

Wound Management Division

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Friday, August 25, 2000

Smith+Nephew

Dockets Management Branch
[HFA-305]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

**RE: Docket No. 00D-1318 - Comments and suggestions on the Draft
Guidance For Industry on Chronic Cutaneous Ulcer and Burn Wounds -
Developing Products for Treatment**

Dear Madam or Sir:

The Smith & Nephew, Inc. Wound Management Division appreciates the opportunity to comment on the Food and Drug Administration's [FDA] draft guidance for industry -- *Chronic Cutaneous Ulcer and Burn Wounds--Developing Products for Treatment*. Availability of this draft guidance document notice was published in the June 28, 2000, *Federal Register* [65 FR 39912].

Smith & Nephew, Inc. is a worldwide leader in health care with a comprehensive and an ever-expanding range of advanced wound care systems, products and services for the management and care of skin and soft tissue wounds and burns. Smith & Nephew, through its wound care products and services, strives to improve patient care and healthcare outcomes.

Our comments and suggestions focus on a number of sections of the draft guidance document.

I. INTRODUCTION

The Introductory Section of the draft guidance document includes an accurate definition of a chronic cutaneous ulcer. However, we believe the draft guidance document does not define "burn wound." We recommend definitions be included. One approach is:

Superficial - includes the epidermis.

Superficial partial thickness - epidermis and uppermost portion of dermis.

Mid-dermal - involve the epidermis to the middle portion of the dermis.

Indeterminate - involve the epidermis and deeper portions of dermis, but exact depth unclear.

Deep partial-thickness - involve the epidermis and to lower portion of the dermis.

Full-thickness - when the epidermis and the dermis are destroyed and extend into subcutaneous fat, muscle, or bone to varying degrees.

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If the FDA intends to include treatment guidelines for superficial, partial-thickness and full-thickness burns, then definitions and treatment guidelines for superficial, partial-thickness and full-thickness burns should be incorporated into this guidance document. For example, for full-thickness burns, a durable, structural, functional and cosmetic closure is often the ultimate goal, but certain, alternative clinical outcomes may be a meaningful interim step towards this goal [e.g., temporary coverage for a certain period of time].

II. CLAIMS

A. GENERAL CONSIDERATIONS

There is increasing evidence to suggest a similarity in deficiencies across chronic wounds. Although there are clearly some differences too, we believe these similarities could be reflected in the clinical trial requirements for new wound indications.

We do not believe that extrapolation across wound types should be unacceptable for other [Category two] claims [e.g., infection control, debridement, pain relief] and separate safety and efficacy data should not *necessarily* be required for each wound type. For example, if a topical antibacterial is shown to be effective in a particular wound type against a specific organism it is not unreasonable to extrapolate that activity to other wound types. We would prefer to leave this open with the option for the sponsor to justify extrapolation where appropriate.

B. CLAIMS RELATED TO IMPROVED WOUND HEALING.

1. Incidence of Complete Wound Closure

The definition of closure – the “or dressing requirements” is unnecessary, could be confusing and should be removed. It is possible that dressings will be used or developed to protect a recently closed wound. In addition the use of compression hosiery post-healing is standard practice in venous leg ulcer care and again this could be confused with “dressings”.

Three month follow up of closed wounds – we understand the motivation for this but believe it should not affect any claim regarding incidence of closure. There are many factors that may cause a wound to recur which are unrelated to the efficacy of the wound-healing product. A three-month follow up for complete closure for burn wounds seems unreasonable since research reveals that healed burn wounds rarely reopen, although follow-up for other endpoints [e.g., cosmetic appearance], is appropriate.

The guidance should address the likelihood of FDA of requiring blinded assessment of wound closure by a third party [assessment of photographs, planimetry etc].

"The clinical benefit of statistically significant decreases in wound size has not been established". The current approach to measuring wound area is probably the most reproducible from patient to patient and we believe does give some value. Alternative approaches that should be considered are significant decreases in wound depth, e.g., improving the wound from stage four to stage three or two pressure sores, or closing the distal end of a tracked fistula or FDU, bearing in mind the reduced risk of infection associated with more benign wound types.

2. Accelerated Wound Closure

Accelerated wound closure is likely to be a more relevant claim in the context of an individual patient. The clinical benefits on the individual level are as important as those of a population. The finding of superiority in time to complete closure may reflect little or no *additional* information about the product but may still be a more relevant claim, and should not be precluded if the data support it. Speed of closure is clinically relevant for diabetic foot ulcers where the breach presents opportunities for limb-threatening infections. We see no valid reason why both claims should not be made if appropriate.

