ALLIANCE OF
WOUND CARE
STAKEHOLDERS
POWER THROUGH COLLECTIVE ADVOCACY™
★CELEBRATING 20 YEARS★

June 28, 2022

K. Dev Verma
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.,
Bldg. 22, Rm. 5327,
Silver Spring, MD 20993
FDA-2021-N-1212

Submitted electronically to www.regulations.gov
Re: Wound Healing Scientific Workshop (Docket No. FDA-2021-N-1212)

Dear Dr. Verma;

On behalf of the Alliance of Wound Care Stakeholders, ("Alliance"), I am pleased to submit an addendum to our original April 26, 2022 comment letter on questions posed by the FDA for its Wound Healing Scientific Workshop. Our original letter focused on answering these questions and also providing the 2015 powerpoint that was the basis for our meeting with CMS' InterCenter Wound Healing Working Group. As indicated in this letter, we intended to supplement it by reinforcing important issues highlighted in both the FDA Workshop and the Alliance of Wound Care Stakeholders Wound Care Evidence Summit™ and submitting recommendations for your consideration.

The Alliance is a non-profit multidisciplinary trade association of physician specialty societies, clinical and patient associations whose mission is to promote evidence-based quality care and access to products and services for people with chronic wounds through effective advocacy and educational outreach in the regulatory, legislative, and public arenas. The Alliance is viewed as the umbrella association for all of wound care since our membership includes not only the clinical and patient associations mentioned but also wound care clinics and business entities (manufacturers and distributors). This letter was written based on the input of all our members. A list of our members can be found on our website:
http://www.woundcarestakeholders.org/about/members

The Alliance commends the FDA on its successful and valuable Wound Healing Scientific Workshop and also thanks the Agency for inviting me to participate as a speaker. In addition, we so appreciate your, Dr. Chang and Dr. Sherafat-Kazemzadeh roles as valued speakers at our Alliance of Wound Care Stakeholders' Wound Care Evidence Summit a month later. During these meetings, there were consistent themes presented which also answered some of the questions posed by the FDA. The Alliance has captured some of these issues below and have provided recommendations with each of them for the Agency to consider adopting. They include, but are not limited to the following:

5225 Pooks Hill Rd | Suite 627S | Bethesda, MD 20814 | T 301.530.7846 | C 301.802.1410
marcia@woundcarestakeholders.org

1. Real World Data and Real World Evidence

Real World Data used for Real World Evidence is valuable and much needed in wound care research. It was discussed in both meetings that current clinical trials designs such as RCTs are not capturing the majority of the patients that our clinicians are treating. These patients are sicker, with multiple comorbid conditions that are usually excluded from RCTs. Enrollment is difficult because of the eligibility criteria which limits the types of patients that can be entered in the trial.

The result is that the patients enrolled in the clinical trials bear little resemblance to the patients being treated. Registries are a great way to capture this data as they collect and consolidate the data from real world patents and real world clinical care. With the help of registries, it is easier to see what is working, in what environments and in what patient population.

In addition, real world registry data can be used to help develop objective scoring systems which will help drive wound care interventions and guide decision making regarding procedures/treatments/products that can effectively be utilized to treat the patient. It is likely that registries and the data collected from them will help in the standardization of wound care practice.

Furthermore, in order for RWE to make a difference to payers and the FDA, researchers must follow a gold standard of reporting and analysis that follows FDA white papers on the subject as well as the guidance papers that have been published in wound care journals. One could think of these gold standards as something like the CONSORT criteria. After they have been developed and distributed, they need to be accepted by all wound care stakeholders as well as journal editors.

The Alliance appreciates that the FDA is evaluating the use of real world data/evidence and we continue to be happy to be a resource for the FDA as it moves forward with real world data/evidence. However, please note that even if the FDA adopts/permits real world data/evidence in wound care trials unless CMS and commercial payers also accept real world data/evidence, it will still be burdensome for manufacturers to conduct one type of trial for the FDA and another for payers for coverage and payment purposes.

Recommendation: It is imperative that the FDA, CMS and stakeholders work together to adopt a solution for the use of real world evidence/data acceptance.

