

F.R.A.I.L. or Recognition of the Adult  
Immobilized Life

Seeking Solutions for the Skin-Related  
Complications of Adults  
with Chronic Illnesses

4424 '00 AUG 28 A 8 August 25, 2000

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, Maryland 20852

**RE: Comments on Docket Number: 00D1318  
Guidance for Industry Chronic Cutaneous Ulcer and  
Burn Wounds Developing Products for Treatment**

Dear Sir/Madem:

Thank you for the opportunity to provide comments on the Guidance for Industry related to Chronic Ulcers. Our group, which consists of physicians, nurses, researchers, and healthcare financial experts, is dedicated to improving the resources available to mobility challenged patients with chronic wounds.

As we indicate in the attached comment document, we look forward to having an opportunity to share our experiences with the agency. The F.R.A.I.L. Board fully supports the development of a guidance document that incorporates consideration of chronic wound research for the frail chronic wound population.

Please feel free to contact us at the address listed on our enclosed brochure to discuss any of the issues addressed in our comments.

**F.R.A.I.L. BOARD MEMBERS**

Enclosures: Comments by the F.R.A.I.L. Board (2 copies)  
Brochure of the F.R.A.I.L. Board (10 copies)

00D-1318

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### Executive Summary

The management of chronic cutaneous ulcers is a rapidly evolving discipline. As the current draft indicates...*outcome measures for chronic cutaneous ulcers and burns are in evolution*. The current draft Guidance for Industry presents a succinct set of guidelines for products seeking to achieve claims related to improved healing, but falls short of providing the same for claims related to improved wound care. The list below indicates the primary areas of concern with the current draft of the Guidance for Industry.

- ◆ The frail population, with chronic cutaneous wounds is underserved;
- ◆ The current draft is heavily focused on wounds that are likely to heal;
- ◆ The section on **Other Considerations Related to Improved Wound Care** should be expanded to specifically address non-healing parameters;
- ◆ **Wound Infection Control** efficacy outcomes *should not* link healing and control of infection as the only measure of efficacy;
- ◆ **Wound Debridement** efficacy should be expanded to include outcomes beyond *thorough removal of necrotic tissue*;
- ◆ **Animal Models for Wounds** should be expanded to include claims associated with Improved Wound Care; and,
- ◆ **Clinical Trial Populations** should be expanded to consider both the type of wound and the indication for management.

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**Comments**

The current draft of the Guidance for Industry for developing products for Chronic Cutaneous Ulcer and Burn Wounds provides ample discussion of the issues associated with wounds that can reasonably be expected to heal. However, product development for wounds that are unlikely to heal is underserved by the current draft. The following comments and observations are offered to provide a perspective on the unique issues related to the chronic cutaneous wounds presented by severely compromised hosts whose product needs would fall under **Section II. Claims, C. Other Considerations Related to Improved Wound Care**. Palliative wound care products would immeasurably improve the quality of life for many frail patients who suffer wounds complicated by multiple co-morbidities that impede and/or prevent complete healing. These products would be directed toward the creation of clean, non-exudating, non-infected, pain-free, and odor-free wounds.

Many chronic skin ulcers can heal or significantly improve by correcting or improving the medical condition causing the wound provided that the patient's general health is good or improving. There are circumstances however, where complete wound healing is not a realistic objective. In patients with progressive advanced disease such as cancer, AIDS, end stage heart, lung, hepatic or renal disease, or degenerative neurologic disease, complete wound repair may not be possible. We consider such patients as frail. Frail patients often present with cutaneous ulcers that are truly chronic and unlikely to respond to *any* topical and/or surgical intervention that would result in sustained closure of wounds. The complicated presentation of the host, with multiple systemic co-morbidities that affect circulation, nutritional status, and immune system, along with untold variability in treatment compliance levels, require us to rethink our goals for chronic wound management.

Although the Introduction to the Guidance for Industry defines chronic cutaneous ulcers

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as wounds that failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure, the document itself leans heavily towards the establishment of complete closure of wounds as *the* key outcome for successful management. This premise dictates that clinical trials be designed to evaluate wounds that will, in fact, heal in contrast to true chronic wounds which, often, do not successfully close.

