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August 25, 2000

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**RE: Docket No. 00D-1318 – Comments and suggestions on the Draft Guidance for Industry on Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment**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

Advanced Tissue Sciences, Inc., is pleased to have the opportunity to comment on the Draft Guidance for Industry on Chronic Cutaneous Ulcer and Burn Wounds--Developing Products for Treatment, as announced in the Federal Register June 28, 2000 (Volume 65, Number 125).

Advanced Tissue Sciences, Inc. is a leader in tissue engineering with an innovative core technology being used to develop a broad range of human-based products for the repair or replacement of damaged and destroyed tissue, including products for the treatment of burns and skin ulcers.

Enclosed, please find Advanced Tissue Sciences comments on the draft guidance.

**Section I: INTRODUCTION (page 1)**

The Introduction of the draft guidance defines chronic cutaneous ulcers and specifically names venous stasis ulcers, diabetic foot ulcers, pressure ulcers, and burn wounds. We suggest that the Agency provide a clear definition of burn wounds and a complete description of the specific types of burn wounds covered by the scope of this guidance (e.g. thermal, electrical, full-thickness, partial-thickness, superficial, etc.). Similarly, we suggest that the definitions and treatment guidelines throughout the document address the full spectrum of burn wound types and definitions. For example, for most burns, a durable, structural, functional, and cosmetic closure is the ideal outcome. However, alternative clinical outcomes (e.g. partial or temporary coverage) may also be considered to be a valuable interim clinical outcome in certain types of burns.

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## **Section II. CLAIMS**

### **B. Claims Related to Improved Wound Healing**

#### **1. Incidence of Complete Wound Closure (page 2)**

The draft guidance defines *complete closure* as “skin closure without drainage or dressing requirements. We suggest that *complete closure* be defined as “complete epithelialization persisting for a clinically relevant interval.” In addition, we suggest that “without dressing requirements” be removed from the definition, as the use of compression hosiery is standard medical care for patients with venous leg ulcers. Furthermore, it is possible that dressings will be used or developed to protect a recently closed wound.

This section of the draft guidance also states that “...subjects remain on study and continue to be evaluated for at least three months following complete closure.” We agree that patients should be followed post-closure. However, we do not believe that this follow-up should be linked to any claim regarding incidence of closure, as there are many factors that contribute to wound recurrence that are not related to product efficacy. In addition, we suggest that this section apply to chronic wounds only. A three-month follow-up for burns to evaluate closure is not appropriate, as incidence of healed burns re-opening is rare.

#### **2. Accelerated Wound Closure (page 3)**

The draft guidance states that “...given a finding of increased incidence of closure, the additional finding of superiority in time to complete closure may reflect little or no additional information about the product.” We suggest that accelerated wound closure does provide valuable information about a product, including the product’s impact on the treatment cost/benefit ratio and a decreased risk of complications for patients. For example, speed of wound closure is clinically relevant for patients with diabetic foot ulcers. Any additional day of “open wound” status with these patients presents an opportunity for the wound to become infected.

The draft guidance also states that “When an improvement time to closure 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*.” This statement is not always the case. For example, this is not true when a landmark analysis (e.g. healing by 12 weeks) is used.

#### **4. Improved Quality of Healing (page 4)**

In this section we would like to suggest that the guidance provide a clear description of acceptable endpoints for cosmesis claims and guidance on acceptable reliable assessment tools to be used to measure these endpoints. We also suggest that this section on “Improved Quality of Healing” be expanded to factors other than improved cosmesis, such as duration of healing.

**Section II. CLAIMS (continued)**

**C. Other Considerations Related to Improved Wound Care**

**1. Wound Pain Control (page 5)**

Defining appropriate measures of pain control has been a challenge in designing clinical protocols. We would like to suggest that the Agency provide specific recommendations for acceptable pain control measurements that can be used to support pain control claims in subsequent product labeling.

**Section IV. CLINICAL TRIAL CONSIDERATIONS**

**C. Assessment/Quantification**

**4. Infection (page 10)**

The draft guidance states, "Quantitative and qualitative culture of a viable tissue biopsy can be used 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 swab specimens." We suggest that the guidance acknowledge that not all wounds can be biopsied and that all experts do not accept the biopsy approach.

**Section IV. CLINICAL TRIAL CONSIDERATIONS**

**D. Population**

**a. Debridement (page 12)**

We are concerned about specifically limiting the use of enzymatic debridement agents, as debridement is a key factor in successful wound healing. Furthermore, it is possible that enzymatic debridement products and their clinical use will be further developed in the future. Sponsors should be permitted to justify their use in appropriately designed clinical trials.

We appreciate the opportunity to provide our comments and suggestions for this draft guidance. We look forward to working with the Agency as it further develops and implements the guidance.

Sincerely,



Stephanie Putnok  
Regulatory Affairs Associate

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