2. Update the June 2006 "Chronic Cutaneous Ulcers and Burn Wounds - Developing Products for Treatment" or Publish a Guidance to Supplement the Recommendations

The FDA issued a guidance in June 2006, "Chronic Cutaneous Ulcers and Burn Wounds - Developing Products for Treatment." This document has not been updated since then. When the Alliance met with CMS' InterCenter Wound Healing Working Group, the issues and recommendations discussed for updating are as relevant today as they were then. Many of these topics were discussed at both of our meetings and we would urge the Agency to take action to update the following important issues in a guidance to supplement the June 2006 Guidance Document recommendations:

- **Updating outdated terminology.** The guidance document utilizes the outdated and clinically inaccurate terminology "skin substitutes" which is now referred to as cellular and/or tissue based products for skin wounds (CTPs) and should be aligned with the ASTM Standard Guide for Categories and Terminology of CTPs (which we have attached).

  In addition, the FDA classification for 510(k) and PMA biological "Cellular and Tissue Based Products for Skin Wounds" as "wound dressings" is also outdated and does not represent the technology or mechanism of action of these products. Here are comparisons of their differences:

  In the ASTM guidance document, these products are defined as such:

  - CTPs--*CTPs are tissue-engineered medical products (TEMPS) that are primarily defined by their composition and comprise viable and/or nonviable human or animal cells, viable and/or nonviable tissues, and may include extracellular matrix components. CTPs may additionally include synthetic components.*
  - Dressings- *Any of various materials utilized to cover and protect wounds.*

  In addition to the differences in their technological composition, they also differ in the following ways:

  - **Clinical use** –
    - CTPs- biological influence in the healing process and the materials are incorporated in whole or in part into the wound/ulcer bed and are not removed unless a complication such as an infection occurs;
    - Dressings- cover and protect the wound/ulcer without exerting any biological effect and are not incorporated into the wound/ulcer bed; are removed from the wound/ulcer one or more times a week
  - **Who applies them**—
    - CTPs -physicians/qualified health professionals who are authorized to perform surgical procedures;
    - Dressings—nurses, therapists and patients in their homes
  - **How they are applied**-
    - CTPs must be applied surgically and fixated, primary and secondary dressings are applied on top of the CTP followed by application of compression or off-loading when needed;
    - Dressings- follow instructions for use to apply and cover the CTP or wound/ulcer

  Furthermore, by using the term "wound dressing" there are negative payment implications outside of the FDA. Many payers are confused with FDA labeling of CTPs as "wound dressings", which causes them to think the products are inert, temporary and and topically applied protective covers and their reimbursement is limited. This can cause significant issues resulting in making CTPs unavailable for the clinician to use and impacting patient access.

Recommendation: (1) FDA should replace the term "skin substitutes" with "cellular and/or tissue based products for skin wounds." (2) FDA should update classifications for CTPs to match the current ASTM terminology which differentiates them from wound dressings.

- **Publish an updated listing of primary and secondary endpoints.**

The 2006 FDA guidance is currently where both industry and researchers obtain their information on how to conduct their clinical trials. Clinicians are all too aware that there are many other measures and endpoints to consider in wound care and the only endpoint "wound closure" is too limiting. During both the FDA Workshop and the Alliance Evidence Summit, there was discussion that additional clinical end points are necessary and that the wound care community supports the advancement of them. At the both the FDA Workshop and the Alliance Evidence Summit, CMS Medical Officer Dr. James Rollins even discussed the need for alternative end points.

The wound care space needs trials with more realistic endpoints, and importantly, endpoints that reflect the patient experience. However, patient-centered outcomes are still in their infancy. While many people when asked what of these outcomes are suitable for wound care studies answer in terms of endpoints like pain or quality-of-life, it is clear from what patients have said that there is much more to this. The wound care community needs to do a better job of figuring out what makes a difference topatients in terms of wound treatments and develop instruments to capture the responses.

The Alliance commends the Wound-care Experts / FDA--Clinical Endpoints Project (WEF-CEP) who has been working with the FDA for over 8 years to create and get primary and secondary end points adopted. The WEF-CEP (now known as the Wound Care Collaborative Community [WCCC]) has developed a list of both primary and secondary endpoints. The primary endpoints recommended (which need to be validated with a specific measurement tool) include the following:

- Percent area reduction (PAR)
- Reduced infection
- Reduced pain / reduced analgesia use
- Increased physical function and ambulation
- Quality of Life
- Cost effectiveness

It is now important that the FDA works with the WCCC, the Alliance and other stakeholders to finalize these primary and secondary endpoints and publish them as an addendum to the 2006 FDA "Chronic Cutaneous Ulcers and Burn Wounds - Developing Products for Treatment" guidance document. Having the FDA formally publish them benefits researchers and industry who will use these in their clinical trials and in meetings with FDA staff so that all stakeholders will have a better understanding of the current thinking on this topic in the Agency. We would request that all three divisions of the FDA be educated on these endpoints to ensure even more productive meetings with researchers and industry in the future.

