ALLIANCE OF

# Wound Care Stakeholders

June 16, 2009

Dr. Sean Tunis
Director
Center for Medical Technology Policy
Inner Harbor Center
400 East Pratt Street, Suite 808
Baltimore, MD 21202

Dear Dr. Tunis;

On behalf of the Alliance of Wound Care Stakeholders ("Alliance"), I am submitting a more comprehensive set of comments on the Center for Medical Technology Policy (CMTP) draft document entitled "Effectiveness Guidance Document (EGD) on Mechanical Interventions for Chronic Wound Healing". This document is a follow up to comments submitted to you on May 21, 2009 by the Alliance in addition to our follow up conference call with you and Dr. Robert Warriner. The Alliance is a multidisciplinary consortium of over 15 physician, clinical, provider, manufacturer and patient organizations whose mission is to promote quality care and patient access to wound care products and services.

Our goal is to work with CMTP to ensure that the EGD will be helpful to all stakeholders who are connected with wound care research. As we have stated previously, it needs to be done correctly. We believe the current process needs to be slowed down and the input of wound care researchers and clinicians included in order for this document to be reflective of current clinical wound care and research. This is a document that the Alliance organizations is taking seriously and believes that all aspects an EGD need to be thoughtfully considered and discussed. We collected comments on the EGD from various wound care organizations, clinicians and researchers in an effort to provide feedback on the document. The overall consensus of those commenting is that the document needs to be rewritten in its entirety. The Alliance would be happy to help you with this effort and has identified a group of wound care clinicians and researchers who would be willing to participate in rewriting the EGD with the Hayes and CMTP staffs.

The following are consolidated comments of the Alliance clinical and research stakeholders. They are provided as discussion points and are not meant to be used as final edits to the current EGD.

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## General Comments

The Alliance is concerned that overall this document suffers from the same fundamental problems as the FDA Guidance for Industry: Chronic Wound Care document which dates back to 2006. This document, as well as the FDA Guidance for Industry, fails to acknowledge two critical issues:

(1) Most wound care technologies fitting into the categories referenced within this document are adjunctive in nature and must be applied over a foundation of effective standard care (which is not defined sufficiently in the document), and, as adjunctive measures, would be expected to have beneficial effects less pronounced than if they represented primary therapeutic interventions.
(2) Additionally, the EGD continues to define the only acceptable endpoint for trials as complete wound healing.

With respect to the endpoints, the EGD does not provide any consideration for any other beneficial effects of technology, ignores adjunctive rather than primary benefits for most technologies, and fails to address surrogate markers for wound healing or use of wound trajectory data. The document also does not address the designed, proposed beneficial effects of the interventions described which may represent intermediate improvements in wound healing by controlling microbial bioburden, splinting soft tissue, controlling exudate, stimulating the elastic properties of skin, or stimulating a specific component of tissue growth.

Currently technologies cannot address these intermediate improvement opportunities because the only acceptable standard is complete wound closure. Complete wound closure applies as a meaningful measure of effectiveness only to therapies or technologies that are primary interventions whose intent is to heal. This concept is not adequately addressed in the current document and fails to resolve an ongoing challenge facing those who develop new technologies or make clinical decisions to use them. Without addressing this concern, the development of new technologies will continue to be impeded. Surrogate issue markers for wound healing or the use of wound trajectory data and any other endpoints specific to the technology intent related to healing should be addressed in this EGD in order to tackle this critical issue.

We would have hoped that in this EDG you would have incorporated principles included in your Jan/Feb 2005 article in Health Affairs, *"A Clinical Research Strategy to Support Shared Decision Making"* and would encourage you to use some of these in your next version of the EDG.

The Alliance also believes that your descriptor for this EGD "Mechanical interventions" is inappropriate. Mechanical devices may be inappropriate overall for the descriptor since the potential range of technologies that could be impacted by this document includes not only mechanical devices such as negative pressure wound therapy but also

topical agents, biological, and systemic interventions such as hyperbaric oxygen treatment.

