



701 Pennsylvania Avenue, NW  
Suite 800  
Washington, D.C. 20004-2654  
Tel: 202 783 8700  
Fax: 202 783 8750  
www.AdvaMed.org

February 29, 2016

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; Medical Device User Fee and Modernization Act;  
Notice to Public of Web Site Location of Fiscal Year 2016 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 2016 (FY 2016) Proposed Guidance Development." Provided below are our thoughts on the prioritization of the proposed FDA CDRH FY2016 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but were not, included in CDRH's FY 2016 plans, our recommendations for guidance documents that should be updated or withdrawn, and responses to the questions posed in the Federal Register Notice.<sup>1</sup>

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.<sup>2</sup>

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<sup>1</sup> 80 Fed. Reg. 81355, December 29, 2015.

<sup>2</sup> We will not comment on those guidance documents that already have been issued since the list was published on December 29, 2015.

## **Part 1: FY 2016 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. For many of these draft guidance documents, AdvaMed has submitted comments to the public docket and FDA should refer to these comments.

Of those final guidance documents on the “A” list, the ones that are of highest priority to our members are:

- *Medical Device Accessories* This guidance is necessary to clear up confusion around definitions and requirements, specifically for “accessories,” “components,” “parts,” and “non-medical devices.”
- *UDI Direct Marking* Direct marking requirements are being implemented, and it is important to have FDA’s requirements defined. Clarity around this guidance would reduce the risk of not meeting statutory compliance dates.
- *Policy for Regulatory Oversight of Laboratory Developed Tests (for IVD companies)* We expect that FDA also will issue a final guidance on FDA Notification and Medical Device Reporting for Laboratory Developed Tests (or LDTs) in conjunction with the policy guidance to support transparency to the public on this information and laboratories’ understanding of registration and adverse event reporting requirements.
- *Use of ISO 10993-1, Biological Evaluation of Medical Devices Part I: Evaluation and Testing (Biocompatibility)* Clear, consistent guidance is necessary and should be consistent with the ISO-10993 standard.
- *Medical Device Reporting (MDR) for Manufacturers* Industry needs clear guidance and efficient reporting requirements.

Followed by:

- *Benefit-Risk Factors to Consider when Reviewing IDE Submissions*
- *Adaptive Design for Medical Device Clinical Studies*
- *Incorporating Patient Preferences into Medical Device Premarket Approvals, Humanitarian Device Exemptions, and De Novo Classifications*
- *Postmarket Surveillance Studies Under Section 522 of the Food, Drug, and Cosmetic Act.*

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

Of the “B” list final guidance documents, only “finalizing existing draft guidance documents” is of high priority to all companies. When guidance documents are in draft for

several years, it is difficult to understand if the draft guidance still reflects FDA's current thinking.

Our IVD companies have assigned a high priority to *Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use* and *Self-Monitoring Blood Glucose Meters for Over-the-Counter (OTC) Use*. AdvaMed member companies have worked to support recent updates to worldwide standards ISO 15197 and CLSI POCT 12-A3. Yet, the draft guidance – like its counterpart OTC guidance – disregarded worldwide standards already in place and implemented worldwide. As a key issue, FDA can and should work to better harmonize with current worldwide regulatory requirements and consensus standards, which represent significant advances in device development and ensure access to safe and effective devices rather than impose new requirements well in excess of current stringent standards for OTC and hospital use implemented worldwide. Importantly, any proposed changes should be scientifically grounded and must hinge on risk-based assessment with ultimate clinical importance and impact on decision making.

FDA should carefully consider comments and support efficient and effective use of standards for its policies, including issuance of these guidances. The impact of these guidances, if implemented as drafted, will likely have far reaching consequences in access and availability to blood glucose meters to healthcare professionals and patients.