Recommendation: FDA publish primary and secondary endpoints as an addendum to the 2006 FDA "Chronic Cutaneous Ulcers and Burn Wounds - Developing Products for Treatment" guidance document.

- **Mechanisms for Modifying and Expanding Claims Need to be Updated and Process Streamlined for the Treatment of More than One Type of Chronic Wound**

  As stated in our 2015 powerpoint and reiterated in both FDA and Alliance meetings, the time from concept to approval is long, expensive and also requires data for each claim. It can take multiple years to perform large clinical studies for every claim and adds tremendous cost to provide RCTs for every claim change. If a product is approved for one type of chronic cutaneous wound type, can the level of evidence required for expansion of claims be significantly reduced? In addition, we would appreciate if FDA could clarify and standardize the use of post market data to modify claims using alternative approaches such as: patient registries, postapproval studies, retrospective studies, and other clinical trial designs to support expansion of wounds treated.

  Another suggestion that was mentioned in both conferences regarding assessing multiple wound types in one trial is for FDA to create a pilot program to conduct larger RCTs that are more pragmatic and include a variety of chronic wound types would be helpful. The FDA has tacitly said that provided such a trial is adequately powered and properly designed it should be approved. Needless to say, these trials should probably not be 510(k) but rather PMAs or BLAs unless the intervention has been classified as a drug.

  Recommendation: The FDA should update as an addendum in its 2006 Guidance Document mechanisms for modifying and expanding claims and streamline the process for the treatment of more than one type of chronic wound.

- **Standard of Care**

  In both conferences and in our 2015 powerpoint, there was much discussion regarding standard of care used in diabetic foot ulcer (offloading) and venous leg ulcers (compression) as well as debridement. The point of addressing it here is to suggest that perhaps a conference or workshop to address this more fully to gain consensus would be appropriate. Once done, the results should be updated in the addendum to the 2006 FDA guidance document.

3. New Technology Innovations in Wound Care

New technology innovations are difficult and costly especially in the current environment. As stated above, real world evidence will open the doors for wound care comparative evaluations and evidence gathered from real life, real patients and real practice settings can help speed innovation.

Most device manufacturers for the last 10 years have followed the path of least resistance using a 510(k) approval and application to wounds that really don't need advanced therapeutics for the most part. Post-

market trials conducted on these devices are for the most part inferior to RCTs conducted under an alternative FDA pathway (PMA, BLA, etc.) There are a few trials underway that may change that paradigm but only because they are part of a BLA. There needs to be a way to incentivize manufacturers to take more risks otherwise the patients and/or wounds that really need advanced therapeutics won't get them and healing rates will remain frozen in time.

In the list of questions posed, the FDA asked about innovations and the types needed. It seems as though again the patient experience may drive some of these innovations only if the FDA adopts the primary and secondary endpoints needed as well as the ability to use real world evidence. Patients certainly would be well serviced by progress in the portability, mobility and enhanced convenience of advanced wound care modalities. Furthermore, apps and digital capabilities can have a huge impact in rural areas and can be used for telemedicine – which has been the focal point recently as a result of the public health emergency. Technologies can help expand access to quality wound care for patients across the United States and globally and can increase convenience for patients. This plays a key role in improving patient compliance with treatment as well.

4. ***Funding of Clinical Trials***

Funding of clinical trials is limited to manufacturers which almost automatically means that government and private payers will claim that the studies are biased. However, there are ways to reduce bias in the studies that should allow for their adoption of them. We would encourage the NIH and other agencies to help fund wound care research.

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We appreciate the opportunity to provide a follow up to our original comment letter. Many of the issues raised could be addressed in follow up conferences such as a critical path innovation meeting (CPIM) or meetings to address a single topic such as standard of care but the time is right for FDA to act on updating important issues contained in its June 2006 guiance document "Chronic Cutaneous Ulcers and Burn Wounds - Developing Products for Treatment" or publishing a guidance to supplement the recommendations.

As we have stated to the Agency in the past, the Alliance is happy to serve as a resource in any capacity.

Sincerely,

Marcia Nusgart R.Ph.

Marcia Nusgart R.Ph.
Executive Director