We do not understand why "accelerated wound closure" needs to be supported by measurements of wound size over time if the treated wounds heal faster than controls in a trial matched for baseline data.

We agree that the accelerated healing claims for burns should distinguish between partial thickness, full thickness, and donor site wounds. Closure of full thickness burns using a product as a temporary cover should be immediate, with a key end-points being provision of a temporary cover until sufficient graft material is available, and preparation of the wound bed for a graft, whereas for partial-thickness burns, a faster wound closure claim is desirable, as stated for donor sites.

3. Facilitation of Surgical Closure

In the reference "...agents that *heal* wounds to the point that surgical closure is more feasible", the meaning of "heal" should be clearly defined.

4. Improved Quality of Healing

The appropriate measure of cosmesis, especially as it relates to scarring continues to be an issue in designing clinical trials for these claims. There are specific recommendations provided in this draft guidance document clarifying the measurement of outcomes in other areas. However, recommendations to appropriately measure cosmesis are not evident in the draft guidance document. Measurement tools regarding scarring, cosmesis and implementation of such tools need to be addressed in this draft guidance document. Independently validated scar measurement tools [e.g., Vancouver scar scale] have been used in previous studies. The use of independent observers is also an option, but can cause issues in feasibility and reproducibility in clinical studies, where scar development is measured over a prolonged period of time when staff turnover invariably occurs.

The Quality of Healing section in the draft guidance document should include more than improved cosmesis – prolonged healing/duration of repair should be addressed in this section rather than in the Incidence of Complete Wound Closure section.

C. OTHER CONSIDERATIONS RELATED TO IMPROVED WOUND CARE

1. Wound Infection Control

“Both outcomes should be assessed and reasonable concordance would be expected.” Removal of infection does not always result in healing in chronic wounds. It may be reasonable to expect that removing infection will facilitate healing of an acute wound but many other factors contribute to the maintenance of a chronic wound and therefore a direct correlation between treatment of infection and chronic wound healing should not be required. Progress towards healing should be viewed as a safety parameter and effect of an anti-infective product on wound healing should rightly be assessed, but it is not appropriate to expect that all anti-infectives should contribute to the wound healing process. It should be sufficient to demonstrate that the product does not impede wound healing. In certain cases the prevention of infection may be seen as the overriding clinical need and the benefit-to-risk ratio of the anti-infective may still be positive even if there is evidence of delay in healing [e.g., silver sulphadiazine cream in major burns - studies have not shown unequivocal proof of lack of effect on wound healing but this is a secondary consideration to prevention of infection in the wound immediately post-burn].

2. Debridement

The effect of a debridement product on wound closure is important, although the requirement to follow consistent, good wound healing practices to ensure a fair comparison is key to minimize additional variability.

Partial debridement is referred to as not being an acceptable endpoint, however partial debridement *may* be sufficient to allow further treatment to be undertaken [e.g., if a wound is debrided to the extent that it is covered with, for example, 70 percent granulation tissue this may be very useful in allowing the surgeon to apply a pinch graft to that portion of the wound] – for example the wound may then become “suitable for grafting”.

3. Wound Pain Control

Pain control is an important factor for both patients and providers, and this document should address the measures that the FDA would find acceptable to allow pain control claims, while also being readily implemented in a clinical environment. In partial-thickness burns, which often involve children for whom pain control is a major factor, this guidance is particularly relevant, particularly if within-patient controls are required. Independently validated pain scales have been used in previous studies, but data have not always been acceptable to include in subsequent product labeling.

III. PRECLINICAL CONSIDERATIONS

Some of the considerations set out in this part of the document can usefully apply to certain medical devices for example medicated dressings and drapes, and combination products regulated as medical devices [e.g., tissue engineered products]. It may be misleading or confusing to the sponsor to specify applicability to only drugs and biologicals when consideration of toxicity and pharmacokinetic issues will be relevant to some devices. If devices are excluded their sponsors will have to operate outside of the guideline when it may be more appropriate to use the guideline as a framework and justify the absence of certain tests [e.g., systemic toxicity where a medicament is not systemically absorbed].

C. TOXICITY STUDIES

"Carcinogenicity studies generally should be conducted for drugs intended to treat chronic ulcers". We would agree that sponsors should address the potential for tumour promotion by referencing literature, history of use and tumourigenicity studies, but consider that long-term carcinogenicity studies should only be required where there is clear evidence from such sources that carcinogenicity is a potential hazard. For many wound treatment agents the minimal systemic absorption and intermittent durations of use should obviate the need for carcinogenicity studies.

