U.S. Food and Drug Administration
Center for Devices and Radiological Health

REGULATORY SCIENCE PRIORITIES (FY2017)

FDA | **U.S. FOOD & DRUG**
ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

Executive Summary

September, 2016

In 2015, CDRH published its first set of regulatory science priorities. We have since refined and improved the process for generating our priorities and are issuing our FY 2017 regulatory science priorities.

The following are the current CDRH's regulatory science priorities:

- Leverage "Big Data" for regulatory decision-making
- Modernize biocompatibility and biological risk evaluation of device materials
- Leverage real-world evidence and employ evidence synthesis across multiple domains in regulatory decision-making
- Advance tests and methods for predicting and monitoring medical device clinical performance
- Develop methods and tools to improve and streamline clinical trial design
- Develop computational modeling technologies to support regulatory decision-making
- Enhance the performance of Digital Health and strengthen medical device cyber-security
- Reduce healthcare associated infections by better understanding the effectiveness of antimicrobials, sterilization and reprocessing of medical devices
- Collect and use patient input in regulatory decision-making
- Leverage precision medicine and biomarkers for predicting medical device performance, disease diagnosis and progression

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Introduction

FDA's Center for Devices and Radiological Health (CDRH) is responsible for assuring the safety, effectiveness, performance and quality of medical devices and radiation-emitting products used to treat, prevent, and diagnose disease.

The mission of CDRH is to protect and promote public health. We assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee. We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.

To support this mission, regulatory science at CDRH is aimed at improving the assessment of the safety, effectiveness, performance and quality of medical devices and radiation-emitting products throughout the product life cycle thereby reducing the time to market, improving safety, and making the process least burdensome. CDRH regulatory science also aims to advance our nation's public health by helping to facilitate device innovations and ensuring that devices using state-of-the art technologies are available to improve and maintain Americans' health.

This document provides a summary of CDRH's top ten regulatory science priorities for FY2017. It also provides an overview of the process that CDRH used to generate these priorities.

Regulatory science drivers at CDRH

CDRH defines regulatory science as science in the service of regulation. It helps ensure that regulatory decisions are well-founded and achieve the desired impact on public health, by developing and applying tools, standards and methodologies to study the safety, effectiveness, quality and performance of medical devices and radiation-emitting products under the total product life cycle framework. In addition it facilitates good decision-making in the areas of premarket evaluation, postmarket surveillance, compliance, and communication and it embraces a broad range of disciplines including engineering, medicine, chemistry, toxicology, epidemiology, statistics and social sciences.

Regulatory science at CDRH is aligned with and supports the Center's mission and vision. CDRH regulatory science must be proactive and anticipate regulatory and public health issues, while also being responsive to emergent issues. It covers a breadth of research needs including:

- Investing in infrastructure (software, hardware, data capacity and sources, lab equipment).

- Developing evaluative tools, approaches or methods.
- Addressing long standing questions (such as topics that consistently raise deficiencies or questions during regulatory review).
- Addressing emerging issues.

In response to the 2011 510(k) Working Group and Utilization of Science in Regulatory Decision-making Task Force reports, CDRH created an action plan to implement recommendations made in these reports. This plan included the formation of the [Center Science Council (CSC)](), an advisory body comprised of Center leadership and CDRH staff, to help the Center meet its public health goals. In accordance with the CSC Charter, the Regulatory Science Subcommittee (RSS) was created in 2013 to proactively enhance medical device innovation, development, safety, quality and effectiveness through developing policies and practices that promote the identification and incorporation of new science and technology into regulatory decision-making. These activities support and promote regulatory science at CDRH.

The necessity of identifying CDRH's regulatory science priorities

The CDRH regulatory science priorities serve as a catalyst to improving the safety, effectiveness, performance and quality of medical devices and radiation-emitting products and to facilitate introducing innovative medical devices into the marketplace. These help focus the Center's attention on the most important regulatory science gaps or needs. These priorities will be reassessed and updated periodically to reflect current regulatory science needs.

CDRH envisions a positive feedback model of regulatory science prioritization and implementation to best serve the Center's mission, vision and to promote efficient use of Center resources.
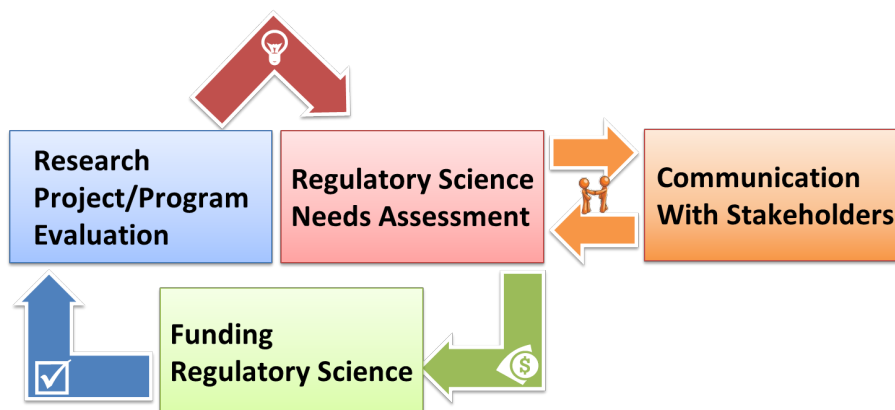
The regulatory science priorities serve as a guide for making strategic intramural research funding decisions to ensure that CDRH research is focused on needs that are relevant and critical to medical devices and radiation-emitting products. The research projects that are funded through intramural sources are evaluated periodically using a

defined set of metrics to ensure the projects are meeting their regulatory science goals and positively impacting public health and regulatory decision-making.

We envision that, collaboratively with our external stakeholders, we can work to maximize the impact of regulatory science research investments which will lead to patients having faster access to more innovative, safer devices with reduced healthcare costs.

Identifying our regulatory science priorities

The regulatory science priorities were identified by the RSS under the direction of the Center Director and the RSS co-chairs. The RSS has used the feedback we received from our staff and senior leadership to improve and optimize the process we used to develop last year's priorities.
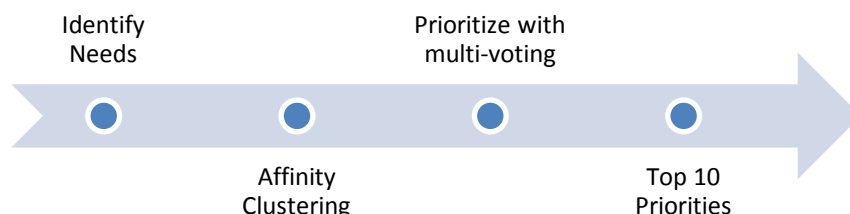
To develop our priorities we used the following approach:

- Regulatory science needs collected in FY2015 were combined with the ones we identified in FY2016.
- Regulatory science needs were clustered according to their affinity.
- The individual needs and their general categories were scored using a set of criteria described below.
- The proposed top ten priorities were reviewed and approved by our senior leadership and Center Director to ensure alignment with our Center's and Agency's priorities.

The regulatory science needs were assessed for their regulatory and public health impact using the following criteria:

- Will addressing the need facilitate medical device innovation and bring new technology to market?
- Will addressing the need enhance or expedite the availability of medical devices and radiation-emitting products while maintaining their safety and effectiveness?
- Will addressing the need facilitate rapid identification of problems, improve our postmarket understanding of the benefit-risk profile of devices or radiation-emitting products and aid future premarket device clearance or approval?

- What is the public health impact of the need?

Differences between the priorities of FY2016 and FY2017

We have increased the outreach within the Center during the regulatory science needs collection period this year resulting in more needs submissions from staff. As a result we were able to identify new topic areas (i.e. clinical trial design and precision medicine) as well as describe existing topic areas in greater detail. Although the area of human factors is not prominently identified as a priority, it is still an unmet need and is reflected in the descriptions of other FY 2017 top ten priorities (e.g. infection control and predicting medical device clinical performance). Patient reported outcome measures and patient preference were combined as patient input and the reprocessing priority was renamed to the more inclusive topic of infection control.

CDRH regulatory science priorities for FY2017

The top ten CDRH regulatory science priorities are listed below. The descriptions of each of the ten priorities reflect the themes of similar needs that clustered together to form the topic area:

Leverage "Big Data" for regulatory decision-making

Big Data warehouses that host genomics, anatomical, biological, clinical trial and device performance and safety data contain a wealth of scientific and clinical information relevant to medical devices. Data from real-world experience, insurance, Medicare and Medicaid claims, clinical trials, imaging and next generation sequencing can help improve medical device designs, become training sets for artificial intelligence devices or be used to develop precision diagnostics. Information from these data warehouses can also help detect potential emerging post-market issues.

Harvesting, validating organizing and disseminating information in these data warehouses can streamline regulatory decision-making throughout the medical device total product lifecycle. It is fundamental to develop the necessary infrastructure, statistical or analytical tools and models, information retrieval and processing for Big Data, relevant to enhancing safety, performance and quality of medical devices.

Modernize biocompatibility and biological risk evaluation of device materials

To determine the safety profile of implantable or patient-contacting medical devices, it is critical to perform biocompatibility evaluation to assess the risk of adverse events. This helps us understand and address the risks posed by the potential presence of harmful chemicals or immune response triggers such as contaminants, manufacturing materials, residues and byproducts as well as device degradation byproducts.

While animal studies have historically been used to predict long-term safety and effectiveness, tests for carcinogenicity, reproductive toxicity and systemic toxicity are expensive, time consuming, use large numbers of animals and sometimes do not provide results that are easily translatable into a human risk assessment. New, less burdensome approaches that are more patient-centric and predictive of real-world device performance are needed to modernize and transform biocompatibility evaluation of medical devices and their materials. The biocompatibility review of device materials could be further enhanced by developing acceptance criteria, which could include multidisciplinary evidence obtained from integrating chemical characterization, computational modeling, device surveillance and emerging risk assessment tools. Modernizing biocompatibility and biological risk evaluation will reduce healthcare costs and patients would have access to safer devices faster.

Leverage real-world evidence and employ evidence synthesis across multiple domains in regulatory decision-making

Currently most regulatory decisions are based on information provided by manufacturers while data from traditional clinical trials is mostly limited to higher risk devices. A vast amount of observational data on device use and performance can be found in healthcare (e.g., electronic health records and claims), registry (device, procedural, disease), and clinical trial (large simple, pragmatic) databases, as well as peer reviewed publications.

These data is underutilized in the review and evaluation of medical devices. Leveraging real-world evidence can supplement traditional clinical data and inform regulatory decision-making. Employing evidence synthesis from across multiple domains will accelerate the medical device pathway to market and improve the detection of potential problems. To enable the use of disparate observational data sources in the regulation of medical devices, investment in data analytics and infrastructure is needed.

Advance tests and methods for predicting and monitoring medical device clinical performance

To better predict and monitor medical device clinical performance, we identified three areas regulatory science can help establish a link between preclinical data and medical device clinical performance: the impact of advanced materials and manufacturing, accelerated aging methods and the effectiveness of smart implant monitoring.

There is a gap in the availability of tools and methodologies that can assess the impact of materials, surface coatings and advanced manufacturing techniques (e.g. 3D printing) on the quality, performance and safety of medical devices. To bridge this gap, we

must improve our understanding of material degradation through processes such as oxidation, corrosion, fretting, flaking and chemical absorption. These degradation processes have a direct impact on the mechanical stability and clinical performance of medical devices and have been associated with adverse events and device recalls.

Accelerated aging and degradation methods are used less frequently due to a lack of validated options. Advancing accelerated testing methods that are validated and demonstrated to correlate with clinical performance would serve to reduce medical device time to market and streamline their approval process.

A new generation of smart implants is emerging. These implants can monitor and report data about the device performance and function, allowing clinicians to better predict potential failures. Non-clinical methods to evaluate the long term monitoring capabilities and predictive capacity of smart implants are necessary and can facilitate bringing this technology to market.

Develop methods and tools to improve and streamline clinical trial design

To evaluate the safety and effectiveness of higher risk medical devices, we require clinical evidence, typically obtained from clinical trials. Medical device clinical trials are faced with unique challenges. For example, some clinical trials for screening, diagnostic or therapeutic medical devices have difficulty recruiting sufficient numbers of patients because of low disease prevalence. A significant number of clinical trials fail due to false hypothesis or endpoints that do not capture all failure modes. The traditional concept of placebo controls borrowed from drug trial designs is not always applicable to medical devices, particularly for active implants.

To address these challenges, we need improved statistical methods as well as clinical trial design tools that would help us understand the safety and effectiveness of medical devices. Examples of tools and methods that are needed are: adaptive clinical trial designs and meta-analysis methods for establishing non-inferiority margins, tools to determine the minimum number of subjects for rare diseases and novel methods for using placebo controls.

Addressing these challenges will increase the success rate of clinical trials, streamline the device approvals process and reduce healthcare costs.

Develop computational modeling technologies to support regulatory decision-making

Computational modeling and simulations are successfully used in many areas for device development and evaluation and for streamlining and reducing the size of animal and human clinical trials. Computational tools have a great potential for reducing healthcare costs. Despite the success to date, there remains a need for improved com-

putational and statistical tools in many areas. For example, improved multi-modality imaging simulation (e.g., x-ray, CT, MRI, US, optical) and realistic, anthropomorphic digital reference material (i.e., phantoms), could enable robust predictions of imaging system performance for a wider range of patient populations.

For example, advancing virtual and hybrid clinical trials for medical imaging will allow us to evaluate new systems, protocols, disease screening and diagnosis. By improving the simulation of implants such as articulating orthopedic devices we can better predict their clinical performance and safety and identify possible adverse events that are not captured by the current battery of non-clinical bench tests.

These sophisticated tools have the potential to enhance, enrich and accelerate medical device evaluation. They can focus and streamline clinical trials, especially in populations where a disease has low prevalence or when implanted devices are expected to function and perform for many years.

Developing representative modeling, simulation and statistical techniques in conjunction with methodologies to assess their credibility, can facilitate faster and safer pathways to market, utilizing least burdensome approaches.

Enhance the performance of Digital Health and medical device cybersecurity

Digital health and cybersecurity are some of the fastest growing areas impacting medical devices. Devices that store patient information are increasingly capable of connecting to other devices, internal networks, the internet or to portable media, exposing them to cybersecurity threats.

To ensure these technologies and technological environments achieve the desired public health impact, research is needed to enhance the performance and cybersecurity of medical devices and software. One way to achieve this is to conduct studies to identify which categories of software modifications could have significant negative effects on device safety or effectiveness. Research is also needed to adapt the common vulnerability scoring system, a standardized method for rating information technology vulnerabilities to include the unique considerations of the healthcare environment. Accomplishing this will enhance the effectiveness of medical device vulnerability assessment. We can also use horizon scanning to identify, filter and prioritize the evaluation of new and emerging health technologies.

By enhancing the performance of digital health and strengthening medical device cybersecurity we will improve the safety and reliability of interconnected medical devices.

Reduce healthcare associated infections by better understanding the effectiveness of antimicrobials, sterilization and reprocessing of medical devices

Contact with infected objects and medical devices is a leading cause of healthcare associated infections. To help address this major public health challenge, CDRH is interested in employing regulatory science in three areas: antimicrobials added to medical devices, sterilization of implantable devices and reprocessing of reusable medical devices.

Current methods for assessing the effectiveness of antimicrobials added on devices do not always consider conditions of use. Due to the practical challenges for conducting clinical trials to evaluate anti-biofilm effectiveness, there is a need to develop standardized, clinically relevant test methods to measure their effectiveness. These methods can include clinically predictive in vitro and in vivo tools and models.

Reusable devices are commonly used in patient care and the designs of many have increased in complexity over time making them more challenging to reprocess. Reusing medical devices introduces the risk of infection transmission to patients between uses if not appropriately reprocessed.

