ALLIANCE OF
WOUND CARE
STAKEHOLDERS
POWER THROUGH COLLECTIVE ADVOCACY

October 24, 2016

Ms. Leslie Kux
Associate Commissioner for Policy
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Rm. 1061,
Rockville, MD 20852

Submitted Electronically to www.regulations.gov

RE: FDA 2016-D-2153 "Use of Real World Evidence to Support Regulatory Decision-making for Medical Devices"

Dear Associate Commissioner Kux:

On behalf of the Alliance of Wound Care Stakeholders ("Alliance"), I am submitting the following comments in response to the FDA draft guidance document on "Use of Real World Evidence to Support Regulatory Decision-making for Medical Devices". The Alliance is a nonprofit multidisciplinary trade association of physician medical specialty societies and clinical associations whose mission is to promote quality care and access to products and services for people with wounds through effective advocacy and educational outreach in the regulatory, legislative, and public arenas. These comments were written with the advice of Alliance clinical specialty societies and organizations that not only possess expert knowledge in complex chronic wounds, but also in wound care research. As such, we have a vested interest in this guidance document. A list of our members can be found at www.woundcarestakeholders.org.

General Comments

The Alliance has long been a proponent of utilizing Real World Evidence (RWE) – especially in wound care. We demonstrated this in our article "Consensus Principles for Wound Care Research Obtained Using a Delphi Process" (Wound Rep Reg (2012) **20** 284–293 © 2012 Wound Healing Society) where one of our principles are "national or formal wound registries should be developed with real-world data collection." A copy of that article is attached for your review.

We commend the FDA for creating this draft guidance document. The Alliance believes that it is an appropriate pathway and a good beginning – although we would like to recommend having Class II medical devices also be included in this guidance document. We also commend Commissioner Califf for his foresight in respect to his commitment to utilize RWE as a "top programmatic priority" in the regulatory process. We also are supportive of CDRH Director Shuren's statements in which he called for the use of data from registries, claims, and electronic health records to support the evaluation of medical devices.

Patients with chronic wounds have serious co-morbid conditions that distinguish them from the patients of

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wound care RCTs. Several factors can be defined that increase the duration and cost of wound care including wound etiology, as well as specific patient factors. These patient factors likely impact the effectiveness of advanced therapeutics in ways that cannot be ascertained by RCTs.

In 2005 the US Wound Registry (USWR) was created. The USWR is an ideal tool for comparative effectiveness research in wound care because it includes real world patients often excluded from RCTs and reflects actual practice. The USWR evaluated the exclusion criteria of all major randomized controlled trials (RCTs) performed in wound care over a decade (1998-2008). It compared those exclusion criteria with the co-morbid conditions, wound characteristics and medications documented among 3,201 patients in 18 hospital based outpatient wound centers. Its findings were that **approximately 75% of real world patients would have been excluded from every major wound healing RCT that brought new products to market over that decade at the "first pass" before study related laboratories or tests would have been performed**.

Through its work, the USWR has confirmed what the Alliance has been stating our comments to regulatory agencies and Medicare Administrative Contractors (MACs) - **RCTs are not able to evaluate the effectiveness of a wound care product or intervention, when more than half of patients are excluded from participation, greatly diminishing the applicability of RCT results to real world populations and evidence based medicine.**

Here are specific examples of how registry data could be used in assessing the safety of a wound care medical device. At the request of the FDA, the USWR was asked to determine the adverse events associated with a particular negative pressure wound therapy device compared to moist wound care prior to the clearance of this device. The adverse events experienced by approximately 1,000 patients treated with NPWT were compared to approximately 10,000 patients undergoing moist wound care in a report provided to the FDA in 2007. No events of bleeding were noted among more than 200 patients who were on Heparin or Coumadin (patients on these drugs were excluded from RCTs involving this device). In addition, the frequency of pain prescription medications, infection and worsening of wounds was less in NPWT wounds than those treated with moist wound care, stratified by wound type and severity. Furthermore, a subset of patients with diabetic foot ulcers (DFUs) was published describing the adverse events of 72 DFUs treated with NPWT vs. 1,299 DFUs not treated with NPWT. The rate of adverse events or complications was not statistically different between the two groups. This early study demonstrated how the USWR can assess safety among a real world patients, particularly those who would have been excluded from RCTs. This is one of many ways that RWE can be helpful not only to the FDA but also the manufacturers who are trying to bring innovative products to market to help treat patients with wounds.

Our specific comments on the draft guidance document follow.

Specific Comments

Generally, the Alliance believes that the draft guidance document is well written and has good concepts. However, the Alliance believes that all the concepts raised in the draft guidance need to be more specific and more examples need to be provided in order to help clarify the concepts being described. For example, it would be helpful for the FDA to clarify how it intends to apply RWE in premarket and postmarket regulatory decisions. The Alliance recommends that the FDA provide more than one example to demonstrate its position.

More specifically, however, there are areas in the draft guidance document in which the Alliance believes clarification is warranted prior to this draft becoming final. These areas include the following:

Informed Consent

The draft guidance document states that the key factors the FDA will assess when looking at data accrual is "whether necessary and adequate patient protections were in place (e.g. de-identified data, maintenance of privacy, and need for informed consent as determined by the reviewing IRB and in compliance with FDA regulations)." The Alliance believes that clarification is required with respect to when informed consent is necessary when utilizing RWE.