#### Draft Guidance Documents

Of those draft guidance documents on the “A” list, the ones that are of highest priority to our members are:

- *Medical Device Decision Support Software* Decision Support Software as it relates to Class III products has a tendency to be viewed as Class III accessories. Clarity in this space may limit the need for pre-submission meetings to determine the necessary regulatory pathway.
- *Use of Symbols in Labeling* While guidance is appreciated, FDA issuance of the final rule is extremely important because revisions to labels to accommodate UDI will benefit from the use of symbols.
- *510(k) Modifications* Recommend issuing this guidance document at the same time as the *Software Modifications* guidance document with a minimum 90-day comment period.
- *Software Modifications* See comment above.
- *Companion Diagnostics Co-Development*

The remainder of the “A” list draft guidance documents are of medium priority or have already been issued.

All of the “B” list draft guidance documents are of medium or low priority or have already been issued, with the exception of the *Dual 510(k) and Clinical Laboratory Improvement*

*Amendments Act (CLIA) Waiver by Application*, which is of high priority to our IVD companies. Improvements to the CLIA waiver process for point of care, rapid diagnostic tests are critically important. FDA already has committed to working with industry to revise the 2008 CLIA waiver study guidance as it relates to demonstrating accuracy and appropriate use of comparable performance between a waived user and a moderately complex laboratory user. Apart from issuance of such revised draft guidance on review expectations for CLIA waiver study design, we would support an additional and separate proposed effort, to better define the dual 510(k)/CLIA waiver process in guidance to further leverage that process and better outline appropriate, flexible criteria for dual submissions. This is very important for POC devices.

### **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 16 priority lists. One example is an update of PMA modifications guidance.

Further, currently the implementation of conforming amendments for the final UDI rule is left to manufacturers to determine FDA’s intention. FDA has not provided industry any guiding rules or data requirements (where applicable) on how to implement conforming amendments. For some of the amendments, it is critical for FDA to provide this information so UDI data are provided in a consistent and usable way – as the UDI is provided in two forms, Auto Identification Data Capture (AIDC) and Human Readable, and by various UDI accredited agencies. The conforming amendments include UDI considerations in the following parts of 21 CFR: Part 803—Medical Device Reporting, Part 806—Corrections and Removals, Part 810—Recalls, Part 820—QSR, Part 821—Device Tracking, and Part 822—Postmarket Surveillance.

### **Part 2: Retrospective Review Guidances**

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

- *Components and Repair (1976)* This should align with Quality System Regulations or be withdrawn.
- *Panel Report and Recommendations on PMA Approvals #P86-5 (Blue Book memo) (1986)* This should align with MDUFA goals.
- *Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices (1996)*
- *Indications for Use Statement (1996)* This is important to understanding the necessary elements of the form and design of the statement. Further, revision is necessary to clarify between “Indications for Use” and “Intended Use.”
- *Points to Consider for Portable Blood Glucose Monitoring Devices Intended for Bedside Use in the Neonate Nursery (1996)* This should be brought more in line

with recent guidance documents. We would like to better understand if this information will be included in the Blood Glucose Monitoring guidance document for Point of Care.

- *Points to Consider for Review of Calibration and Quality Control Labeling for In Vitro Diagnostic Devices (1996)* If this information is in more recent guidance, recommend withdrawal.
- *510(k) Quality Review Program (Blue Book Memo I96-1) (1996)* This should be in line with more recent guidance and process or withdrawn and has been largely supplanted by the Refuse to Accept policy.
- *Medical Device Reporting: An Overview (1996)*
- *Guidance Document For Testing Bone Anchor Devices (1996)*
- *Guidance Document for Testing Biodegradable Polymer Implant Devices (1996)*
- *Suggested Format for IDE Progress Report (1996)*
- *Continued Access to Investigational Devices During PMA Preparation and Review, July 15 1996 (Blue Book Memo D96-1)*
- *MDR Guidance Document No. 1 – IOL – E1996004 (1996)*
- *Memorandum of Understanding Regarding Patient Labeling Review (Blue Book Memo #G96-3) (1996)*
- *Guidance Document for the Submission of Tumor Associated Antigen Premarket Notifications, [510(k)], to FDA (1996)* This needs to be updated with FDA's current expectations (e.g., with regard to data analysis, etc.). There is more information in decision summaries than in this guidance.
- *Review Criteria for Assessment of Professional Use Human Chorionic Gonadotropin (hCG) In Vitro Diagnostic Devices (IVDs) (1996)*
- *The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors (2006)* This should be updated in line with recent guidance.
- *Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable* This document is a critical component to IVD innovation. We strongly support the FDA's current and longstanding requirements that protect human subjects and allow diagnostic clinical test developers to continue vital clinical research and the development of innovative and breakthrough diagnostic technologies. This policy is essential to ensure research and development in groundbreaking technologies, including those used in precision medicine and treatment of rare disease.