In addition, the EGD does not provide different definitions or explanations for the various study types.The EGD implies that all effectiveness studies will be prospective. The Alliance believes the EGD should include the use of retrospective studies and evidence registry studies. (Several wound management organizations maintain robust wound care databases. These databases contain longitudinal wound care outcome data which could be mined to assess effectiveness of specific technologies and systems of care.) The Alliance believes that the EGD should identify and define specific acceptable types of retrospective and evidence registry studies including but not limited to randomized controlled clinical trials, observational cohort or prospective registry studies, data base mining and even case reporting.

Finally, the Alliance submits that the EGD seems to have a "cookie cutter" approach and criteria that may apply to pressure ulcers may not apply to venous stasis ulcers. We would be willing to help you with differentiating those issues as they apply to each wound care type.

## Specific Comments

### ***Page 5 Paragraph 1.***

The EGD contains multiple and contradictory definitions for "chronic" wounds throughout the document. One definition describes a chronic wound as "fails to respond to standard therapy within 3 months or 90 days". We have concerns with this definition for the following reasons:

1. We question where this definition comes from since there is nothing in the literature – or in clinical practice - to support this.
2. The typical standard for RCT's is: Subjects must have had the wound open for at least 4-6 weeks from day one on screening visit. Ulcers which decrease in area by >30% during the screening 1 or 2 week run-in period are usually disqualified.
3. We have concerns that if this definition is 90 days, it will be included in payers' coverage policies. The current definition for chronic wound in Medicare coverage policies for 'advanced technologies' included in the guidance document are based on wounds that failed to show progress to healing in one month. At the 2005 MCAC Meeting on Chronic Wounds, CMS staff were challenged even on where the timeframe for 30 days was issued.

As such, the Alliance recommends that the sentence, "chronic wounds may also be defined in terms of chronicity – that is a wound that fails to respond to standard therapy within 3 months" be deleted.

### ***Page 5, Paragraph 2.***

We believe that the document incorrectly links systemic hyperbaric oxygen therapy with local oxygen and then proceeds to incorrectly classify both as mechanical devices. The FDA does not consider local oxygen to wounds as hyperbaric oxygen therapy. Systemic hyperbaric oxygen treatment is not a mechanical intervention. It is a systemic intervention. All of the available published data on mechanisms of action supporting wound healing in infected or ischemic hypoxic wounds identifies the effects of elevating intra-arterial PO2 and on that basis wound tissue PO2 and the resulting induced effects of tissue hyperoxia. Also, the substantial body of literature on the mechanisms of systemic hyperbaric oxygen treatment have not been linked to topical oxygen therapy which has been linked in this document. The Alliance recommends the terminology be changed to: "systemic hyperbaric oxygen therapy" and "topical oxygen therapy." In addition, mechanical devices are an inappropriate overall descriptor.

***Page 6 Top of the Page***

The EGD makes reference to investigational technology. The Alliance would like to know who is defining what is investigational technology? Furthermore, we would like to know why investigational technology is being discussed in this section as opposed to other types of technology. Clarification on these issues would be helpful.

***Page 6 Patient Population***

*Characteristics of the Target Study Group*

**Patient Population**: The EGD refers to "real world patients". The Alliance would like to obtain clarification on what CMTP defines as "real world patients".

**Wound type**: The EGD states, "either only one wound type should be included, or data should be presented separately for each wound type and group comparisons should be planned a priori". This language is not reasonable and the Alliance would like to suggest alternative language. We suggest the following: "Either only one wound type (i.e., venous ulcers, diabetic ulcers, or pressure ulcers) or multiple wound types sharing a common etiology of wound healing failure addressed by the specific technology should be included, or data presented separately for each wound type and group comparisons should be planned a priori. Current restrictions requiring separate clinical trials for each wound diagnosis have the potential to limit advances in technology development and application that can negatively impact patient outcomes and increase the costs of care."

**Mix of patients:** In this section, the EGD refers to risk factors. There are many other risk factors: cardiovascular disease, diabetes, obesity, PVD, than those identified in the EGD. As such the Alliance recommends that the sentence read, "Risk factors that could slow healing include, but are not limited to: cardiovascular disease, diabetes, obesity, PVD, systemic steroid or immunosuppressant use (as in diabetic transplant recipients) and smoking". In addition, it should be pointed out that the EGD suggests inclusion of patients with co-morbidities that may slow healing (systemic steroids,

immunosuppressives) and also lists systemic steroids and immunosuppressives as exclusion criteria. This is contradictory.

