for drugs intended to treat chronic ulcers.[5] For biological products, the 2-year chronic bioassay and carcinogenicity study currently used for drugs is generally inappropriate due to species specificity and immunogenicity of the product. However, data in rodent initiation-promotion carcinogenesis models support the potential of various grow factors to act as tumor promoters. Current unresolved issues regarding the carcinogenic and tumorigenic potential of wound healing products include the likelihood of tumor promotion in the proposed patient populations and the additic susceptibility of patients exposed to environmental or other potential carcinogens example, systemic chemotherapy). Sponsors are encouraged to address this issue referencing the existing scientific literature, and evaluating the potential of the te: agent to stimulate the growth of normal and/or malignant cells that express the receptor for the agent.

Reproductive and developmental toxicology studies are recommended for wound products administered to women of child-bearing potential.[6]

Genotoxicity studies should be performed for all nonbiological drugs. These stud are indicated for a biotechnology-derived product only when supported by appropriate scientific rationale.[7]

IV. CLINICAL TRIAL CONSIDERATIONS

This section consists of specific points to consider for wound indication trials. It not intended as general guidance on trial design.[8]

A. Absorption Studies

For topical drug, biological, and combination products, phase 1 evaluations shou include quantitation of absorption through the wound. Systemic bioavailability o topically applied products is generally assessed using standard pharmacokinetic measurements with serial serum sampling. Systemic uptake is influenced by wou factors such as size and vascularity, as well as product characteristics such as molecular weight, chemical composition, and the presence of excipients. In the c of growth factors, relatively little (<1%) absorption typically occurs from chronic ulcer sites, but these amounts might be clinically significant because some growt factors are active in vitro at nanogram concentrations. For this reason, it is impor to perform sensitive assays against serum background.

For products that are absorbed from the wound bed, the systemic dose depends o several factors: the concentration of the active ingredient, the total body surface a treated, the volume applied, frequency of application, and duration of contact wit wound.

Safety and pharmacokinetic studies for topical wound products should usually be conducted in patients with the indication sought, since absorption through intact s of a normal volunteer would not predict absorption in a wound.

B. Irritancy or Sensitization

When preclinical studies or previous clinical experience suggest that a topical pr might induce clinically significant dermatitis, irritancy or sensitivity testing in no volunteers is recommended prior to trials in patients, since superimposed dermati deleterious to wounds. The need for routine testing of the final formulation deper on the product, and sponsors are encouraged to discuss dermal toxicity testing wi the appropriate Center before initiating the studies.

C. Assessment/Quantification

The tools to assess endpoints for a clinical trial should be both prespecified and standardized across clinical sites. For example, if photographs are to be used for measurement and documentation, the lighting and type of camera should be spec Scoring systems for wounds can be used at baseline to determine eligibility for st as well as for periodic wound assessment during the study. The use of accepted assessment systems is recommended (e.g., Wagner, International Association of Enterostomal Therapists). Proposals for novel assessment systems should include validation data.

Methodologies for quantifying wound characteristics are continually being developed, and sponsors are encouraged to discuss new approaches for their trial with the Agency. Regardless of the methodology, the following variables should addressed in all clinical trials for wound indication products.

1. Ulcer Classification

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

sonography to quantify venous or arterial insufficiency, transcutaneous oxygen tension (t_cpO_2) measurements, ankle/brachial index, filament testing to quantify sensory neuropathy, measurement of laboratory markers for diabetes mellitus, an histopathology of ulcer biopsies to exclude neoplastic, immune-mediated, or prin infectious disease.

2. Wound Size

Quantitative measurements of wound size are routinely used to assess initial wou size before and after debridement, as well as progress toward closure. For ulcers tend to be superficial, such as venous stasis ulcers, the area of the wound opening should be measured. This can be accomplished by tracing the wound perimeter o measuring maximal width and length. 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 probing the maximal depth is a frequen used method. For other ulcers, such as pressure ulcers, molds can be used to prov precise measurement of volume and/or surface area. Alternatively, semi-quantita measurements can be achieved using the maximal width/length/depth and shape coefficient.