The FDA has long recognized the vital role of de-identified specimens in the development and evaluation of medical technology. FDA's requirements for leftover specimens have enabled manufacturers to successfully advance clinically validated products through the U.S. regulatory process. Biorepositories of stored specimens allow for this research to occur and also allow test developers to rapidly respond to potential

outbreaks or public health threats. Without FDA's current policy – that provides the flexibility to utilize de-identified, leftover specimens – very few of these critical products would be available in the U.S. Not only do we support the policy, but it should be retained in its current form to assure continued viability of research and innovation in the best interests of the public health.

- *Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act*
- *Real-Time Premarket Approval Application (PMA) Supplements (2006)*
- *Compliance with Section 301 of the Medical Device User Fee and Modernization Act of 2002, as amended - Prominent and Conspicuous Mark of Manufacturers on Single-Use Devices (2006)*
- *Validation Data in Premarket Notifications Submissions (510(k)s) for Reprocessed Single-Use Medical Devices (2006)*
- *Exemption from Certain Reporting and Recordkeeping Requirements for Television Receivers and Computer Monitors with Cathode Ray Tubes (WITHDRAW) (2006)*

### **Part 3: Responses to Questions Posed in Federal Register Notice**

**1. *Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices: EMC assessment is a vital part of ensuring that risks associated with performance degradation of electrically-powered medical devices associated with electromagnetic interference are adequately addressed. CDRH recently published a short draft guidance entitled “Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices” (Ref. 6) to provide a framework for promoting consistent submission and review of EMC information in premarket submissions. In addition, CDRH plans to also draft a more detailed guidance on this topic to provide more comprehensive information and transparency to stakeholders regarding the information necessary to support an EMC claim.***

- a. There has been increasing use of electromagnetic emitters (e.g., radio-frequency identification, electronic article surveillance gates, metal detectors) in the environments where medical devices operate. What methods are used to determine EMC of devices exposed to these common emitters?*

EMC of medical devices is evaluated in accordance with IEC60601-1-2, which is an international standard where the experts have determined the appropriate levels for testing for both susceptibility and emissions. Additional testing is typically conducted based on FDA feedback/concerns regarding RFID, microwaves, etc. but these tests have not resulted in any value over testing as mandated by the experts per IEC60601-1-2.

Tests typically conducted include:

- Analysis of signal signature (signal-level, frequency, modulation) based on study of literature specifications of special technologies, results of already completed investigations and own investigations with antenna /probes and frequency analyzers at intended environment
  - Analysis of medical electrical equipment if such threats can result in principle in a hazard
  - Verification of the immunity against such emitters by using test methods described in IEC – 60601-1-2:2014
- b. *Given that basic safety, as defined in the IEC 60601-1 family of standards, does not include effectiveness, how is device performance evaluated differently than device safety for EMC? Specifically, are pass/fail criteria chosen such that they will address both performance and safety for each EMC test? Alternatively, are safety and performance tested separately?*

IEC60601-1-2 has examples of criteria to be evaluated, including the need to establish “essential performance” which includes safety and performance necessary for basic safety. These may be tested together if they can be monitored in aggregate; alternatively, there may be a need to conduct several rounds of testing to monitor the “essential performance” and/or different operating modes if a worst case mode cannot be defined.