The only reference to informed consent in the guidance document is in the statement identified above. Yet, the Alliance believes that informed consent is not always possible when utilizing RWE. For example: When RWD from a patient registry (such as the USWR) are retrospectively analyzed for the purpose of a 522, informed consent is not required nor should it be. Real world data, by definition, is data collected in the course of routine clinical care and no extra data can be collected specifically for the purpose of research. However, the FDA guidance document details the manner in which RWD might be used for both post market surveillance and the expansion of coverage indications. Therefore, IF the FDA is going to allow real world data for the expansion of coverage indications – can it be data collected without a specific informed consent? This needs to not only be clarified, it also needs to be detailed specifically in the draft guidance document.

As such, the Alliance requests clarification regarding when it is necessary to obtain informed consent when utilizing RWE with multiple examples being provided.

Investigational Device Exemption (IDE)

Clear criteria and rules would be of great value when issuing a guidance document with respect to RWE. The examples given in the draft guidance of when an IDE is necessary for the collection of RWD do not provide sufficient information to allow criteria or rules to be discerned, and as such do not provide useful information about when an IDE is necessary. There are several provisions within the portion of the draft guidance document with respect to IDE that need to be clarified and expanded upon which include:

1. The FDA describes three factors that can impact the decision of whether an IDE is necessary in Section IV (B). In the draft, the FDA states, "Whether the collection of RWD could be subject to the IDE regulations depends in part on whether that collection constitutes a clinical investigation. Several factors can inform this determination, including the purpose for which the data is being gathered, whether the process for gathering the data would influence treatment decisions, and whether the rights, safety and welfare of human subjects are impacted, among other things."

In reviewing this draft, the Alliance recommends that the FDA provide further explanation of these three factors, so IRBs and other entities can make correct decisions regarding the need for an IDE.

2. Furthermore, the draft guidance states, "Because the gathering of RWD is unique from traditional investigations, the determination of whether an IDE is required should be made on a case-by-case basis, and we recommend that you contact FDA about whether an IDE is required in cases where RWD collection is

initiated for purposes of determining the safety and effectiveness of a device."

The Alliance has concerns about this statement and questions, "Is there a process in place at the FDA so that notification on whether an IDE is required will be issued in a timely fashion?" The guidance does not address this. Our concern is that the FDA may not have the resources to make this determination in a timely fashion for every research project that may involve the collection of RWE unless it is limited to commercially sponsored research.

3. For circumstances in which the use of RWE is collected for purposes other than establishing safety and efficacy, the draft states, "The FDA does not regulate the practice of medicine, and recognizes that some RWE is collected for purposes other than establishing the premarket safety and effectiveness of a device, such as the collection of information related to the actual use by clinicians of an approved or cleared device and/or treatment approaches for a particular disease or condition. Such observations may include RWE from a use of a medical device that was not within the cleared or approved indications for use. When such RWE collection is not intended to determine the safety and effectiveness of the device for purposes of supporting a marketing application to FDA, it would likely not meet the definition of a clinical investigation, and the IDE regulations would not necessarily apply."

The Alliance recommends that the FDA provide clarification with respect to the criteria that apply to the determination that a given research project "would likely not" meet the definition of a clinical investigation, and the IDE regulations "would not necessarily apply", so that sponsors and IRBs can make accurate and compliant decisions regarding the need for an IDE without going to FDA for a formal opinion each time – which would be time consuming and costly. We recommend that the FDA provide specific examples since they would be very helpful.

4. In Section VI (A), the draft guidance provides two examples of the use of RWD for expanded indications for use. However, in both cases it is not clear what criteria was used to make the determinations that an IDE was either required or not. As such, the Alliance recommends that the FDA provide the criteria used in reaching these contrasting decisions regarding the necessity for an IDE. Furthermore, the Alliance recommends that more examples are provided to highlight the FDA's thinking in this area.

5. The Alliance is particularly interested in Section VI (B) of the draft guidance which addresses post-market surveillance studies under Section 522. However, when reviewing the information contained in the draft guidance, the Alliance could not determine whether an IDE was required for these types of studies. This particular section of the draft guidance should have clear criteria with examples provided. As such, the Alliance requests that the FDA state whether or not an IDE is required for these studies, and the criteria by which the decision is reached. Examples provided would not only be helpful, they are necessary in providing the additional clarification within this section of the guidance document

6. Section VI(C) of the draft guidance addresses post-approval device surveillance as a condition of approval. While an example was provided, once again, it was not clear what criteria was used to make the determination that an IDE was not necessary. As such, the Alliance recommends that the FDA state whether or not an IDE is required, and the criteria by which the decision is reached. Examples provided would not only be helpful, they are necessary in providing the additional clarification within this section of the guidance document.

7. Since the Alliance has worked with the USWR, and many of our clinical association members are

creating registries, the Alliance is always very interested in any guidance with respect to registry use. In this case, the use of a registry as a control group in a clinical study of a new device is addressed in this guidance document in Section VI (D). As we have repeatedly stated in our comments, it is unclear whether an IDE is required and whether the registry is considered to fall under the IDE. The Alliance recommends that the FDA provide further clarification and examples to help clear up any uncertainty with regards to the use of a registry as a control group in a clinical study for a new device.

Conclusion

The Alliance commends and supports the FDA's efforts to provide clarity and guidance related to how RWE can be used when assessing regulatory decision making for medical devices. However in order to be effective in this area, the draft guidance document needs to written more clearly with multiple specific examples provided. Clarity and examples will ensure that RWE is utilized appropriately, compliant decisions are made in using RWE, and appropriate consent is obtained when necessary. The Alliance also would like to recommend that Class II devices be included in this guidance as we believe that RWE can be utilized effectively in the manner described in this draft for Class II and III devices.

The Alliance appreciates the opportunity to provide the FDA with our comments. If you require additional information or have any questions, please do not hesitate to contact me.

Sincerely,

Marcia Nusgart R. Ph.

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Executive Director