For acute burns, it is important to determine as well as possible the depth of targe burn wounds, as this parameter affects both the choice of standard of care regime and the expected time to healing. The distinction between partial, full thickness, a indeterminate wounds is currently based on clinical judgment. Clinical parameter include appearance of the tissue, sensation, and bleeding upon debridement. Validated test methods for determining burn depth do not exist currently, but biop and Doppler measurement of blood flow are sometimes used. Wound depth heterogeneity is often an impediment to quantitative measures, and burn depth extension in the first 24 to 48 hours following injury frequently necessitates reassessment of wound severity and treatment. Initial clinical assessment of full thickness wounds should be confirmed by comparison to the total body surface a 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 o donor site.

3. Wound Imaging

Photographic and wound imaging procedures standardized across all study sites should be used to document the wound appearance at each clinic visit and to corroborate the measurements captured in the case report form.

4. Infection

Infection should be assessed clinically by symptoms and signs that include purul drainage, erythema, warmth, exudation, odor, pain, fever, and leukocytosis. Feve pain, and leukocytosis may be absent, however, especially in patients with diabet foot ulcers. Quantitative and qualitative culture of a viable tissue biopsy can be u at baseline to help determine if the wound is infected or merely colonized and to guide appropriate anti-microbial therapy. This method is generally preferred to

quantitative and/or qualitative culture of swab specimens.[9]

D. Population

The choice of patient population for inclusion in clinical trials depends on the typ wound.

1. Chronic Cutaneous Ulcers

Three of the major categories of chronic cutaneous ulcers are diabetic ulcers, ven stasis ulcers, and pressure ulcers. In general, separate trials should be conducted f each type of chronic ulcer because they have very different etiologies and potenti different responses to therapy. 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 an used.

Variability can be reduced by specifying enrollment criteria that exclude conditic known to impede healing. For example, specifying a range for ulcer size will avo ulcers that would be expected to close rapidly with little intervention (e.g., < 1 cn and ulcers that would be less likely to close during a trial (e.g., > 50 cm^2). Howe if demonstration of efficacy is limited to ulcers of a specific size, and the ability t extrapolate to smaller or larger ulcers is unclear, the labeled indication may be similarly limited.

2. Burns

The population for burn trials is usually defined by the extent and depth of the bu injury. For most burn wound claims, it is important to determine, to the extent possible, the depth of target wounds, since this determines the standard of care ar the expected time to healing.

Important characteristics of the burn include its cause (thermal, chemical, electric anatomic location, depth (full or partial thickness), duration, and extent (% total b surface area). Patient characteristics that affect burn wound healing include age, nutritional status, underlying medical conditions, and the presence of concomitan injury (e.g., head trauma, inhalation injury, bone fractures). Patients with serious burns commonly receive multiple concomitant treatments, making it sometimes difficult to detect a treatment effect. For this reason, it is advisable to enroll patie with the least serious burns that still permit assessment of the product's claimed benefit. However, it may also be important to assess the effects of the study treat used in conjunction with commonly used concomitant therapies.

When patients with full thickness burns are studied, donor sites for autografts are sometimes selected as the target wound. As noted earlier, although the patient population is one and the same, demonstrating the safety and efficacy of a produc a donor site wound does not support the safety and efficacy of the product for bu wounds, because burn wounds differ in clinically significant ways from surgical wounds.

E. Standard Care

Standard care in the context of this guidance refers to wound care in a clinical tri other than the experimental product. Good standard care procedures in a wound t 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 genera advisable that all participating centers agree to use the same procedures. If standa care procedures are not uniform, it is important that the sample size and collected data be adequate to assess the impact of wound care variations on outcomes and treatment response.