Device performance is evaluated as a system, separately from EMC safety testing. Performance (effectiveness) is conducted separately from the EMC safety testing conducted under the IEC 60601 family of standards, as noted above, and includes testing based on clinical usage consistent with the proposed indications for use of the device. This is an appropriate practice, utilizing the IEC 60601 family of standards for general EMC safety, and preclinical and medical expertise in animal and other laboratory testing of the device specific performance.

- c. *When networks (wired or wireless) are determined to be necessary for device performance, how are they included as a system when tested for EMC?*

Networks are attached and monitored as part of the EMC testing – devices are evaluated as a system. The monitoring during EMC testing is at a high level, but there are network standards that can be used if networking is part of the “essential performance” or safety of the device. A network simulator could be used during EMC testing. Such devices are referenced as associated equipment (CISPR 16-2-1:2014, definition 3.1.4).

- d. *The use of “third party” components can significantly affect the MC of the medical device system. How are device systems evaluated for EMC when off-the-shelf components such as smartphones, tablets, or PCs are intended to be used in the device system?*

If the component is critical to safety or performance, it should be tested as part of the system. Representative, worst-case components can be used for testing in most cases, and typically these components have to comply with standards regarding emissions and susceptibility. The risk management process for a device will drive the appropriate level of evaluation.

The criteria are listed in IEC 60601-1-2:2014 clauses 4.2 and 8.8. Only suppliers are accepted that deliver accompanying documents with specifications and reliable test results (from accredited labs).

- e. *Medical devices, like most electronic products, go through various design changes that can affect the EMC of the device system. The changes or modifications can occur after initial EMC testing. What factors and methods are used to determine how device changes or modifications (e.g., software, firmware, hardware) will affect EMC and how is it determined when partial or complete EMC re-testing of a device is needed?*

Changes are assessed by EMC engineers/electronics experts with long-time experience, through established risk mitigation procedures in consultation with third party testing facilities, for impact on EMC. A test plan is developed based on the scope of the specific change. This is done as part of the quality management/design control process.

- f. *The use of magnetic resonance (MR) imaging technology on medical device users and patients is increasing. MR imaging incorporates very strong magnetic and electric fields that can have very significant effects on the safety and effectiveness of medical devices, especially electrically active devices. How is MR safety and compatibility addressed for electrically active medical devices intended for use in the MR environment? How is MR safety addressed (e.g. labeling or other) for electrically active medical devices not intended for use in the MR environment?*

There are standards/guidance documents available for testing devices for use in an MR environment (see IEC 60601-2-33), and labeling is applied when tested per these requirements. MR safety is addressed by not allowing non-MR labeled devices in the MR environment. IEC 60601-1-2:2014 covers it as “special environment” in annex E (Determination of immunity test levels for special environments). Additionally, other committees responsible for particular standards should consider the intended environment and should specify relevant requirements.

- g. *Several medical device EMC consensus standards specify the information to be conveyed to the user regarding device EMC. Is this information sufficient? If not, what additional type of information is typically provided to help the user manage the risks associated with medical device EMC and how is this information conveyed?*

The information required by the consensus standards is comprehensive and adequate and can be used by technical equipment personnel in the health care facility to ensure coexistence if there is a concern. If anything, the required information is too much for the average user to comprehend, and the standards could be improved by simplifying the required information.

For the responsible organization (entity accountable for the use and maintenance of an ME EQUIPMENT or an ME SYSTEM) the information should be in the accompanying documents and should include considerations for installation of the ME EQUIPMENT.

For operators (person handling equipment), the possibility to get EMC-information should be realized on the display. Information should give hints how to verify if an occurring unwanted reaction is related to EMC and what “simple mitigations” can be performed (e.g., separation of RF emitting device like mobiles).

