AdvaMed
Advanced Medical Technology Association

December 11, 2020

Division of Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2020-N-1762: Public Workshop - Orthopedic Device-Related Infections

Dear Sir or Madam:

The Advanced Medical Technology Association ("AdvaMed") is pleased to provide comments on the Food and Drug Administration's (FDA's or "Agency") November 13, 2020 Public Workshop on Orthopedic Device-Related Infections.

The Advanced Medical Technology Association (AdvaMed) is the world's largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

AdvaMed commends FDA for holding the November 13, 2020 Public Workshop – which is intended to be the first in a series of workshops – on the serious and consequential topic of orthopedic device-related infections. We are encouraged by FDA's interest in addressing the unmet clinical needs related to these infections, and FDA's stated interest in continuing the dialogue on this issue with key stakeholders to make real change for U.S. patients in need.

While the impact of orthopedic device-related infections has been known by those who treat these infections for some time, the statistics, human impact and costs shared at the workshop serve to expose a broader audience to these sobering and highly concerning facts.

It is worth highlighting some of the significant points and information shared at the workshop. Dr. Javad Parvizi, M.D., Vice Chairman of Research, Thomas Jefferson University, detailed key facts below.

The incident of orthopedic device-related infections was reported as follows:

- Total knee arthroplasty is estimated between 1 to 3%;
- Total hip arthroplasty is estimated between .05 to 2%;
- Shoulder arthroplasty is estimated between 1.1 to 3.8%;
- Closed low-energy fracture fixation is estimated at ~1%;
- Complex open tibia fracture fixation is estimated at >30%; and
- Spine implants is estimated at 0.7 to 16%.

As related by Dr. Parvizi and other clinicians at the workshop, the effects of infections on orthopedic patients are devastating including: delayed healing, multiple operations, sepsis, long courses of IV antibiotic therapy, chronic wounds, permanent functional loss, amputation of limbs, neurologic compromise and loss of life. Additionally, there are clear quality of life and socio-economic impacts, as was highlighted during the workshop. As pointed out so eloquently by a number of the workshop participants, behind these statistics are individual patients who must try to overcome the significant challenges posed by these infections with the help and care of their providers.

In addition to the patient impact, orthopedic device-related infections add substantial costs to the healthcare system including increased length of stays and higher readmission rates. As Dr. Parvizi noted, the economic burden associated with just periprosthetic total knee arthroplasty (TKA) and total hip arthroplasty (THA) infections alone is estimated at over $1.6 billion between 2001 and 2020.

During Session 4 of the Public Workshop titled: Advance Development of Needed Orthopedic Device Technologies: (Physician Community, Device Manufacturers, Academia, Governmental Agencies, Regulators and Patients), Dr. Parvizi discussed the relatively low rate of orthopedic device-related infections which creates challenges for proving clinical benefit – the need for extremely large numbers of patients and multi-site clinical trials over multiple years to obtain the statistical power typically expected within gold standard clinical trials. As commented by Dr. Parvizi, from an industry perspective, it is unlikely the expense related to such a large, multi-year trial can be justified by the limited return on investment. Dr. Parvizi outlined a number of alternative regulatory approaches FDA could take to encourage and expedite approval of anti-infective technologies.

Additionally, Dr. Paul Tornetta, III, Chief, Department of Orthopedic Surgery, Boston University School of Medicine, argued that he "would very clearly change my practice for one less infection a year in my patients" and "that we [clinicians] don't need to know if something is completely effective in high-level risk reduction … we need to know that it is safe." Dr. Tornetta proposed a regulatory approach that is focused on collection of pre-clinical animal efficacy and human safety

data that includes a small controlled study in humans to demonstrate safety followed by post-market surveillance of the device using real-world evidence for efficacy and labeling.