A number of standard procedures for ulcer and burn care are widely accepted. Th appropriate procedures to specify in clinical trials will evolve as care for wound a burn indications evolves. Several professional groups have initiated development care guidelines for ulcers and burns. Although the Agency does not require adher to any specific guidance, the basic guiding principle is that standard care regimer wound trials should optimize conditions for healing and be prospectively defined 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 unifc application across study centers. It is important to specify in the case report form (CRF), at each visit the type of ulcer or burn care actually delivered (for example extent of debridement, use of concomitant medications). For outpatients, the CRI should also capture compliance with standard care measures, such as wound dres off-loading, and dietary intake. The value of study site consistency in standard ca for reducing variation cannot be over-emphasized because of the profound effect these procedures have on clinical outcome for burns and chronic wounds. Nonetheless, in some cases it may be important to assess the effect of experiment treatment with common variations of standard care procedures.

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 of pressure and diabetic foot ulcers

· Compression therapy for venous stasis ulcers

· Establishment of adequate circulation for arterial ulcers

· Maintenance of a moist wound environment

· Infection control

· Nutritional support, including blood glucose control for diabetic ulcer pat

· Bowel and bladder care for patients with pressure ulcers at risk for contamination

a. Debridement

The presence of necrotic tissue, sinus tracts, exudation or transudation, and

infection of soft and hard tissues can interfere with ulcer healing. Appropri debridement procedures for the indicated ulcer should be specifically defin in the protocol. To avoid bias and confounding of treatment effect, ulcer debridement should precede evaluation of ulcer extent and infection. Enzymatic debriding agents, like other concomitant topical products, can confound results in wound product trials and generally should be avoided.

The need for additional debridement, performed after study treatment has started, may indicate product-induced wound deterioration. As such it shou be documented on CRFs and included in analysis of product safety and efficacy. Discontinuation might be indicated in early trials where little is known about product safety, but not in later trials, when standard debriden procedures may be indicated to optimize patient care (e.g., on-going remov callus as part of standard care for diabetic ulcers).

b. Off-loading/Compression

Relief of pressure is critical to outcome for chronic ulcers. Pressure is the principal cause of decubitus ulcers and off-loading is often difficult to standardize because equipment (e.g., type of bed) may not be available at a sites, and compliance with study procedures is labor intensive (e.g., turning these critical aspects of effective therapeutic intervention cannot be standardized across all sites, it is important to specify the actual care delive in CRFs and to consider concomitant care in the efficacy analysis. For diab foot ulcers, off-loading choices (e.g., casting) must be weighed against the to apply study treatments and monitor outcome. Similar considerations are important in choosing compression methods for venous stasis ulcers. Every attempt should be made to define a regimen that can be uniformly applied across sites and deviations should be captured in the CRFs.

c. Maintenance of a Moist Wound Environment

Maintenance of a moist wound environment is generally accepted standard for all chronic cutaneous ulcers. In choosing test dosing regimens, it is help to consider limitations imposed by various standard care dressings. In case where there is a sound rationale for the expected benefit of a test product, b its use is not compatible with established standard care dressings, alteratio standard care can usually be safely implemented by including adequate discontinuation rules.

d. Infection Control

Absence of frank infection is critical for treatment success of all wound products, regardless of the claim. For this reason, wound products whose c is not anti-infective are usually tested in patients with uninfected target ulc (noting the distinction between colonization and frank infection of an ulcer Acceptable ulcers for enrollment can often be achieved during a run-in per with thorough debridement and other good standard care procedures. A hig incidence of true infection (as opposed to colonization) is present at baselin for diabetic foot ulcers. It may not always be necessary to exclude infected diabetic foot ulcers if the infection does not involve underlying structures a is responding to standard systemic anti-microbial therapy. In such cases, it especially important that the protocol clearly delineate adequate rules for

patient discontinuation due to wound deterioration on-study. As for all discontinued patients, safety assessment should continue throughout the tri and these patients should be included in efficacy analysis.