- 2. *Utilizing Animal Studies to Evaluate the Safety of Organ Preservation Devices and Solutions: While the national transplant waiting list continues to grow, rates of donation and transplant remain stagnant. On average, 22 people die each day waiting for a transplant. The dire deficit in organ transplants has propelled a new wave of innovation in perfusion-based organ preservation technologies. With such innovation also comes the challenge of demonstrating that these new technologies, when evaluated in animal models, are sufficiently safe for early clinical experience. After animal organs undergo preservation using a new organ transport device or solution, there are generally two models to assess post-reperfusion injury: (1) An in vivo model in which the organ is transplanted into a surrogate recipient animal and (2) an ex vivo model in which the organ is reperfused under simulated transplant conditions. FDA intends to develop guidance to provide recommendations for utilizing both in vivo and ex vivo models to evaluate emerging organ preservation technologies. Prior to drafting our recommendations in a future guidance document, FDA invites comments on the following questions:***

AdvaMed will not be providing responses to this particular set of questions.

**Additional Questions:**

- a. *The cover page of each guidance document includes contact information for questions regarding the guidance, and a list of CDRH Offices that have generally contributed to the drafting of the guidance. Is the list of CDRH Offices involved in the drafting of the guidance informative? What other administrative information should be included on the cover page?*

It is a positive thing to list the contact information for a particular guidance document, particularly when more than one office is involved. A group email account, behind which FDA sorts out internally who should answer, would be

sufficient if a specific contact is not available. It would, however, be helpful for that contact information to be relevant throughout the life of the guidance document. For example, some guidance documents list individuals as the contact for the document. These individuals may change responsibilities or leave FDA during the lifetime of the guidance document. Similarly, when organizations are listed as being the contact for the document, FDA can reorganize and either change the responsibilities of an organization or eliminate the organization altogether. It may be helpful for FDA to list the contact person (or organization) on the FDA website, so that it is easy to be kept current.

Further, the offices involved, and even the personnel involved, are beneficial from a historical perspective in understanding the document. Even more important than who worked on drafting the guidance, as noted above, the group at FDA responsible for interpreting and maintaining the guidance should be identified, and FDA should have a process for addressing questions related to the guidance. This could be on the FDA website if not in the document.

Additional information that is helpful on the cover page is the date published, as well as the primary contact for any comments.

- b. *CDRH is committed to the continual improvement of the quality of guidance documents and we are seeking to identify examples of quality guidance documents. Are there specific guidance documents published in the past 5 years that were particularly informative and helpful that could serve as models for future guidance documents? Please provide the title of the guidance documents and briefly describe what specific aspects were informative and helpful?*

*Content of Premarket Submissions for Management of Cybersecurity in Medical Devices (Issued October 2014):* The specific content for what is required in premarket submissions is clear and straightforward in defining the expectations and deliverables, and it is easy to follow. The guidance provided is appropriate and balanced.

*Mobile Medical Applications:* The numerous examples were very valuable.

*Requests for Feedback on Medical Device Submissions:* This guidance clearly defined the process. It is well-written, organized, and thorough. It provides all options with sufficient detail and leaves very few, if any, questions related to this process.

- c. *Has the enhanced Guidance Document Search feature on the FDA Web site (<http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>) improved searchability of guidances? Are there any suggestions for how the search feature could be improved?*

The enhanced Guidance Document Search feature has improved the searchability of guidance documents and has been very helpful in quickly retrieving documents. The search tool is quick and provides a nice status overview of the documents in the results. However, there are times that the search feature is not always the best at capturing a guidance (or multiple guidance documents with the same keyword) if the exact name is not inserted into the search field. An option to conduct a full-text search of guidance documents would be potentially valuable. Additionally, it would be helpful to provide a guidance document hierarchy or matrix defining the relationship between documents as part of the search function.

Thank you for the opportunity to submit these comments.

Sincerely,

/s/

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