Development of evaluable and validated non-healing parameters for chronic wounds should be incorporated into the Guidance for Industry as legitimate outcome measures for improved wound healing. Pain relief, debridement, type and amount of healthy granulation, odor control and infection prophylaxis, are examples of treatment goals that can be translated to product efficacy. Improving the quality of life and/or the independence level of a frail patient with a chronic skin wounds should be considered as important and meaningful efficacy parameters which could be accurately and reproducibly measured in clinical trials. For example, rather than a change and/or closure of a wound's surface area, prospectively defined measures of "*wound integrity*" could be developed and validated for this unique population of complicated chronic wound sufferers. One measure of wound integrity could be improvement in the character and quality of granulation tissue. Healthy granulation tissue protects deeper tissues, prevents infection and is considered a sign of wound improvement. Other measures can be cutaneous undermining, type and amount of exudate, odor, pain and inflammation.

We agree with the agency's view that efficacy parameters whether objective or subjective need to be validated to demonstrate the clinical significance of what is measured.

The current draft Guidance for Industry under Section II. CLAIMS, C. **Other Considerations Related to Improved Wound Care** *does* recognize that some products for wound care are designed to offer *important patient benefits, without improving the incidence or timing of closure relative to standard care*. This section of the current draft is the *key* area that

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we would like to see further expanded. Development of the non-healing parameters for the frail population described above should be incorporated into this section. For the purposes of facilitating product options for the frail population, we prefer the following definition for chronic wounds: Chronic wounds including pressure ulcers, venous ischemic (arterial) ulcers, diabetic foot ulcers, and inflammatory ulcers are caused by underlying factors such as immobility, poor circulation (venous or arterial), neuropathy, and several other chronic medical conditions which are not or cannot be corrected.

The discussion in this section under **1. Wound Infection Control**, indicates that two measures are necessary to establish efficacy outcomes for a topical product; that is, *healing and control of infection*. The draft further indicates that there should be *concordance* between these two outcomes. We do not agree. For example, an ischemic (arterial) ulcer in a patient who is inoperable, limits management options to the symptomatic control of infection as the only *realistic* goal. Control of infection is a key factor in achieving the objective of increased independence for activities of daily living for many patients with chronic wounds. Patients can be taught to live with wounds provided that the wound remains stable and/or slowly improves.

Wound care experts do not agree on what constitutes infection of a chronic wound. The clinical signs of acute wound infection may not be applicable to chronic long standing skin ulcers. Even quantitative microbiology of chronic wounds is questionable. The greater than 10 to the fifth standard was shown to be the amount of pathogenic bacteria that would impede graft take. This value should not be interpreted to chronic wound infection as it is not validated. Chronic wound debridement and infection are definitions in progress and should be treated as such in the agency's guidance documents. The agency should welcome novel efforts for the implementation of efficacy parameters that deal with infection and debridement provided that those parameters can be measured and validated. The truth is that we know very little about chronic wound healing but we know more about management strategies to improve wound stability.

The discussion in this section under **2. Debridement**, identifies some *generally accepted* concepts such as; *the presence of necrotic tissue inhibits healing by interfering with tissue repair and promoting microbial growth*. This supposition has not been clinically validated. Wound care experts do not agree on the value of chronic wound debridement and don't know what really constitutes nonviable tissue. Furthermore, amount or type of necrotic tissue over a pressure ulcer does not correlate with wound bioburden levels. It is known that wounds heal in spite of gross contamination and even in the presence of nonviable tissues. For example, blister wounds heal faster and with less complications when the necrotic blister roof (epidermis) is left intact. Although providing a clean, odor-free wound environment is a non-healing objective that we support for the frail population, achievement of *thorough debridement* may not be a reasonable goal for the frail patient. For this patient group, alternative outcome measures, or, an entirely different debridement category needs to be developed. These products would focus on efficacy based on it's ability to provide a stable, non-exudating wound bed. Conservative debridement options that balance patient comfort with wound debridement are desirable and development of such therapies should not be discouraged by a guidance document that recommends only a narrow band of approaches as proof of efficacy.

**Section III. PRECLINICAL CONSIDERATIONS** incorporates the assumption of complete healing as the primary endpoint of clinical trials. To encourage wound care product development which provide palliative treatment options, the balance of safety and efficacy should tip toward safety. Product efficacy associated with claims for improved wound care should focus on the palliative objectives described earlier in this document.

**Section IV. CLINICAL TRIAL CONSIDERATIONS** discusses some considerations for wound indication trials. The patient characteristics that are generally associated with a population that presents with chronic cutaneous wounds, defined in the current draft as those

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wounds that *do not progress through an orderly series of events to produce a durable structural, functional, and cosmetic closure*, must also be considered in designing clinical trials. For example the measurement of wound size included in this section under **C. Assessment/Quantification, 2. Wound Size**, discusses the use of molds as a precise way to measure volume and/or surface area. For the frail patient presenting with pressure ulcers, there are frequently several other care priorities that prevent the *practicality* of performing volume measurement. The agency should welcome multi-center clinical trials in nursing home settings where chronic wound patients reside and take into consideration the difficulty of standardization when weighing the importance of statistical outcomes.

