CDRH's Regulatory Science Priorities

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Introduction

The 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.

To support CDRH's mission, regulatory science 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.

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. As part of its mission, the RSS develops and regularly updates CDRH's regulatory science priorities.

CDRH's Regulatory Science Priorities

The purpose of CDRH regulatory science priorities are to:

- serve as a catalyst to improving the safety, effectiveness, performance and quality of medical devices and radiation-emitting products.
- facilitate introducing innovative medical devices into the marketplace.
- focus the Center's attention on the most important regulatory science gaps or needs.
- serve as a guide for making strategic intramural research funding decisions to ensure relevancy of medical devices and radiation-emitting products.

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

The process of 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. In the previous regulatory science prioritizations

at CDRH (FY16 & FY17), a call for regulatory science needs was made to Center staff. Upon comparing the final priority lists generated from those calls, very little changed to the overarching categories/themes of the priorities, and many of the priorities aligned with the Center's 2018-2020 strategic plan. Therefore, the decision was made to retain the previous categories and focus on revising the priority descriptions.

The priorities were developed using the following approach:

- Subject matter experts (SMEs) within CDRH were identified for each of the priority categories.
- Small focus groups consisting of RSS members and SMEs were formed to identify important regulatory science challenges and areas of opportunity within their priority area that should be addressed during the next several years.
- The individual challenges and opportunities were refined and prioritized 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.

Assessment of our regulatory science priorities used 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?

CDRH regulatory science priorities

The top ten CDRH regulatory science priorities are listed alphabetically below.

Leverage "Big Data" for regulatory decision-making

Rigorous evaluation of health technologies can benefit immensely from multidisciplinary evidence synthesis utilizing "big data"[1] from sources capturing genomic, anatomical, biological, clinical, epidemiologic, patient experience, and other information pertaining to medical devices and their interactions with the human body. Synthesized evidence from such data sources can inform medical device evaluation, optimize development of new designs and device iterations, support the development of datasets for training and testing artificial intelligence (AI) devices, be used for developing precision diagnostics and therapeutics to improve device-related health care, or enhance safety signal detection.

Objectives:

- Develop methods to design and deploy large datasets and methods for mining such databases for signals and new information. This includes a fundamental understanding of database design and both theoretical and practical experience in developing data mining methods/tools.
- Develop tools and methods for the assessment of inferences derived from Big Data engines, including:
    - o Modeling tools for simulating or augmenting Big Data datasets with relevant statistical properties for use in the development of validation of strategies for the evaluation of Big Data AI based medical devices.
    - o Methods for the characterization of dataset sample size adequacy, as well as coverage of relevant patient and test heterogeneities while accounting metrics for quality
    - o Standards for training, validation, and testing of Big Data AI systems.
    - o Tools that enable Big Data algorithm development and assessment in the presence of weak or missing reference standards as well as multilevel truth by disease class, anatomical location, and other parameters.
    - o Statistical methods for quantitative decision analysis from diverse data sources.
    - o Data visualization tools that facilitate interpretability of signals and inferences derived from Big Data sets.

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[1] For the purpose of this document, Big Data refers to the study and applications of data sets that are so big and complex that traditional data processing application software are inadequate to deal with them. Big Data generally encompasses characteristics of Volume, Variety, Velocity, Veracity, Variability, and Complexity. Source: https://en.wikipedia.org/wiki/Big_data and https://www.sas.com/en_us/in-sights/big-data/what-is-big-data.html

Modernize biocompatibility and biological risk evaluation of device materials

Biocompatibility evaluations are performed to support the safety profile of patient-contacting medical devices. While traditional biocompatibility assessments have involved extensive animal testing, the results from these animal studies may not be predictive of the outcomes experienced by patients and a priority for the FDA (as outlined in the FDA's Predictive Toxicology Roadmap) is to enhance the agency's predictive toxicology capabilities. Towards that goal, efforts should be made to employ alternatives to *in vivo* testing such as leveraging information from *in vitro* testing, medical device adverse event reports, electronic health information derived from registries, healthcare claims data, and electronic health records. In addition, for more accurate, timely adverse event monitoring and reporting to occur, there is also a need to generate consensus on the terminology to be used when describing adverse incidents related to implanted devices.