If an ulcer becomes infected during a study for a topical wound product, ar the investigator prescribes topical anti-microbial treatment, it is recommen that the patient be discontinued from study treatment. Use of concomitant topical medication is discouraged in trials for topical products to avoid confounding of safety and efficacy outcomes.

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, discontinuation might be indicated in early trials, where little is known abo product safety and where infection may signal test product-induced deterioration of the wound, but not in later trials where such therapy would considered standard care (e.g., systemic antimicrobial therapy for diabetic ulcers).

e. Wound Cleansing

Agents used for wound cleansing should be bland (e.g., normal saline) bec some cleansers retard healing, or can cause irritation and sensitization. The regimen should be prespecified in the protocol.

f. Nutritional Support

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 t inclusion criteria encompass patients significantly above or below ideal bo weight (e.g., cachectic patients with pressure ulcers). Maintenance of normoglycemia is an important factor for patients with diabetic ulcers.

2. Standard Care Considerations for Burns

Standard care for serious burns includes careful attention to the following parame

- Hemodynamic resuscitation
- Management of comorbidities
- Timely burn debridement and/or excision
- Wound closure
- Infection control
- Pain control
- Nutritional support

· Rehabilitation, including passive range of motion when burns overly joint

Because large burn centers tend to have well-established, distinct standard care regimens, analysis of data in 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.

F. Safety Considerations

Specific points to consider for wound products are listed below.

1. Effects of the Product on the Wound

All wound treatment trials should include an evaluation of the product's effect on healing process, as a safety outcome. Deterioration of target wounds can manifes erythema, pain, discharge, infection, tissue necrosis, requirement for repeat debridement or other surgical intervention (i.e., amputation), and/or increase in u size. Undesirable alterations of soft tissues, ligaments, periosteum, or joint capsu underlying deep wounds should also be evaluated, depending on the nature of the product. For detailed information about wound product microbiology, please see attachments.

2. Immune Reactions

For biological products and some drugs, immunogenicity is generally addressed l measuring antibody titers prior to and after the treatment. Further immunologic characterization may be recommended, since the development of an immune response can render the product inactive (neutralizing antibodies), and/or induce acute or chronic immune reactions (e.g., anaphylaxis, contact sensitization, autoimmune disease).

3. 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 monitoring group be used for masked trials when the known or suspected risk is significant, and/or the study population is critically ill (e.g., seriously burned patients).

4. Patient Discontinuation

Discontinuation criteria evolve as the safety database for the wound product grov Because the active ingredient(s) or the vehicle of topical wound products may ex deleterious effect on healing, patients should be discontinued from study treatme signs or symptoms suggest wound deterioration during early trials. Once reasona 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 claim anc type of wound. Subjects who are discontinued from study treatment should rema the study for safety assessment and efficacy analysis.

G. Study Design Considerations

1. Randomization and Stratification

Randomization is particularly important to reduce bias in trials for wound indicat because standard care wound management procedures and baseline wound characteristics have a profound effect on outcome. Because some degree of varia in these factors across patients and sites is unavoidable, stratification by study ce is recommended to ensure balance between the arms. In some cases, it may be appropriate to prospectively stratify randomization by other important covariates such as wound size or duration, but the number of variables used for stratificatio should be very limited. Variables thought to affect outcome should be considered the analysis whether or not used for stratification (see Statistical Considerations).

2. Comparator Arms

A vehicle control arm is recommended for most wound product studies, with identical standard care procedures included in both the vehicle and investigationa product arms. To evaluate the safety and effect of the vehicle, a study arm treatec with standard care alone is recommended in phase 2 for topical wound products, the safety of the vehicle has not been previously demonstrated.