IV. CLINICAL TRIAL CONSIDERATIONS

A. ABSORPTION STUDIES

While the requirement for adequate bioavailability studies is appreciated it should be recognized by the FDA that pharmacokinetic studies on products applied to wounds are inevitably non-standardized. This is alluded to in the second and third paragraphs, but because of the many factors affecting absorption, the value of such studies in predicting systemic exposure should be carefully considered. Factors such as age, nutritional status, local and systemic circulatory problems, ambulation, site, depth, physical condition of the wound etc can all have major influences on the amount of drug absorbed, so the relevance of particular studies should be considered on a case by case basis and not required as a standard.

D. POPULATION

As noted in our comments on "Claims", there is increasing evidence to suggest a similarity in deficiencies across chronic wounds. Although there are clearly differences too, we believe these similarities should be reflected in the clinical trial requirements for new wound types, and that extrapolation across different wound types may be justified as our understanding increases.

1. Chronic Cutaneous Ulcers

Extrapolation to healing of larger ulcers may be problematic in some circumstances, however we do not see why extrapolation to smaller ulcers could not be permitted.

E. STANDARD CARE

a. Debridement

Specifically identifying enzymatic debriding agents is felt to be too specific at this stage. Debridement is recognized as a key factor in successful healing of wounds and is often difficult to standardize in clinical studies. Future product and clinical developments may lead to enzymatic debridement becoming an acceptable approach to standardize debridement of certain wounds. Specifically making reference to these products at this stage may therefore be premature. Sponsors should be permitted to justify the use of enzymatic debriders in appropriately designed trials.

b. Off-loading/Compression

We recommend this section be expanded to include a statement such as: "The regimen of standard care should not only be uniform, but also should accurately reflect a realistic clinical treatment protocol, not one used primarily for a particular clinical trial." For example, standard care in the treatment of diabetic foot ulcers requiring total non-weight bearing or continuous limb elevation should be avoided, as the results achieved in these situations will not accurately reflect the true clinical application, and therefore may drive healing data that may be misleading.

2. Standard Care Considerations for Burns

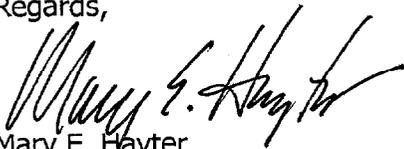
Standard care should also include careful attention to prevention of scarring [e.g., current use of pressure garments], and overall improvement in quality of life of both patients.

G. STUDY DESIGN CONSIDERATIONS

The use of masking in the treatment of burns is often problematic, as frequently within-patient comparisons are used and benefits are often immediately recognizable, particularly in relation to pain control. Continued treatment with a control treatment under these conditions is often both practically and ethically an issue for patients and providers. Guidance on how to handle these situations is requested.

Thank you for the opportunity to provide input on this draft guidance document and your attention to the issues raised above. We welcome the opportunity to work with the Food and Drug Administration as it implements this important guidance document.

Regards,



Mary E. Hayter
Manager, Health Economics/Government Affairs

From 

Date 8.25.00

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Your Internal Billing Reference

To Recipient's Name Deekets Management Branch Phone

Company Food & Drug Administration

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Room 1061

City Rockville State MD ZIP 20852



4a Express Package Service
 FedEx Priority Overnight Next business morning
 FedEx Standard Overnight Next business afternoon
 FedEx First Overnight Earliest next business morning delivery to select locations

FedEx 2Day* Second business day
 FedEx Express Saver* Third business day
* FedEx Letter Rate not available Minimum charge: One-pound rate

4b Express Freight Service
 FedEx 1Day Freight* Next business day
 FedEx 2Day Freight Second business day
 FedEx 3Day Freight Third business day
* Delivery commitment may be later in some areas.

* Call for Confirmation: _____
 * Declared value limit \$500

5 Packaging
 FedEx Letter*
 FedEx Pak*
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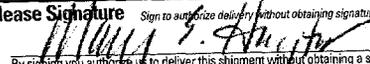
6 Special Handling
 Saturday Delivery Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
 Sunday Delivery Available for FedEx Priority Overnight to select ZIP codes
 HOLD Weekday at FedEx Location Not available with FedEx First Overnight
 HOLD Saturday at FedEx Location Available for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods?
One box must be checked.
 No Yes As per attached Shipper's Declaration Yes Shipper's Declaration not required Dry Ice Dry Ice, 9 UN 1845 x kg
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Total Packages	Total Weight	Total Declared Value*	Total Charges
		\$.00	Credit Card Auth

* Our liability is limited to \$100 unless you declare a higher value. See back for details.

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