To enhance biocompatibility efforts in general, there should be a focus on optimizing testing used to support biocompatibility evaluations, developing alternatives to in vivo studies, and standardizing methods and terminology.

Objectives:

- Optimize biocompatibility test methods to include:
  - Sample preparation and chemical characterization methods for hydrogel, in situ polymerizing absorbable, and nanomaterial devices
  - Assessment of tissue remodeling and proinflammatory potential
  - Identification of clinically relevant biomarkers
- Advance alternatives to *in vivo* biocompatibility testing, including models (e.g. *in vitro, ex-vivo*, etc.) and frameworks capable of leveraging clinical, animal, and material information not obtained through biocompatibility testing to be used as a substitute or to justify performing more focused safety analyses
- Develop regulatory science-based qualification criteria for in vitro alternatives to in vivo biocompatibility testing
- Define chemical equivalence more explicitly to include developing standard methods or approaches for determination
- Standardize terminology pertaining to implant-related adverse outcomes in humans based on comprehensive review of medical device adverse events reports (MDRs) and electronic health information to identify clinical signs of toxicity
- Develop biocompatibility testing with improved sensitivity, greater predictability, and low incidence of false negatives to make it possible to detect and mitigate potential issues earlier in the product life cycle

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

Real-world data (RWD) are those routinely generated during healthcare delivery and collected in sources such as electronic health records, healthcare claims databases, health-monitoring devices, and registries. When quality is assured, evidence generated from these data (i.e. real-world evidence, or RWE) can provide valuable information on the safety and effectiveness of medical devices. From issuing guidance on the use of RWE to initiatives such as the National Evaluation System for health Technology (NEST) and the Medical Device Safety Action Plan, CDRH has demonstrated a commitment to improving the use of RWE and ensuring that the FDA is consistently first among the world's regulatory agencies to identify and act upon safety signals related to medical devices.

Continued innovation in real-world data (RWD) infrastructure and methodology is needed to overcome the challenges to leveraging the full potential of RWE. Specifically, development and validation of minimal core datasets and methodologies are needed to improve the efficient capture, linkage, and analysis of data from real-world data sources. For RWD to serve as a source of evidence for regulatory decision-making, it must be reliable and clinically relevant to address premarket and post-market regulatory questions. Stakeholders must work collaboratively to develop data quality standards and encourage their adoption to improve the quality, interoperability and usability of RWD for medical device evaluation. In addition, regulators need tools to enhance their ability to assess the fitness of use and capability of RWD to address regulatory questions throughout a device's lifecycle. Finally, to realize the objectives described in the CDRH Medical Device Safety Action Plan, novel methods are needed to support active surveillance and advance signal detection and evaluation using RWD sources.

Objectives:

- Advance methodologies to generate clinical evidence from RWD sufficient to support regulatory use by:
    - Incorporating RWD sources in innovative clinical trial designs
    - Developing and validating tools and models that assess fitness of RWD to support regulatory decision making
    - Developing and validating methods to predict device performance using RWD
    - Identifying high priority areas for development of RWD source methodology that meet stakeholder needs using a collaborative approach
- Develop core data elements and data sets for device categories to support regulatory decision making
- Develop standards for data quality and data sources that increase the quality, interoperability, and usability of RWD for supplementing the information typically used for clinical trials

- Design and optimize data infrastructure to facilitate information exchange and data extraction.

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

Monitoring and predicting the clinical performance of medical devices is crucial to ensuring their quality, safety, and effectiveness. It is also essential for promoting innovation and reducing the regulatory burden for clinical data. These efforts must also align with those involving the use of big data and real-world data (RWD) within the medical device space.

Objectives:

- Develop new tools to assess emerging paradigm shifts in integrative medicine (e.g., wearable technology, telemedicine)
- Use virtual reality, artificial intelligence, and simulators to characterize and optimize human factors and their impact on device performance to reduce patient and operator variability
- Develop transformative technologies to establish new clinical performance metrics:
  - Assess device performance using microphysiological systems (e.g., organ-on-a-chip with human cells)
  - Identify, assess, and develop biomarker-based methods
  - Compare image-based and invasive (e.g. histology, cannulation) evidence to evaluate subject variability and long-term device performance
  - Evaluate monitoring and predictive technologies through verification, validation, and uncertainty quantification and by context of use
- Validate accelerated testing approaches to predict long-term functional performance to make new technologies available to patients faster and safer
- Improve biological relevance of numerical and physical models of human anatomy and physiology to reduce clinical trial burden and improve predictive power of bench tests
- Use the science of "dynamic materials" and engineering principles to understand and manipulate biological phenomena (e.g., biofilms, regenerated tissue, metastasis) and to inform the design of biomaterials.

