Division of Dockets Management Staff (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 2019 Proposed Guidance Development

Dear Sir or Madam:

The Advanced Medical Technology Association (“AdvaMed”) appreciates the opportunity to comment on the Center for Devices and Radiological Health’s (“CDRH’s”) Fiscal Year 2019 (“FY 2019”) Proposed Guidance Development.

AdvaMed is the world’s largest association representing manufacturers of medical devices, diagnostic products, and medical technology. AdvaMed’s member companies range from the largest to the smallest medical product innovators and manufacturers, with nearly 70 percent of our members generating less than $100 million in annual sales. AdvaMed’s member companies produce innovations that transform health care through earlier disease detection, less invasive procedures, and more effective treatments.

We appreciate the Food and Drug Administration’s (“FDA’s” or “Agency’s”) efforts to promote transparency into its guidance priorities and to provide an opportunity for public input. Provided below is our feedback on the prioritization of the proposed FDA CDRH FY 2019 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but were not included in CDRH’s FY 2019 plans, and our recommendations for guidance documents that should be updated or withdrawn.

We prioritized the documents contained in the Food and Drug Administration’s “A-List” and “B-List” according to whether they were a “high,” “medium,” or “low” priority to our member companies. 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.¹

¹ We will not generally comment on guidance documents that already have been issued since the CDRH FY 2019 Priority List was published. In limited cases where FDA subsequently issued a draft guidance, we recommend finalization of the guidances and continuation as A-List priorities for finalization.
Part 1: FY 2019 Lists of Prioritized Medical Device Guidance Documents

Final Guidance Documents

As a general note, we recommend that FDA finalize several of the draft guidances that it has issued within the last year. AdvaMed has submitted comments on these docket priorities and requests that FDA refer to those comments, which provide critical feedback and support meaningful implementation.

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

- **The Least Burdensome Provisions: Concept and Principles:** Since 1997, Congress has directed FDA to take a least burdensome approach to medical device premarket evaluation to eliminate unnecessary burdens that may delay the marketing of beneficial new products, while maintaining FDA’s high statutory bar to demonstrate safety and effectiveness for clearance and approval. Application of least burdensome principles preserves FDA and industry time and resources, while providing patients with timely access to life-saving and life-enhancing devices.

- **Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program:** Sponsors need a reliable mechanism to understand, discuss with FDA, and meet FDA expectations before FDA begins marketing submission review. Such a mechanism helps provide clarity and certainty. Finalizing this guidance will promote timely patient access to new and improved devices.

- **Breakthrough Devices Program:** This guidance supports FDA’s, industry’s, and patients’ shared goal of giving patients timely access to devices that effectively diagnose or treat life-threatening or irreversibly debilitating diseases or conditions. As there may not be alternative treatments available for these diseases or conditions, fostering prompt access is critical.

- **Expansion of the Abbreviated 510(k) Program: Demonstrating Substantial Equivalence through Performance Criteria:** We appreciate FDA’s attempt to offer additional opportunities to establish substantial equivalence through the Expanded Abbreviated 510(k) pathway. The current 510(k) pathways (Traditional, Special and Abbreviated) have served patients and industry well. Through legislation and changes in FDA policy, the 510(k) processes have evolved as innovation and technology have changed. FDA holds companies to high standards by ensuring that new devices meet current safety and performance expectations. Industry is committed to producing devices that meet the highest standards. Companies strive to produce devices that meet their customers’ current needs as well as ensure compliance with the robust federal laws that impose significant penalties (recalls and legal actions) when devices do not comply with the law. If properly defined and implemented, this new pathway potentially complements the current 510(k) pathways, all of which assure that patients have
timely access to safe, effective and high-quality medical devices. In finalizing this guidance, FDA should attend to the issues and proposed solutions raised in AdvaMed’s comments in response to the draft guidance.

- **Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act:** We believe the draft guidance will help clarify a number of policies and guidances and we support timely finalization.

- **Clinical and Patient Decision Support Software:** We believe the Clinical and Patient Decision Support Software (“CDS”) Draft Guidance takes an important step in clarifying the types of software that are, or are not, subject to FDA’s regulatory oversight. In finalizing this guidance, FDA should attend to the issues and proposed solutions raised in AdvaMed’s comments in response to the draft guidance.

- **Content of Premarket Submissions for Cybersecurity of Medical Devices of Moderate and Major Level of Concern:** FDA issued the draft guidance after it released this list and we support timely finalization of the newly-issued draft guidance. Cybersecurity is an increasing concern for all connected medical devices. We believe it is important to understand FDA’s expectations for premarket submissions for these devices so that industry can provide adequate information for FDA review and, in partnership with FDA, help protect patients from cybersecurity threats.

- **Multiple Function Device Products: Policy and Considerations:** We appreciate FDA’s decision to apply the policies espoused in the draft guidance to all medical devices with multiple functions, regardless of whether they contain software. In finalizing this guidance, FDA should attend to the issues and proposed solutions raised in AdvaMed’s comments in response to the draft guidance.

- **The Special 510(k) Program:** The Special 510(k) Program is a well-established regulatory tool and we appreciate this draft guidance, which would expand the types of changes that could be made pursuant to the program. Use of the program reduces workload for both FDA and industry, expediting innovative products to market, while continuing to ensure patient safety.

- **Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (“CLIA”) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices:** Point-of-care diagnostics are an incredibly important aspect of today’s healthcare. With the increasing need for timely point-of-care diagnostics from emerging infectious diseases to antibiotic resistance, this is a priority public health matter for physicians to have these critical tests as part of today’s modern healthcare system. We appreciate FDA’s reissuance of these draft guidances to support appropriate and flexible study designs and to improve the review process to support innovation and the public health. Once this comment period closes, we encourage FDA to prioritize finalization on the A-List.
• **Recommendations for Dual 510(k) and Clinical Laboratory Improvement Amendments Waiver by Application Studies:** Point-of-care diagnostics are an incredibly important aspect of today’s healthcare. With the increasing need for timely point-of-care diagnostics from emerging infection disease to antibiotic resistance, this is a priority public health matter for physicians to have these critical tests as part of today’s modern healthcare system. We appreciate FDA’s reissuance of these draft guidances to support appropriate and flexible study designs and to improve the review process to support innovation and the public health. Once this comment period closes, we encourage FDA to prioritize finalization on the A-List.

• **Patient Engagement in Clinical Trials:** Patient input into medical device clinical trial design may confer significant benefits, including enrollment and retention of patients, collection of meaningful information, and successful trial completion. Guidance outlining FDA’s current thinking on the topic could provide helpful clarity.

Of those final guidance documents on the A-List, we have also identified ones that were identified as “medium priority” by our members. While we support the inclusion of these on the A-List, they are of somewhat lower priority to our members. Those final guidances include:

• **Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions:** FDA recognizes in this draft guidance the uncertainty in making benefit-risk determinations for some medical devices, including breakthrough products and products that target small or underserved patient populations. Making these devices available both serves patients and provides meaningful clinical experience to inform review of follow-on devices. Importantly, even as products with some uncertainty enter the market, there are postmarket surveillance protections to monitor their safety and effectiveness, and postmarket data collection to advance product iteration and innovation.

• **Humanitarian Device Exemption (“HDE”) Program:** Interest in improving medical products for dealing with orphan diseases transcends regulatory boundaries. AdvaMed supports FDA’s efforts to provide greater clarity regarding the criteria FDA staff uses to determine if “probable benefit” has been demonstrated for marketing authorizations of Humanitarian Use Devices (“HUDs”). In finalizing this guidance, FDA should attend to the issues and proposed solutions raised in AdvaMed’s comments on the draft guidance.

Furthermore, we recommend moving the issuance of the following final guidances from the B-List to the A-List:

• **Replacement Reagent and Instrument Family Policy for In Vitro Diagnostic Devices:** Clear and consistent application of the FDA Replacement Reagent and Instrument Family Policy supports diagnostic innovation. This policy is not only important, but a core policy critical to
advances and evolution of modern instrumentation, which are a cornerstone of patient care and promote an effective and transparent regulatory process. We greatly appreciate FDA’s issuance of the draft guidance and thoughtful consideration of policy refinement. We seek finalization of the draft guidance as soon as possible.

• **Unique Device Identification System: Form and Content of the Unique Device Identifier (“UDI”):** UDI compliance milestones are fast approaching and this guidance, and the one identified below, are key for a fully implemented UDI system. There is a great deal of current industry effort in creating final form and content of UDI as part of the efforts to comply with the European Medical Device Regulation (“EU MDR”). Understanding FDA current thinking on this topic, especially as it relates to form and content of UDI, is important for alignment of these efforts globally.

• **Unique Device Identification: Convenience Kits:** UDI compliance milestones are fast approaching and this guidance, and the one identified above, are key to a fully implemented UDI system.

• **Medical X-Ray Imaging Devices Conformance with International Electrotechnical Commission (“IEC”) Standards:** AdvaMed supports the concept underpinning this draft guidance of substituting conformance with specified IEC standards for compliance with the performance standards established by FDA in 21 C.F.R. Part 1000 (“Subchapter J”).

In addition, we have identified multiple draft guidances for which we believe issuance of a final version should be included on the A-List, but final versions are not included on either the “A” or “B” lists:

• **Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product:** This draft guidance captured substantial FDA expertise in personalized medicine and is a positive step in supporting innovators that are developing new safe and effective diagnostic technologies to advance personalized medicine in the United States.

• **Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk:** We appreciate FDA’s issuance of this draft guidance that describes an optional streamlined submission process for determining whether use of an investigational *in vitro* diagnostic (“IVD”) in a clinical trial for an oncology therapeutic is considered significant risk (“SR”), nonsignificant risk (“NSR”), or exempt.

• **Investigational IVDs Used in Clinical Investigations of Therapeutic Products:** This draft guidance helpfully outlines practical principles and key considerations for sponsors of clinical investigations of therapeutic products that also include investigational *in vitro* diagnostics (“IVDs”) and Institutional Review Boards (“IRBs”) that review these investigations.
• **Process to Request a Review of FDA’s Decision Not to Issue Certain Export Certificates for Devices; Draft Guidance for Industry and Food and Drug Administration Staff:** FDARA section 704 requires FDA to finalize this guidance “not later than 1 year after the close of the comment period for such guidance . . . .” That one-year period expires on November 15, 2019, and FDA must publish final guidance by that time. This guidance is essential to permit manufacturers to export products that FDA deems safe and effective for U.S. citizens. In finalizing this guidance, FDA should attend to the concerns and proposed solutions raised in AdvaMed’s comments in response to the draft guidance.

• **Principles and Procedures for the Recognition and/or Withdrawal of Voluntary Consensus Standards:** We support final guidance to reflect the process for requesting recognition of standards, the response process, and principles to consider when evaluating such requests.

• **Coronary Drug-Eluting Stents-Non-Clinical and Clinical Studies and Coronary Drug-Eluting Stents-Companion Document:** We appreciate FDA’s reissuance for public comment of these two draft guidances, originally issued in March 2008. Updating these long-standing draft guidances, which had been used by FDA and industry for ten years, will provide information on expectations for the latest stent technology, i.e., absorbable drug-eluting stents. Furthermore, both FDA and industry now have ten years of experience with these draft guidances and have gained insights about the technology surrounding drug-eluting stents and the shared knowledge can be reflected in the revised guidances, once finalized. We consider finalization of these draft guidances to be high-priority.

**Draft Guidance Documents**

Of those draft guidance documents on the A-List, the ones that are of highest priority to our members are:

• **Nonbinding Feedback After Certain FDA Inspections of Device Establishments:** Publication of this guidance in 2019 is a requirement in FDARA section 702. Establishment operators face significant sanctions if they do not correct observations identified during FDA inspections. Consequently, they often invest massive time and resources in corrections without confidence that these measures meet FDA expectations. The nonbinding feedback mechanisms better assures that proposed corrections align with FDA’s view of the remediation that should occur. The mechanism also offers establishment operators the benefit of FDA’s experience.

• **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices:** The current guidance document is over 13 years old (2005) and software practices have changed significantly since that time. Updating this guidance document would reflect current software development life cycle (“SDLC”) practices and documentation.
Of those draft guidance documents on the A-List, we have also identified ones that are of medium priority to our members. While we support the inclusion of these on the A-List, they are of somewhat lower priority. Those draft guidances include:

- **Computer Software Assurance for Manufacturing, Operations, and Quality System Software**: Programmable and automated manufacturing, operations, and quality system tools are increasingly deployed in industry and can provide overall improvement in quality systems and product quality. Guidance about the proper verification, validation, and quality control of computer software and the QSR system would provide helpful clarity.

- **Lifecycle Regulatory Requirements of Medical Device Servicing (Device Servicer vs Remanufacturer)**: AdvaMed continues to advocate for regulation to establish regulatory requirements for third-party servicers and remarketers in the interest of public health and safety. FDA indicated in its May 2018 report to Congress that it does regulate device remanufacturers and that it would issue guidance to distinguish between the two entities. FDA recently issued a white paper on this topic and is planning a public meeting on the topic in December 2018. AdvaMed is still reviewing the white paper and will provide comments on the paper and the workshop to the FDA docket.

- **Guidance on an Accreditation Scheme for Conformity Assessment of Medical Devices to FDA-Recognized Consensus Standards (“ASCA”)**: FDARA requires FDA to issue draft guidance by September 30, 2019. We support the Agency’s use of international voluntary consensus standards to meet regulatory requirements, which will further efforts to harmonize global medical technology regulations.

In addition, we have identified documents for which we would recommend that FDA add the issuance of a draft guidance to the A-List:

- **FDARA Inspection Reforms**: FDARA section 702 requires FDA to issue draft guidance in 2019 for processes and standards beyond the provision of nonbinding feedback. Additional topics include advance notification of inspections, regular communications during inspections, and a standard inspection time to occur over consecutive days. FDA’s draft guidance must cover all the topics specified in FDARA section 702, not just nonbinding feedback.

- **Leveraging Artificial Intelligence (“AI”) and/or Machine Learning (“ML”) in medical devices**: We seek guidance on FDA thinking regarding how to leverage artificial intelligence and/or machine learning in medical devices, particularly regarding how to manage post-deployment dynamic or periodic updates to the algorithm based on new data. We request FDA’s risk-based guidance on submission content and design control evidence needed for using AI and/or ML in a medical device.
Part 2: Retrospective Review Guidances

We support FDA’s retrospective review of targeted guidances. We believe it would facilitate our development of future comments if, in future CDRH Priority lists, FDA could organize the guidances subject to the retrospective review by topic. If FDA continues to organize the retrospective review by year, we believe it would be helpful to do so in chronological order. Nonetheless, for purposes of these comments, we will generally continue to organize our input to the targeted retrospective review by year as organized by FDA.

❖ 1989

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

- **Labeling - Regulatory Requirements for Medical Devices (FDA 89-4203):** Labeling regulations (21 C.F.R. Part 801) have been modified and the guidance document should be updated to reflect those modifications. For instance, the document should reference the UDI requirement and the recent regulation regarding use of symbols. We also recommend aligning the document with ISO standards to support uniformity across countries.

❖ 1999

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

❖ **Premarket Notification [510(k)] Submissions for Testing for Skin Sensitization to Chemicals in Natural Rubber Products:** Labeling of products is now standardized to address this issue.

❖ **In Vitro Diagnostic Fibrin Monomer Paracoagulation Test:** We believe this guidance is out of date.

❖ **Immunotoxicity Testing Guidance:** We would propose reviewing this guidance with respect to more recent FDA guidance on the use of ISO 10993-1.

❖ **Off-the-Shelf Software Use in Medical Devices:** Off-the-Shelf (“OTS”) software use is increasing; many medical devices may contain as much OTS software as original/proprietary software. We recommend that FDA update and revise this guidance to be consistent with current software practices and to align with the premarket and postmarket cybersecurity guidances. Specifically, we would propose revising to include OTS software use in mobile apps and other digital health products, cybersecurity of devices containing OTS software and current documentation required in premarket applications based on Level of Concern.
Guidance on Electrosurgical Devices and the Application of the Performance Standard for Electrode Lead Wires and Patient Cables: The standards referenced in this guidance are out of date.

2009

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

- **Recommendations for Anti-Nuclear Antibody ("ANA") Test System Premarket (510(k)) Submissions**: We believe this guidance is out of date.

- **Manufacturer’s Notification of the Intent to Use an Accredited Person under the Accredited Persons Inspection Program Authorized by Section 228 of the Food and Drug Administration Amendments Act of 2007 ("FDAAA")**: We agree with FDA’s statement that this guidance document should be assessed in light of changes to the Federal Food, Drug, and Cosmetic Act ("FDC Act") since the guidance’s publication.

- **Procedures for Handling Post-Approval Studies Imposed by PMA Order**: We would propose updating this guidance, including consideration of appropriate timelines for post-approval studies in light of lag for reimbursement, product training, patient and physician recruitment/enrollment issues and other delays in uptake of the device.

- **Inspection by Accredited Persons Under The Medical Device User Fee and Modernization Act of 2002 and the FDA Amendments Act of 2007; Accreditation Criteria**: We agree with FDA’s statement that this guidance document should be assessed in light of changes to the FDC Act since the guidance’s publication.

- **In Vitro Diagnostic 2009 H1N1 Tests for Use in the 2009 H1N1 Emergency**: We believe this guidance is no longer relevant.

**Other—Guidances Recommended for Revision**

- **Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"**: We request that FDA update this guidance to provide additional insight into FDA current thinking regarding implementation of biocompatibility standards, including ISO 10993-1, 10993-17, ISO 10993-18 and ISO 18562.

- **Total Product Life Cycle: Infusion Pump – Premarket Notification [510(k)] Submissions**: Safety assurance cases ("SACs") are not a proven risk management tool for infusion pumps and require companies to duplicate information already contained in the 510(k) in a separate assurance case format. Since FDA first adopted SACs, FDA has issued a plethora of guidances which apply broadly to all device types or have special relevance for infusion pumps (e.g.,
cybersecurity and human factors). In addition, standards relevant to infusion pumps have been significantly strengthened since FDA adopted the SAC. We would encourage FDA to revise this guidance to include a reasonable and flexible alternative to the SAC.

- **Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices:** The use of real-world evidence (“RWE”) to support regulatory submissions and other regulatory decisions is increasingly prevalent and important. We would request updated guidance that reflects lessons learned and responds to questions not addressed in the guidance. For instance, the guidance is silent regarding MDR reporting requirements when utilizing the various available registries, databases and other tools for RWE. Understanding FDA’s expectations regarding this topic can support industry in developing strategies in using RWE to support regulatory submissions.

- **Commercially Distributed Analyte Specific Reagents (“ASRs”): Frequently Asked Questions - Guidance for Industry and FDA Staff (withdrawal):** This guidance, issued September 14, 2007, is outdated and should be considered for withdrawal, consistent with FDA’s retrospective review of guidance.

- **Antimicrobial Susceptibility Test (“AST”) Systems - Frequently Asked Questions:** We seek updated guidance reflecting FDA’s recent changes to 510(k) requirements for ASTs, including both discs and automated systems. The guidance document entitled, “Review Criteria for Assessment of Antimicrobial Susceptibility Test Discs” was withdrawn in August 2017 and the guidance document entitled, “Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems,” published in March 2007, does not reflect Agency current practice. Updated guidance outlining FDA current thinking regarding ASTs would provide clarity and transparency.

Thank you for the opportunity to submit these comments.

Sincerely,

/s/

Jamie Wolszon
Associate Vice President
Technology and Regulatory Affairs