AdvaMed supports key recommendations made by Dr. Tornetta (above) and Dr. Parvizi, reiterated here:

- Improve the definition of clinical benefit as 'any positive therapeutic effect.'
- Utilize surrogate endpoints as opposed to randomized placebo-controlled trials (RPCT).
- Allow stepwise submissions with limited labeling followed by-broader submissions encompassing larger patient populations and clinical anatomies.
- Maintain a priority focus on high-risk patient groups.

Robert Durgin, Worldwide Vice President, Regulatory Affairs, DePuy Synthes Companies, Johnson & Johnson, reaffirmed many of Dr. Parvizi's recommendations and emphasized a need to act with more flexibility noting that the benefit-risk profile associated with these technologies must evolve. Mr. Durgin respectfully suggested regulatory flexibility in order to best serve patients in the U.S.; flexibility in both evidence expectations (e.g., safety data or preclinical data and real-world evidence versus clinical and efficacy data) as well as labeling considerations. Industry fully supports these recommendations.

It is important to understand that the benefit-risk calculation related to addressing orthopedic device-related infection is likely very different from elective total joint replacement (TJR) procedures. For elective TJR, the risks of delayed access to a prosthetic device is relatively low because patients, in many cases, can postpone surgery and/or utilize alternative approaches or treatment (e.g., use of pain treatments, bracing technologies, steroids and/or hyaluronic acid). As a result, demonstration of clinical benefit through collection of both safety and effectiveness data is essential.

In contrast to elective procedures, treatment of orthopedic device-related infection is both urgent and time-sensitive and there are few treatment alternatives. As a result, it can be reasonably argued that demonstration of safety should take precedence over demonstration of efficacy. In other words, given the devastating impact of orthopedic device-related infections on patients, for clearance or approval of new innovative anti-infective or anti-microbial technologies, we believe there is value in considering a regulatory approach which focuses on ensuring that there are no safety risks over a regulatory approach which requires both safety and clinical efficacy data.

We would note that FDA's total product life-cycle vision, along with other approaches FDA has implemented, enable a more cohesive pre- and post-market regulatory approach for products targeting orthopedic device-related infections. During the workshop, we were also pleased to see that FDA highlighted that its definition of valid scientific evidence includes alternatives to randomized clinical trials that may provide for more efficient approaches to data collection including for example, use of historical controls, registries, published literature and claims data. FDA's pre- and post-market balance approach provides the opportunity to shift clinical efficacy data requirements from the pre-market to the post-market setting.

In the case of anti-infective or anti-microbial technologies, a pre-market study focusing on safety could be followed up by either a registry and/or real-world evidence (RWE) post-market study. Importantly, a similar approach has been used successfully in support of certain CE-marked devices. Notified bodies have allowed market access based on smaller safety-focused data with a commitment to a robust, post-market clinical follow-up study. It should also be noted that without approved anti-infective or anti-microbial technologies, clinicians continue to treat infection based on their expertise and off-label use of antibiotics. The current paradigm in itself adds risk with surgeons being forced to use products off-label with possible risks associated with variable dosing, lack of controls for administration of antibiotics, etc.

AdvaMed respectfully offers the following additional proposals:

1. FDA should consider real-world evidence strategies and/or post-market clinical follow-up data to obtain U.S. on-label indications, especially for products already approved OUS.
2. Development of draft guidance documents, whitepapers, or other materials. AdvaMed's Orthopedic Sector is willing to work with FDA to help advance thoughts on new regulatory and evidence generation strategies to address this challenging problem.

We are very encouraged by and support FDA's vision to accelerate bringing innovative technologies targeting orthopedic device-related infections to the U.S. market. These device solutions have been made available OUS. AdvaMed believes we owe it to U.S. patients to change the current paradigm. In order to be successful in this important endeavor, we encourage FDA leadership to clearly transmit its vision to the reviewer level to ensure appropriate implementation occurs.

In closing, we greatly appreciate the opportunity to provide input on this significant public health issue. Please don't hesitate to contact me if I can help answer any questions.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs