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March 10, 2015

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

RE: Docket No. FDA-2012-N-1021; Fiscal Year 2015 Proposed Guidance Development

Dear Sir or Madam:

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatment. Our members range from the smallest to the largest medical technology innovators.

AdvaMed appreciates the opportunity to comment on CDRH's "Fiscal Year 2015 (FY 2015) Proposed Guidance Development." Provided below are our thoughts on the prioritization of the proposed FDA CDRH FY2015 guidance documents to be developed, along with our recommendations for guidance documents that we believe should be, but were not, included in CDRH's FY 2015 plans, our recommendations for guidance documents that should be updated or withdrawn, and responses to the questions posed in the Federal Register Notice.[1]

We prioritized the documents contained in FDA's "A" and "B" lists according to whether they were a "high," "medium," or "low" priority to our member companies. "High priority" documents are those that have the potential to broadly affect industry, have high impact on routine administrative and/or review procedures at FDA, address an area where guidance may be currently lacking, or it is required under the MDUFA III commitment letter or FDASIA legislation. "Medium priority" documents also may broadly impact industry, but may not be absolutely critical to FDA's routine administrative and/or review procedures. "Low priority" documents have a lesser impact on FDA procedures or address a subject that is highly specialized or narrowly focused. As FDA can appreciate, AdvaMed's membership comprises a breadth of manufacturers of medical devices, and we hope that our comments and additional guidance recommendations will be meaningfully considered in finalization of FDA's guidance development priorities.[2]

1 80 Fed. Reg. 1424, January 9, 2015.

2 We will not comment on those "A" list guidance documents that already have been issued since the list was published on January 9, 2015.

Part 1: FY 2015 Lists of Prioritized Medical Device Guidance Documents

Final Guidance Documents

As a general point, we strongly recommend that *all* existing draft guidance documents for which the comment period is closed be finalized as soon as possible. Of those final guidance documents on the "A" list, the ones that are of highest priority to our members are:

- *Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval*
- *Framework for Regulatory Oversight of Laboratory Developed Tests*
- *FDA Notification and Medical Device Reporting for Laboratory Developed Tests*
- *Use of ISO 10993-1, Biological Evaluation of Medical Devices Part I: Evaluation and Testing (Biocompatibility)*

Followed by:

- *Applying Human Factors & Usability Engineering to Optimize Medical Device Design*
- *510(k) Submissions for Medical Devices that Include Antimicrobial Agents*
- *Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval*
- *Expedited Access for Premarket Approval of Medical Devices Intended for Unmet Need for Life Threatening of Irreversibly Debilitating Diseases or Conditions*
- *Intent to Exempt Certain Class II and Class I Reserved Medical Devices From Premarket Notification Requirements*
- *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*
- *Submission and Review of Sterility Information in 510(k) Submissions for Devices Labeled as Sterile*

The remainder of the "A" list final draft guidance documents can be moved to the "B" list or already have been issued.

Draft Guidance Documents

All of the "A" list draft guidance documents are of medium priority to AdvaMed, with the exception of the *Medical Device Decision Support Software* guidance document, which is high priority (we note that two of the four have already been published (*General Wellness Products* and *Medical Device Accessories*).

Of the "B" list draft guidance documents, AdvaMed recommends that the *Use of Symbols in Labeling* be moved to the "A" list, and the rest are of medium or low priority.

High Priority Guidance Documents Not Included in the "A" or "B" Lists

There are a number of guidance documents/guidance document topics that are required according to the MDUFA III Commitment letter and/or FDASIA, have been draft for several years, or are of high priority to industry because of a lack of transparency/ predictability that were not included in the FY 15 priority lists. These include:

- PMA modifications (update)
- Manufacturing site changes (update)
- Update to *Internet/Social Media Platforms with Character Space Limitations; Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices.*
- Device-Specific Guidance Documents:
    - Co-development guidance
    - Guidance on non-molecular types of multi-marker panels

Part 2: Retrospective Review Guidances

AdvaMed recommends that the following guidance documents be updated/revised:

- *Guidance on Premarket Notification [510(k)] Submissions for Short-Term and Long-Term Intravascular Catheters*
- *Guidance for 510(k)s on Cholesterol Tests for Clinical Laboratory, Physicians' Office Laboratory and Home Use*
- *User Instruction for Medical Products (Laser Notice 44)*
- *Labeling of Laser Products (Laser Notice 45)*
- *Guidance for Industry – Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software*
- *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.*
- *Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features*
- *Guidance for Industry - Review Criteria for Assessment of C Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays*
- *Guidance for Industry and FDA Staff: A Pilot Program to Evaluate a Proposed Globally Harmonized Alternative for Premarket Procedures*
- *Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s*

Part 3: Responses to Questions Posed in Federal Register Notice

1. ***Patient Matched Instrumentation for Orthopedics: These devices are patient-specific instrumentation, created from patient imaging scans with the use of segmentation and planning software, to affect a surgeon's surgical plan intraoperatively. A guidance document addressing the basic elements to be addressed in a 510(k) submission for patient matched instrumentation for all joint replacement product areas will help provide transparency to industry as to the level and types of information requested for review of these devices.***

   a. *What methods are used to determine that all phases of the design process, including those that rely on execution by a trained employee and/or by software, function as intended? How is variability controlled across planning personnel and across different patient pathologies?*

      The first step toward minimizing the variability of specific instrument planning is to establish processing protocols based on the validation labs in which appropriate results are gained. These procedures are then used to train personnel in a patient-specific instrument planning system. This training must occur with a structured training program.

      Once a team of trained employees is in place, they must have access to a central procedure. This documentation must include instructions for the personnel to complete the necessary tasks.

      To reduce variability across the trained employees who have access to the procedural documents, there must be a validation study. In that study, several trained employees should complete the same surgical plan using the same surgical inputs. The results must show that, given the same inputs, each employee's pre-operative report would result in the implant selection and placement within an industry-determined acceptable range of error.

      After an employee is fully trained and the system variability is minimized, there must also be a step in the planning process for quality control or review by a second, fully trained employee. This review step should include an examination of the initial work further reducing the variability of an individual working on various pathologies.

      Steps performed either partially or fully automatically by a computer program must be tested and validated respective to the level of risk to the patient if the program fails and goes undetected.

      For example, ensuring that the scan segmentation software and the CAD software used to design the patient-specific instrument are performing properly is critical to the success of the instrument. But if the support software (e.g., Microsoft Word, PowerPoint, or Adobe Acrobat) used to present a pre-operative plan to the

surgeon fails, there is no report. This would prevent any approval of the plan and subsequent manufacture of the guides. The functionality of this support software should not require the same level of scrutiny because there is no risk to the patient.

Finally, in addition to the methods above, the surgeon must review the results of every pre-operative plan. The variability among the processing personnel must result in a pre-operative plan that matches the surgeon's intentions (i.e., the surgeon's prescribed alignment preferences). This plan must clearly communicate all of the critical elements of the patient's anatomy related to the procedure so that the surgeon can make an informed decision. If the plan is not what the surgeon wants, the surgeon must have the ability to review and provide feedback to the parent company. All changes must be reviewed and approved by the surgeon before manufacture of the guides can commence.

b. What impact does preoperative planning of the surgical procedure to create a guide have on implant performance? What parameters are critical to creating an effective preoperative plan with respect to device performance? Please provide a justification for your response.

Implant performance is a complicated metric with many different factors affecting the results. While implant sizing and alignment are significant factors in the survivorship and success of an implant, other health conditions (e.g., age, body mass index, bone quality, activity level, etc.) unrelated to the procedure are also important factors. For companies who have pre-operative navigation systems, this subtopic is no different than traditional orthopedic instrumentation.

For companies that have pre-operative navigation systems focusing on the goal of providing a well-aligned and sized orthopedic implant, when comparing an instrument system with a pre-operative plan and a patient-specific instrument to a system comprised of adjustable/traditional instruments, it is important to note that each system uses instruments. Every instrument has the potential for misuse by a surgeon leading to either positive or negative results. When used according to directions for use, both systems, theoretically, will provide successful results and implant performances that are equivalent to the other system. It is difficult to state that a pre-operative navigation instrument can provide statistically better results than a traditional instrumentation system that is used successfully.

Implant performance can be heavily dependent on the surgeon's choice in implant size. An implant that is too large or too small or has the wrong sizing ratio may not last as long as the correctly sized implant for each patient. While traditional instrumentation provides the necessary tools to accurately select the appropriate size implants to use in each case, surgeons often still pre-operatively use x-rays and x-ray templates of implants to help their decisions. With a pre-operative navigation system, the surgeon has the ability to use a 3D template which contains more available information about the patient's bones than a 2D x-ray. With the

option to adjust the pre-operative plan, the surgeon can also make slight adjustments to the plan to optimize the implant position for the appropriate size and alignment. Theoretically, providing better tools and more information to the surgeons pre-operatively should lead to better sizing choices and therefore better implant performance.

A manufacturer of patient-specific instruments should validate any new system to be equivalent in alignment results to a traditional instrumentation system by comparing that post-operative alignment to the proposed alignment in the pre-operative plan. In addition, a surgeon variability study should be completed that shows that the same patient-specific instrument, when used on the same (probably cadaveric) patient by different surgeons would result in alignments that are identical within an industry acceptable range of error according to published literature.

Another method of ensuring that an implant is aligned properly (theoretically leading to better performance) is to prevent implants from being aligned improperly. While seemingly obvious, a manufacturer of patient-specific instruments should design double checks into the system to help prevent the instruments from being used incorrectly. If the double checks result in an unacceptable alignment as compared to the pre-operative plan, the surgeon would be able to switch to traditional instrumentation during the procedure without any risk to the patient or risk to the implant alignment.

Other potential benefits of the pre-operative navigation technology that may indirectly relate to device performance are subjective and/or would need to be studied. These other factors may include; a reduced learning curve for new surgeon users, fewer steps in a procedure, reduced OR time, reduced statistical outliers of alignment results, and increased knowledge of the procedure prior to the case.

As with any instrument system, the most critical parameters are the inputs that are used to make important decisions. For a pre-operative navigation system, the inputs are the image/scan (e.g., CT or MRI) and the surgeon's instructions (prescribed alignment preferences). The scan must be provided according to the manufacturer's protocol, and the surgeon's instructions must be clear and understood. However, if the surgeon isn't clear, he/she has the option to make changes to the pre-operative plan until the plan is as desired.

c. How extensive is the interaction among the approving surgeon and the planning personnel when developing and approving a preoperative plan?

The collaboration between the surgeon and the planning personnel is critical to the success of this technology. The surgeon, as a medical professional, should always instruct and direct the planning personnel through various communication methods to complete the surgical plan according to his/her preferences. The pre-

operative plan is the surgeon's prescription for each individual patient, therefore he/she must provide all necessary inputs or information to the planning personnel, and then he/she must approve the end result of the planning process.

This interaction must always occur in at least one step during the planning process; after the plan has been proposed. Two optional additional interactions could occur during the planning process but may not always be required; before the planning begins and during the planning.

Before the planning begins, the surgeon should provide a series of inputs or instructions to the planning personnel. This information could be conveyed by answering a series of questions, selecting set and defined choices of common surgical preferences, or free form comments/instructions. The surgeon may establish a set of parameters that are the same for every case, or he/she must have the option to alter the default parameters based on each patient's condition. These inputs are used by the planning personnel to complete the pre-operative plan.

During the process of planning the case, due to a unique patient condition, there may be a need for the employee of the instrument manufacturer to communicate with the surgeon to obtain additional inputs. The collaboration at this step could be initiated by either the surgeon or the employee. The additional collaboration and subsequent inputs may be iterative and as extensive as necessary so that the planning personnel can complete the pre-operative plan according to the surgeon's intentions.

Prior to the completion of the process, the surgeon must review the work and results of the pre-operative plan. At a minimum, a detailed alignment plan (with the alignment settings, implant specifications, views, measurements, and potential unique aspects of the case) needs to be appropriately communicated such that the surgeon is making a fully informed decision as to the treatment plan to determine if it is appropriate. If the surgeon disagrees or has questions with anything in the plan, the process must be repeated or clarified until the plan matches the surgeon's intentions. The surgeon must approve the final plan in order to formally complete the planning process.

d. When the manufacturers of patient-matched instruments do not manufacture the implant system or have a formal business agreement with the implant manufacturer, what information requires monitoring to ensure that modifications to the implant system or implantation recommendations do not affect the performance of the patient-matched instrumentation?

There are many challenges to a scenario in which the implant manufacturer does not also manufacture the patient-specific instrumentation when there is no formal business agreement between the companies. To alleviate many unnecessary risks, a formal business agreement should be in place.

Assuming an agreement is in place, all changes by the implant manufacturer to either the implants or the accompanying instrumentation must be communicated to the patient-specific instrument manufacturer in advance of releasing any new or modified products. If a change is significant enough that it requires a new 510(k) submission by the implant manufacturer, the patient-specific instrument manufacturer should also be required to submit a new 510(k) for the mating instrumentation.

Regardless of whether a business agreement is in place or not, the patient-matched instrument manufacturer should closely monitor the complaints of the system. Any complaints related to any mating components between the systems of the two companies should be investigated and addressed as expeditiously as possible.

If there is no business agreement in place, the patient-specific instrument manufacturer must routinely monitor the implant system for changes. The pre-operative navigation company must have a clear validation procedure in place in order to update their system if a change to the implants or instruments from the other company is found.

In the scenario in which there is a failure between the systems of the two companies, there must be a backup option (typically provided by the implant manufacturer) in the surgical technique so that the procedure can be completed successfully and without risk to the patient.

2. ***Medical Devices Intended for Aesthetic Use: As the U.S. population continues to age, use of medical devices for aesthetic purposes is expanding. Given the absence of generally accepted metrics for selecting patients and evaluating medical device performance for aesthetic uses, there are many challenges in collecting and interpreting clinical data that might support clearance or approval of aesthetic- use devices. Another difficulty in such studies is understanding patients' perspectives on product safety and effectiveness, which are important in defining the benefit/risk ratio for any new treatment.***

   a. Do the use of validated scales that depict varying degrees of change in body features (e.g., wrinkle severity, mid-face volume) result in clinically meaningful assessment of product effectiveness? Under what circumstances would the use of a validated scale not be clinically meaningful?

   Some tools could be used to assess home use products or to determine if the product is a "customer solution" that is a combination with an aesthetic use device.

3. Dual 510(k) and Clinical Laboratory Improvements Amendments (CLIA) Waiver by Application: A Dual 510(k) and CLIA Waiver by Application ("Dual") is a regulatory submission requesting both 510(k) clearance and CLIA Waiver

approval. Under the Dual program, a Dual must be preceded by a presubmission during which the strategy for addressing both regulatory requirements is discussed. After the presubmission, the Dual 510(k) and Waiver by Application are submitted as a single regulatory submission. A guidance document addressing considerations for the design of clinical studies used to support both CLIA Waiver approval and 510(k) clearance will provide transparency on the level and types of information to provide FDA. FDA anticipates this will help focus the Dual presubmissions and potentially shorten the review process for the Dual submission.

a. Of what challenges should FDA be aware in drafting this guidance document?

While there is potential benefit in further clarification by FDA regarding the Dual submission process, there are a number of issues yet to be addressed in the CLIA Waiver process overall, and we suggest that FDA address the outstanding issues in the CLIA Waiver process as outlined in prior AdvaMed comments.

This includes providing guidance on:

- Combining clinical studies in order to cover both 510(k) and CLIA requirements.
- Combining the risk analysis to cover both 510(k) and CLIA requirements.
- Combining clinical site selection/criteria to cover both 510(k) and CLIA requirements.
- Combining labeling requirements to cover both 510(k) and CLIA requirements.

Thank you for the opportunity to submit these comments.

Sincerely,

/s/

Sharon A. Segal, Ph.D.
Vice President, Technology and Regulatory Affairs