Develop methods and tools to improve and streamline clinical trial design

To evaluate the safety and effectiveness of medical devices, the FDA may require evidence obtained from clinical studies. Medical device clinical studies face unique challenges compared to other medical products. For therapeutics, the double-blind, randomized, placebo-controlled study design would not pose too many logistical and ethical challenges for majority of clinical trials for drugs. In contrast, despite

investigators' best efforts, such ideal study design is not always technically or ethically feasible for medical devices. For example, it may not always be ethical to include a highly invasive procedure to place sham implantable devices or to mask the treatment assignments from care providers of study participants. Furthermore, some medical devices (e.g., novel imaging devices in radiology and pathology including artificial intelligence applications in these areas) are evaluated in reader studies, which measure the diagnostic performance of physicians using patient images to detect disease.

To address these and other challenges, research efforts should focus on developing consistency, exploring other data sources, and promoting novel clinical trial designs and methodologies that may develop into experiential training for FDA staff, industry and clinicians.

Objectives:

- Promote novel methodologies for clinical trial design by:

    o Developing novel clinical trial designs and methodologies (especially for diagnostic and imaging devices)

- Enhance consistency within clinical trial design and execution by:
    o Conducting validation studies of novel versus traditional methods to ensure validity and reliability of outcomes

    o Developing a tracking system of studies using other data sources and novel methodologies for regulatory decision making

    o Developing tools and standards for consistent use of other data sources in regulatory submissions

Develop computational modeling technologies to support regulatory decision-making

Computational modeling of medical devices can streamline development and reduce burdens associated with pre-market device evaluation. It can also reveal important information not available from traditional *in vivo* or *in vitro* assessments such as serious and unexpected adverse events that are undetectable within a study sample but occur frequently enough within the intended population to be of concern. As interest in medical device related computational modeling grows, it will be important to both monitor current usage and identify areas

where simulation might be more broadly leveraged to enhance public health. The appropriate and expanded use of modeling and simulation in regulatory submissions requires stakeholders to develop processes and approaches that promote consistency in the way modeling is conducted and reviewed. To best leverage the potential of computational modeling for medical devices, our focus should be on understanding its current usage and identifying unexplored gaps/opportunities, establishing criteria for simulation best practices, and developing validated models and example use cases.

Objectives:

- Establish infrastructure for tracking simulation usage within regulatory submissions in real-time including creating a database of submitted computational models
- Identify device areas in which experimental test data is difficult to obtain and focus development efforts within those areas
- Develop benchmarks and end-to-end examples of credible models in multiple device areas using the ASME Verification and Validation 40 (V&V40) standard (e.g., in the form of "mock submissions")
- Establish appraisal metrics for companies to certify their simulation practices (model development and validation processes, etc.)

Enhance the performance of Digital Health and medical device cybersecurity

Digital health and cybersecurity are related, but distinct areas within the medical device space. Digital health is the broader category and includes electronic technology that generates outputs utilized in medical decision-making a such as artificial intelligence (AI), software as a medical device (SaMD), and mobile medical applications. Cybersecurity is the protection of electronic medical devices from criminal or unauthorized access and manipulation.

Innovative methods and technologies will need to be developed to protect the integrity of medical device performance and enhance security as devices become more interconnected and autonomous which makes them increasingly vulnerable to cyberattacks and unobserved malfunction. Medical device stakeholders need a firm understanding of cybersecurity considerations, risks, and mitigation options at the device and systems levels. Further, as interest increases in using AI in medical devices, developing approaches to evaluating AI, particularly within an intended context of use, will be important to enhance consistency of regulatory submissions and the review process.