**Setting of care**: "Clinic" should also be included.

***Page 7 Exclusion Criteria***

The exclusion criteria guidelines may be too excessive in some cases. This can jeopardize the generalization of the RCT results to real world populations. In addition, each of the exclusion criteria need to be further defined since each wound care type could have its own set of exclusion criteria. Furthermore, as in our previous comments on "chronic wound", we have concerns regarding the wound duration is less than three months and needs to be better defined. It is our understanding that even the typical standard for RCTs is: subjects must have had the wound open for at least 4-6 weeks from day one on screening visit. Ulcers which decrease in area by greater than 30% during the screening one or two week run-in period are usually disqualified.

This exclusion criteria needs to be addressed further especially in the cases of diabetic ulcer since some of these may not apply.

***Page 7- Characteristics of a Control Group***

The EGD needs to define what is standard care as well as usual care. Since both are referenced in the document without being defined, there could be confusion on what constitutes the differences are between the two. An example would be that trial comparison control groups are described as standard care (accepted) and 'usual care' (not-acceptable) without clarification of what the difference is in these two methods of care. Thus, we recommend that both terms be defined.

***Page 8 – Characteristics of a Control Group***

*Third Bullet-Control Patients*

The EGD states that control patients should receive standard care alone, and standard care is defined as "best practice at the time of the study". How will this practice be determined? Who will determine what the best practice is at the time of the study?

Furthermore, it is not clear from the language whether all elements listed are required in order to meet the "standard of care". This needs to be further clarified. Moreover, one of the items listed under standard care is wound cleansing. The Alliance would like the terms "wound cleansing" and "infection control" further defined. It is unclear whether the provider uses standard infection control precautions when treating the wound (i.e., sterile field, contact precautions, etc) or that medications are used to treat infection.

Finally, under Unna boot, you incorrectly included pressure ulcers rather than venous insufficiency. It is not appropriate to list pressure ulcers here and as such needs to be changed.

## ***Page 9 Study Site***

The wound and patient parameters should be the determining factor not the locality of the patient. If the studies are performed at referral centers that specialize in wound patients (Mayo, Cleveland Clinic, or university settings), then there would be greater access to patients. As such, the Alliance recommends that the EGD state that a balance of sites should be considered to represent all patient populations collectively across sites.

The EGD recommends that for complex devices, researchers must be completely trained and should be proficient in using the investigational technology. Previous institutional experience with the technology of interest is required. However the Alliance believes that institutional experience is too limiting and it should be sufficient to require training and proficiency only.

## ***Page 9- Study Design Considerations***

An RCT is recommended and blinding is recommended for the evaluation of chronic wound healing is a blanket statement and does not reflect individual technologies. The document should not and cannot address current and future trial design. In addition, there are no surrogate measures discussed in this section.

## ***Page 10 – Blinding***

The Alliance has significant problems with the blinding section of the EGD. Blinding for hyperbaric oxygen treatment for wound healing or limb salvage studies by providing a sham treatment has the potential to add unnecessary risk to the patient receiving the sham and requires that monoplace chambers be reconfigured to be compressed with air. (increased cost, increased risk that mistake in compression gas selection could lead to decompression sickness in patient). Abidia has addressed this issue with respect to hyperbaric oxygen treatment clinical trials that do not involve assessment of neurospychometric parameters (as would be required in studies of carbon monoxide poisoning or acute neurological injury). This document cannot and should not attempt to define clinical trial design and "blinding" for specific current and future technologies. The intent of the technology should determine the endpoints of the clinical trial and its design. Wound healing trajectories should be considered as a surrogate for final wound healing as an outcome to reduce the cost of studies and to enable technologies to become available in a more reasonable time frame.

## ***Page 12 – Outcome Measures and Endpoints***

The Alliance has significant objections to section 6 where only wound closure is viewed as an acceptable outcome. Wound closure is problematic when a technology or intervention is designed to (1) control infection (as in the case of HBO in some applications) or (2) produce another clinically significant intermediate effect that supports but is not primary wound closure. Such an approach has additional negative effects:

1. Ignores the adjunctive rather than primary benefits of most technologies
2. Fails to address surrogate markers for wound healing or use of wound trajectory data

We believe that the intent of the technology would be the driver of what the endpoints should be.