Again, parameters that do not encompass healing are desirable (i.e., improvement in ADL, independence of patients, reduction of wound related tasks, work load for care givers etc). Smaller studies with fewer patients, designed to include multi-center participation would be good. This single consideration in study design would decrease the time necessary for each site to enter the required number of patients and thereby encourage study participation. The frail patient population with wounds need products designed for palliative management. These products should be considered as a separate category of products, with different regulatory requirements than products that claim "accelerated healing."

Under section **C. Assessment/Quantification, 1. Ulcer Classification**, we believe that consideration should be given to those ulcers with multiple etiologies. Pressure ulcers, the cutaneous ulcer classification with the broadest definition, includes ulcers over bony prominences that occur as a result of sustained pressure. This definition provides only a very cursory description of the factors that often contribute to the incidence of this classification of ulcers. These wounds are often complicated by circulatory, immune, and nutritional factors that influence their incidence and severity. Frail patients are generally immobile. Immobility is an etiology for chronic wounds. Immobility can lead to pressure ulcers, chronic venous insufficiency and

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peripheral vascular disease. Therefore the frail patient often has a variety of chronic wounds or the etiologies are mixed. For example, the frail patient may have developed a heel ulcer secondary to pressure but cannot heal because of arterial occlusive disease. The testing suggested in this section of the draft assumes that a single ulcer classification will be assigned to each wound evaluated. We urge the Guidance for Industry to expand the ulcer classification section to include multiple etiology/origin wounds and recognize the age and characteristics of ulcers as a criteria for defining a group of ulcers with specific support goals that may or may not include complete closure depending upon the viable medical and surgical options available.

Under section **D. Population**, cites valid evidence for wound care studies which are designed to select a population with skin wounds that are healthy enough to completely heal. Discussion includes a suggestion to reduce variability *by specifying enrollment criteria that exclude conditions known to impede healing*. This is a CRITICAL flaw in the current draft. Limitations created by variability in patient and care giver compliance as well as the availability of viable surgical and medical options, requires providers to support chronic wounds without the benefit or expectation of complete wound closure. In reality, the goals for managing chronic cutaneous ulcers for the frail population must be far more palliative in nature. We believe strongly that the Guidance for Industry must include standardized testing recommendations for products designed to support the palliative management of complicated multiple etiology chronic wounds. These wounds, although unlikely to completely heal, are certainly amendable to improvements in overall wound integrity, improved patient independence and treatment compliance, and reduced care giver burden. Treatment objectives are frequently limited to providing symptomatic relief, such a pain control, edema control, infection prophylaxis, prevention of deterioration, odor and exudate management, and achievement of modest goals for increased patient independence.

The current draft Guidance for Industry indicated that the population of chronic cutaneous

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ulcers, which includes *diabetic ulcers, venous stasis ulcers, and pressure ulcers* should have separate trials. Recognition of the heterogeneous nature of the chronic cutaneous ulcer group is crucial to the support for standardized testing of products designed specifically for the management of complicated, often, non-healing chronic wounds. As the current draft indicates the study population *should reflect the population for which the product will be indicated for use*. Again, clinical trials designed for the demonstration of efficacy of non-healing parameters that promote wound integrity, patient comfort, and improved independence related to the performance of ADL's can and should be conducted using the heterogeneous patient population described above.

Discussion under section **E. Standard Care** recognizes, "standard care" may not be uniform across all clinical trial sites, indicating that, although *a number of standard procedures for ulcer and burn care are widely accepted*, they are, by no means, universally practiced or advocated. This again, presents a critical consideration that the Guidance for Industry must reflect. The AHCPR Guideline for Treatment of Pressure Ulcers reviewed all available evidence to support or eliminate the more commonly practiced standards of care related to pressure ulcers. At the time of publication ( 1992) most recommendations were NOT supported by randomized clinical trials, but rather were the recommendations of clinical experts. For the purposes of testing the efficacy of claims of chronic wound products, we believe that the CONSISTENT application of a selected standard of care for a clinical trial is more important than selecting from standards listed in the current draft Guidance for Industry. For example, *the establishment of adequate circulation for arterial ulcers*, is unlikely to be a realistic objective for patient's presenting with advanced circulatory disease. This patient group often has long history of unresponsiveness to medical management and/or are judged to be poor surgical candidates.