Within patient control designs have been used in trials of topical products intend for serious burns, in an attempt to minimize the heterogeneity characteristic of th patient population. However, this approach compromises the evaluation of syster toxicity, necessitating additional controls or studies to collect adequate safety dat

3. Masking

In general, masking (blinding) of patients and investigators to the treatment recei will reduce bias and should be employed when feasible. Early studies of topical wound indication products often require an arm that receives only standard care, addition to an arm receiving vehicle, to establish whether the vehicle has an effec healing. Often the standard care only arm cannot be masked. In other cases, especially in some devices, it is impractical or unethical to implement a control treatment that mimics the test product and allows masking. In these types of situations, assessment by a third party masked evaluator should be considered.

H. Statistical Considerations Specific for Wound Product Trials

This section addresses issues that present special considerations for wound produ trials.[10]

1. Significance Tests

Analysis should be prespecified in the protocol. For *incidence of closure* endpoin categorical techniques are recommended (e.g., X^2 tests of homogeneity or logisti regression). For *time to closure* endpoints, outcome survival analyses are perform For most wound trials, the center or investigator is almost always needed as a fac in the analysis, due to variations in standard of care. When appropriate, comparis of the survival curves can be done by using a Mantel-Haenszel statistic or by the Proportional Hazards Model, which allows for co-variate adjustment (including a adjustment for center). If rate of healing is being considered, growth curve model can be used to analyze the rate of healing.

2. Missing Values and Imputation

Missing values can affect the interpretation of a dataset, and for that reason steps should be taken to avoid them. When a substantial portion of values is missing, concerns arise about the adequacy of the trial. For that reason, a plan to account f missing values should be included in the protocol. The worst case outcome can b used to determine the maximal effect of missing values.

3. Data Transformation and Covariate Analyses

Prospective stratification should balance the arms for the one or two most import variables in the wound claim. Covariate analyses should be employed to adjust fc variables that affect the outcome. These covariates should be prespecified, and th analyses should also 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 si 5 cm^2 duration of the ulcer > 1 year). The covariate should be used as a continuo variable. Exploratory analyses may examine subgroups defined by various cut po but when a particular cut point is deemed to be important in guiding the use of th product (e.g., ulcers greater than 10 cm do not respond), this cut point should be prospectively identified and studied in a clinical trial.

ATTACHMENT: Wound Product Quality Microbiology

Because a wound represents a breach in the body's natural barrier to microbial invasion, the final formulation of topical products used for the treatment of woun or burns should be sterile to avoid introducing exogenous microorganisms. Guid on validation of the manufacture of sterile products can be found in the FDA's *Submission Documentation for Sterilization Process Validation in Applications f Human and Veterinary Drug Products* (November 1994). Methods for performin sterility tests on drug products are currently found in USP 23 Supplement 8 <71> "Sterility Tests."

To avoid contamination of a sterile product, it is preferable for wound products t packaged in single-use containers. However, if packaged in multi-use containers, wound products should either include a preservative system or possess innate ant microbial activity. Anti-microbial preservatives should not be used as a substitut good manufacturing practices. The anti-microbial activity of the product, with (o without) a preservative system, should be demonstrated by performing a microbi challenge test such as the Antimicrobial Effectiveness Test USP 24 Supplement 8 <51>. The minimum acceptable limit for the content of preservatives in a produc should be demonstrated as microbiologically effective by performing a microbial challenge test of the formulation with an amount of preservative less than or equ the minimum amount specified as acceptable. For the purpose of application approval, stability data on pilot-scale batches should include results from microb challenge studies performed on the product at appropriate intervals. Typically, microbial challenge studies are conducted initially, annually, and at expiration. Chemical assays of preservative content should also be performed at all test poin Upon demonstration of the anti-microbial effectiveness of the minimum specifie preservative concentration, chemical assays of the preservative may be sufficient

demonstrate the maintenance of adequate anti-microbial activity for annual batch placed into stability testing. For biological products, testing should be done to en that the preservative does not compromise biological activity.