Objectives:

- Pilot the use of a benchmark test set for the use of artificial intelligence (AI) in medical devices
- Develop a full test case and/or methodology for adaptive algorithm use in medical device submissions

- Develop framework on how to structure post launch real world evidence data to support clinical claim modification
- Investigate and evaluate strategies to detect and assess the performance of artificial intelligence algorithms including employing synthetic data sets, leveraging the Medical Device Development Tool program, identifying novel methods, and conducting statistical analyses of regulatory device submissions
- Develop and deploy secure medical device reference architectures that support the needs of the clinical use environment by:
  o applying formal methods
  o leveraging hardware and software reuse
  o facilitating timely updates and patching
  o highlighting failures and collecting forensically sound evidence of performance
- Develop methods for efficiently communicating design vulnerabilities such as tools for analyzing cybersecurity risk (e.g. threat modeling, attack trees)

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

The risk of patient infection resulting from improperly processed medical devices is a critical concern. As medical devices become increasingly complex in design and materials, reprocessing challenges for these devices increase correspondingly. A multidisciplinary and collaborative approach, by the infection control community and standards bodies will improve patient safety, as medical devices continue to evolve.

Objectives:

- Developing and characterizing methods for continuous improvement and validation of the performance of reprocessing (cleaning, disinfection and sterilization) of reusable medical devices.
- Developing and validating methods for the detection, characterization, removal and prevention of biofilms and biofouling, with focus on development of clinically-relevant biofilm models representative of real world medical device concerns.
- Developing and validating methods for evaluation of the performance and device-specific risks/benefit analyses associated with the use of antimicrobial agents and materials.

Collect and use patient input in regulatory decision-making

Patients are the experts in living with their disease or condition. Increasingly, we are looking to patients to help inform patient-centric medical product development, including the outcomes that are important to patients and the benefit-risk tradeoffs patients are willing to accept. The systematic aggregation of patient perspectives includes

patient preference information (PPI) and patient-reported outcomes (PROs) which can be used as valid scientific evidence in medical product development. PPI can be used to determine outcomes that are most important to patients, set performance goals, or identify subpopulations of patients, within a disease group, whose benefit-risk tradeoffs differ from the larger population. PROs are a measurement of a patient's health status that comes directly from them without interpretation by anyone else. To utilize patient input most effectively, stakeholders need to develop and refine different methods and tools to elicit, collect, and analyze high quality PPI as well as develop, adapt, and use PRO measures in a fit-for-purpose context.

Objectives:

- Explore different methodological approaches to adapting PRO measures to be fit for purpose
- Develop methods to incorporate patient-generated data sources with other data sources to generate valid scientific evidence
- Explore methods to recruit diverse patients and understand how patient heterogeneity may or may not affect the generalizability of the results
- Understand the applicability of patient input studies in a regulatory context
- Develop methods to determine the appropriate sample size for patient input studies
- Develop methods and data sources to identify and recruit patients to provide input for research studies.

Leverage precision medicine and biomarkers for predicting medical device performance, disease diagnosis and progression

Precision medicine and biomarkers are crucial for diagnosis, patient treatment, and assessing disease progression. It is important to learn, evolve, and integrate information as it develops over time and to understand how standards, methods and options for Precision Medicine work in in the clinical setting.

Objectives:

- Develop methods to assess decision making and therapeutic tools, triage and screening of biomarkers, and companion or complementary diagnostics
  - o Define what clinical information is necessary to address Precision Medicine decision-making for a given product or product category
  - o Extract and analyze clinical efficacy data to better understand how results of clinical testing relate to performance
  - o Develop *in-silico* reference data for the most prevalent diseases requiring medical device intervention (cardiovascular, neuro)
  - o Develop MDDT tools for evaluating biomarkers (e.g., annotated databases, statistical tests, etc.)

- Define the context and intended use of biomarkers (e.g., tissue biomarkers, molecular biomarkers, blood and sputum, and imaging) to address clinical or pre-clinical outcomes and ensure meaningful use of medical devices
  - Establish valid biomarker clinical association links to the intended use
  - Research and develop imaging methods to find correlations between bi-omarkers in clinical use and outcome (e.g., proteomics/genomics, genetic research, epidemiological studies)
- Research new, and expand upon current, methods in precision medicine to im-prove personalized medical devices
  - Create cell-based human and microbial reference materials
- Collaborate with stakeholders to create consistent standards and best practices that support patient health and safety (e.g., industry, Centers for Medicare and Medicaid Services, etc.)
  - Determine necessary requirements for analytical validation and cross-validation to ensure safety and effectiveness
  - Promote data sharing through collaborative communities and incentive programs.