The standard of care that describes wound cleansing indicates that cleansing *should be bland because some cleansers retard healing*. Again, complete wound healing is not a practical

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goal for the frail patient. Evaluation of cleansing agents should be expanded to include the palliative outcomes discussed above.

Nutritional support evaluation assumes that the capture of the effective absorption of nutritional intake in a complicated patient population is attainable through simple chemistry and body weight assessments. The measurement of uptake and utilization of nutritional interventions have not been established, and therefore are very unreliable measures of any product's influence on a patient population with chronic cutaneous wounds.

To summarize the perspective of our group, we believe the time has come to recognize that the management of chronic cutaneous wounds must acknowledge and standardize the extension of wound outcomes to include non-healing parameters. These non-healing parameters should focus on the support of improved patient functioning, reduction of pain, improve treatment compliance, simplify topical management, and improve overall integrity of wounds. The establishment of prospectively defined and validated criteria must be created to support the organized and systematic development of products that legitimately offer improved wound care claims other than healing.

The revision of this Guidance for Industry offers an opportunity for the agency to encourage product development and clinical research for a frail patient population that is largely ignored. The publication of said guidance document for the conduct of clinical trials is very influential in guiding the product development efforts for the pharmaceutical industry. If we continue to design chronic wound care trials aimed exclusively at wound closure, then study subjects are pre-selected to be healthy enough to heal. The question then becomes are these really chronic wounds? The problem remains, and the population that suffers chronic wounds complicated by contributing comorbidities are excluded from the process, and therefore the benefits of improved management options.

Our Board would like the opportunity to share our experience with the agency in order to craft a guidance document for chronic wound research which takes into consideration the frail chronic wound population.

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**Executive Summary**

The management of chronic cutaneous ulcers is a rapidly evolving discipline. As the current draft indicates...*outcome measures for chronic cutaneous ulcers and burns are in evolution*. The current draft Guidance for Industry presents a succinct set of guidelines for products seeking to achieve claims related to improved healing, but falls short of providing the same for claims related to improved wound care. The list below indicates the primary areas of concern with the current draft of the Guidance for Industry.

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**Section III. PRECLINICAL CONSIDERATIONS** incorporates the assumption of complete healing as the primary endpoint of clinical trials. To encourage wound care product development which provide palliative treatment options, the balance of safety and efficacy should tip toward safety. Product efficacy associated with claims for improved wound care should focus on the palliative objectives described earlier in this document.

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To summarize the perspective of our group, we believe the time has come to recognize that the management of chronic cutaneous wounds must acknowledge and standardize the extension of wound outcomes to include non-healing parameters. These non-healing parameters should focus on the support of improved patient functioning, reduction of pain, improve treatment compliance, simplify topical management, and improve overall integrity of wounds. The establishment of prospectively defined and validated criteria must be created to support the organized and systematic development of products that legitimately offer improved wound care claims other than healing.

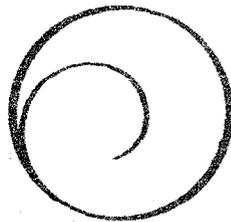
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**F.R.A.I.L. BOARD MEMBERS**

## Our Mission

To bring recognition, dignity, and realistic wound management options to a growing population of adults suffering the consequences of mobility challenges.



The graying of America brings a population that must cope with the management of multiple illnesses. Often those illnesses restrict activity, reduce resistance, and ultimately impair the healing capability of skin wounds. Providing this population realistic solutions that improve quality and comfort is the primary goal of the F.R.A.I.L. Board.

## Goals

Define affected adult population.

Determine this population's prevalence within extended care facilities in the U.S.A.

Establish realistic wound management goals that support the quality, safety, and comfort objectives of both patients and their families.

Develop guidelines of care for palliative management of wounds.

Educate the healthcare industry about the unique treatment and wound management objectives for the F.R.A.I.L. population.

F.R.A.I.L. Board Members

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San Diego Hospice

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Byron Health Center

Richard Montana  
Patient Advocate

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Plastic Surgery Research

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University Wound Healing Centers

David R. Thomas, M.D., FACP  
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MCMeehan@HCICConsulting.com

Seeking Solutions for the Skin-Related  
Complications of Adults with  
Chronic Illnesses

Board Activity Made Possible Through a Grant from

For  
Recognition  
of the  
Adult  
Immoblized  
Life