To minimize patient harm from inadequately reprocessed devices and to enhance the safety, effectiveness, performance and quality of these devices, it is critical to develop a comprehensive approach to address the effectiveness of reprocessing techniques. Approaches should include enhancing device design to identify features that ensure clean-ability, incorporating human factors into the drafting of reprocessing instructions, development of novel reprocessing methodologies, validation of methods for reprocessing including cleaning and high level disinfection, development of validated markers indicative of successful reprocessing and surveillance of reprocessed devices for adverse events in healthcare facilities.

Collect and use patient input in regulatory decision-making

Patients are increasingly providing their input to spur patient-centric medical product development and to inform patient-centric regulation. Patient preference studies can be used to determine the outcomes that are most important to patients or identify subpopulations of patients within a disease group whose benefit-risk tradeoffs differ from the larger population that may impact regulatory decisions.

To utilize patient preference information most effectively, we need to study the different methods and tools to elicit and collect high quality patient preference information.

Identifying the attributes, such as how much risk a patient living with the burden of a disease would be willing to tolerate, in exchange for a certain benefit and the factors associated with this determination, is critical to informing the regulatory decision-making. At the same time we must also understand how to best communicate attributes and benefits, risks, uncertainly and harm to patients.
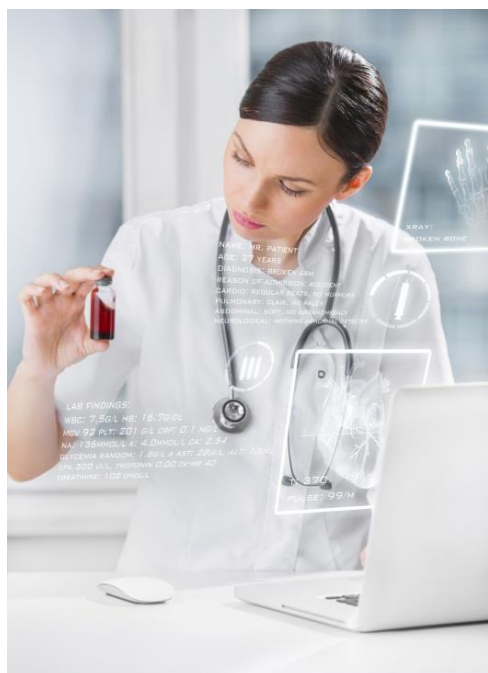
Leverage precision medicine and biomarkers for predicting medical device performance, disease diagnosis and progression

An emphasis on precision medicine during the device lifecycle could be a means to obtaining better focused indications and clinical studies as well as device optimization. Regulatory science for precision medicine includes research efforts such as developing patient-specific cell models to test medical devices. These endeavors could provide non-clinical methods for predicting device-drug interactions and the scientific foundation for stem-cell diagnostic tests for use in precision medicine. We need to assess the consistency and variability of these tests relative to clinical outcomes in order to facilitate regulatory approval and make the resulting technologies available to patients.

Development of clinical diagnostic assays, software and other tools that promote standardization of in vitro tools for a precision medicine approach that predicts clinical performance are necessary to expedite the use and to improve the quality of medical devices.

Characterization data of existing samples and analytes is needed where no agreed-upon reference standards exist. For areas such as next generation sequencing and precision medicine, such characterization may take effort and data input from multiple stakeholders. Tools and related infrastructure are necessary to coordinate both physical reference materials and all available data in a way that facilitates easy access to device developers. For example, the areas of in vitro diagnostics, next generation sequencing and precision medicine can benefit from the development of a quality database that describes the characterization of reference panel materials and facilitates the transition from current laboratory developed and research tests to the in vitro diagnostics market.

The identification of biomarkers is crucial for diagnosis of mild forms of certain types of trauma (e.g. traumatic brain injury) and early stage disease, to ensure early treatment during critical therapeutic windows. Biomarkers can play a critical role in evaluating disease progression and can also aid in the development of novel therapeutic and medical device treatment modalities. Further, biomarkers that are indicative of biomaterial (i.e., tissue-specific biomarkers) or device performance in patient subgroups and predict individual susceptibility to certain adverse events are required for

development and implementation of device-related precision medicine applications. An efficient discovery of device-related biomarkers and generation of biomarker-based functional evidence for clinical and regulatory decision-making requires reutilization and integration of Big Data.