This issue, as a current FDA requirement, has forced all trials to address primary wound closure even if the technology would not be expected to support wound healing to closure (anti-infective dressings, etc.). Also, the 16 week endpoint recommended could exclude many patients, especially on the HBO side, that will ultimately heal.

The EGD states, " The composite outcome could be the time to wound closure or time to heal depending on the population and the nature of the wounds being studied." The Alliance would like clarification on this point. Is the time to heal considered when one first sees granulation?

***Page 12-13***

The EGD lists primary endpoints as recommendations to consider and includes large and complex wounds. The Alliance would like further clarification as to what is considered large and complex wounds. Furthermore, we would like clarification on the point that complete wound closure for large or complex wounds occurs at 16 weeks? Similarly, the bullet for incidence of amputations is incomplete. It should read, "Incidence of distal and proximal amputations (diabetic and arterial ulcers only). The Alliance questions why the evaluation of wound closure must be performed independently by at least by two evaluators. This is burdensome and requires experts in healing to be available at all sites in addition to the investigators. This will be a problem for cost/ access and practicality.

One of the secondary endpoints listed in the EGD is pain during dressing changes. The Alliance would like to know would one measure pain during/after debridement also? Also, tissue maceration is not clearly definable.

**Wound healing trajectories**- The EGD states, "Reliable wound tracings require specialized expertise, and an appropriate training program is required". The Alliance would like clarification regarding what is an appropriate training program? Can the program be done by a computerized system? It is not clear from this document. Furthermore, the EGD states, "the person tracing the wounds should be blinded to treatment allocation:" The Alliance questions why this is necessary. Not all studies will be blinded so why does the person tracing the wounds need to be blinded to treatment allocation?

***Page 14***

The EGD states, " disease specific scales are not available for symptoms, quality of life and functional status for patients with chronic wounds". The Alliance would like to know what the reference is for this language. Functional status is an extremely important outcome.

***Page 15 – Length of Follow Up or Study Duration***

The first bullet in discussing the length of follow up recommended for assessing primary endpoints is "minimum 16 weeks to assess incidence of wound closure" . The Alliance does not agree with this statement. First, this is too long and assumes the patient continues to be compliant with off-loading, compression, skin care, pressure relief, just to name a few. It also assumes that the patient has no medical condition relapse or complication that impacts healing quality. The Alliance recommends 2-3 weeks as a more accurate and reasonable timeframe.

The second bullet states, "Minimum 12 months to assess recurrence of the same wound (Vuerstaek et al., 2006)". The Alliance disagrees with this length of time. There are too many personal factors that are not in the control of the medical community to ensure that the wound will not reoccur. This requirement will be directly impacted by patient compliance to post healing instruction and not truly reflective of the effectiveness of the therapy. We disagree with this length of time as a measure for recurrence.

***Page 17 Economic Evaluations***

First – in the second paragraph, you state, " appropriate costs to include would be supplies associated with wound dressing, antibiotics costs, costs associated with orthopedic devices…" However this statement should read, costs associated with prosthetic devices. Furthermore, in the list of examples of acceptable CE calculations the EGD lists cost per amputation averted. How will this be measured? Are these the patients in which wound care is the last option before amputation?

***Page 24 Study Design and Planning***

The EGD requires one or more board certified physician with demonstrated expertise in wound healing to have medical responsibility for the study. We do not agree that only a physician is required for this type of study. By stating this, we submit that this requirement will limit study options. As such, this requirement should be deleted.

***Page 24 – Patient Management***

The EGD states that a trained nursing staff is involved in patient care etc. We do not agree with this sentence as written. The Alliance believes that other health care practitioners are involved in the patient care and this should be reflected in this section. Specifically, the Alliance recommends that the sentence be changed to "a specially trained multidisciplinary staff is involved in patient care, such as but not limited to, wound dressing changes or debridement and maintains patients' clinical records.

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The Alliance supports the concept of an EGD, but wants to ensure that it does reflect the current wound care clinical research and the thinking of wound care clinicians and researchers. We are delighted to work with you in developing the next version of the document and in further discussing this issue with you on our next conference call.

Sincerely,

Marcia Nusgart R.Ph.

Marcia Nusgart
Executive Director