Some products cannot withstand sterilization processes because they degrade wh heated or irradiated, and they are not filterable. If a wound product cannot be manufactured to be sterile, it should have a very low bioburden (e.g., _10 cfu/g o mL). Bioburden testing should be performed according to a validated test proced such as USP 23 <61> "Microbial Limit Tests" at appropriate, defined time points during stability studies. Additionally, bioburden testing should include identificat of recovered microorganisms to exclude potentially deleterious organisms.

Standards for validation of sterilization of medical devices

ISO 11137:1995 Sterilization of health care products -- Requirements for validati and routine control -- radiation sterilization

ISO 11135:1994 Medical Devices -- Validation and routine control of ethylene o sterilization

ISO 11134:1994 Sterilization of health care products -- Requirements for validati and routine control -- Industrial moist heat sterilization (available in English only

[1] This guidance has been prepared by the Center for Drug Evaluation and Resear (CDER), the Center for Biologics Evaluation and Research (CBER), and the Cen for Devices and Radiologic Health (CDRH) at the Food and Drug Administratior (FDA). This guidance document represents the Agency's current thinking on developing treatment for chronic cutaneous ulcers and burn wounds. It does not create or confer any rights for or on any person and does not operate to bind FDA the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] This document applies only to those medical devices for which clinical studies required

[3] In 1998, the Agency published a series of draft guidances on developing drugs t treat antimicrobials. Two of those guidances may be of interest: *Developing Antimicrobial Drugs - General Consideration for Clinical Trials* (July 1998) and *Uncomplicated and Complicated Skin and Skin Structure Infections - Developing Anitmicrobial Drugs for Treatment* (July 1998). Once these guidances have been finalized, they will reflect the Agency's views on developing antimicrobial drug products.

[4] General guidance for preclinical testing of drugs and biologics can be found in recent International Conference on Harmonisation (ICH) documents, including *M Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (November 1997) and *S6 Pre-Clinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (November 1997).

For devices, general guidance for assessing preclinical safety can be found in *Blu Book Memorandum #G95-1 Use of International Standard ISO-10993 and Biolo*

Evaluation of Medical Devices Part-1: Evaluation and Testing (May 1995). See the draft *Guidance for the Preparation of an IDE Submission for an Interactive Wound and Burn Dressing* , which was published on (April 1995) and is being finalized.

[5] Guidance for drug carcinogenicity studies can be found in the ICH documents entitled, *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996) and *S1C Dose Selection for Carcinogenicity Stud of Pharmaceuticals* (March 1995), Addendum (July 1997).

[6] General guidance on preclinical study designs can be found in the ICH docume *S5A Detection of Toxicity to Reproduction for Medicinal Products* (September 1

[7] Further guidance is available in the following ICH documents: *S2A Specific Asp of Regulatory Genotoxicity Tests for Pharmaceuticals* (November 1997) and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* (November 1997). The ICH document *S5A Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (September 1994) provides further discussion regarding biological products.

[8] General guidance on this topic can be found in ICH documents *E8 General Considerations for Clinical Trials* (December 1997) and *E9 Statistical Principals Clinical Trials* (September 1998). A draft guidance, *E10 Choice of Control Grou Clinical Trials,* also was published on this topic in September 1999; once finalize will reflect the Agency's thinking on clinical trial considerations.

[9] As noted under Claims (footnote 3), the Agency published in July 1998 a series draft guidances on drugs to treat antimicrobials, including uncomplicated and complicated skin infections. These guidances currently are being finalized.

[10] General guidance also is available about data analyses, for example *ICH E9 Statistical Principles for Clinical Trials* (September 1998).

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUL 25 2003

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 76N-0482

TO: Dockets Management Branch, HFA-305

☑ The attached material should be placed on public display under the above referenced Docket No.

☑ This material should be cross-referenced to Comment No. CP7, LET10, EMC1

Charles J. Ganley, M.D.

Attachment