How is FDA Supporting Medical Device Innovation

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U.S. Food and Drug Administration

AAKP/GW University
Inaugural Global Innovations in Patient-Centered Kidney Care Summit
Washington, DC
May 23, 2019
CDRH’s Mission is: Protect and Promote Public Health

Assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation emitting products.....

Provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee.....

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.
Patients are at the Heart of What We Do

CDRH Vision
Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world
Are you part of the Problem or part of the Solution?
The Challenge

1,800 Dedicated “CDRHers”

190,000 Regulated Devices

18,000 Device Manufacturing Firms

21,000 Device Manufacturing Facilities Worldwide
Little has Changed in Dialysis Technology in Nearly 60 Years

Outcomes Remain Poor

“If we are going to keep patients alive by artificial means, we then incur the responsibility to see that it is a good life and an enjoyable life.”

– Willem Kolff, 1968, pioneer of hemodialysis and artificial organs
<table>
<thead>
<tr>
<th></th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk level</strong></td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Sufficient information for controls?</strong></td>
<td>General</td>
<td>General &amp; Special</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Premarket review?</strong></td>
<td>Mostly exempt</td>
<td>510(k) De Novo</td>
<td>PMA</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>Tongue depressor, Stethoscope</td>
<td>Endoscopes Infusion pumps Dialysis systems Dialysis catheters</td>
<td>Cardiac ablation catheters, Coronary artery stents Extracorporeal columns</td>
</tr>
<tr>
<td></td>
<td>Class II</td>
<td>Class III</td>
<td></td>
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<tr>
<td>----------------------</td>
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<td></td>
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<tr>
<td>Premarket Path</td>
<td>510(k)</td>
<td>De Novo</td>
<td>PMA</td>
</tr>
<tr>
<td>Predicate?</td>
<td>Identified</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Appropriate for ...</td>
<td>“me also”</td>
<td>Innovative lower risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Regulatory standard</td>
<td>“substantial equivalence”</td>
<td>Controls provide reasonable assurance for reclassification</td>
<td>Reasonable assurance of safety and effectiveness</td>
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<tr>
<td>Permission</td>
<td>“cleared’”</td>
<td>“granted”</td>
<td>“approved”</td>
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<tr>
<td>Clinical data?</td>
<td>10-15%</td>
<td>Most</td>
<td>Almost always</td>
</tr>
<tr>
<td>Time to approval</td>
<td>4-6 months</td>
<td>6-9 months</td>
<td>1-2 years</td>
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</table>
FDA as Innovator: Strategy

- Revolutionize the Evidence Generation Paradigm
- Transform the Device Regulatory Framework
- Evolve the Role of the FDA
Public Private Partnerships

• Medical Device and Innovation Consortium (MDIC)
• Kidney Health Initiative (KHI)
• KidneyX Innovation Accelerator
MDIC is a public-private partnership created with the sole objective of advancing regulatory science of medical devices to more effectively and efficiently bridge the “Valley of Death” for patient benefit.
2012: A public private partnership between the American Society of Nephrology (ASN) and the US Food and Drug Administration (FDA)

Has brought stakeholders together to foster innovation to address patient’s need for alternatives to dialysis for renal replacement therapy (RRT)
Technology Roadmap
for Innovative Approaches to Renal Replacement Therapy

Goals of the KHI RRT technology Roadmap:
• Spur innovation in the RRT field
• Attract industry/academic investment in developing RRT solutions
• Encourage internationally oriented multi-disciplinary approach
• Accelerate availability and adoption of commercially viable solutions
• Ensure patient/care partner preferences are incorporated
• Optimize processes regarding reimbursement
Future State: Improved QoL

**IMPROVED PATIENT QUALITY OF LIFE**

- Minimized impact/intrusion of therapy on family and social life
- Improved ability to work and travel
- Increased mobility and physical activity
- Increased treatment choices
- Liberalized diet and fluid regulation
- Reduced medication burden
- Reduced disease and treatment complications
- Reduced disease maintenance and interventions
- Reduced financial impact

Enhanced Dialysis
Portable/Wearable
Biohybrid/Implantable
Regenerated Kidney
KidneyX Innovation Accelerator

- Kidney Innovation Accelerator (KidneyX) is a public-private partnership between HHS and ASN intended to accelerate breakthroughs and innovations in kidney care
- Provide merit based, non-dilutive funding via a series of prize competitions
- Supports coordination across HHS Agencies (FDA, CMS and NIH) to clarify the path toward commercialization and patient access to innovative products
- The RRT Roadmap will guide the priority funding choices of KidneyX 1.0
- FDA has played a key role in these efforts
Multiple Approaches to Supporting Device Innovation

- Pre-Clinical Testing
- Clinical Studies
- Pre-Market Application
- Post-Market

- Real World Evidence
  - Breakthrough Devices Program
  - Early Feasibility Studies
- Pre-/Post-Market Balance
- Patient Engagement
Early Feasibility Study Program

- Voluntary, informal program for devices in an early stage of development to be evaluated in a small human clinical study in the US

- Flexible approaches to address risk while protecting human subjects

- Tools for communicating device evaluation strategy

- Significant training effort and identification of representatives from each pre-market review area
Key Policies for EFS Program

• “Right Testing at the Right Time”
  • Comprehensive testing during early phases of device development may add cost without significant return
  • However, informative nonclinical testing should be completed

• Possible to leverage data from earlier versions of the device

• Unknowns and risk can be addressed by...
  • Using clinical mitigations to provide patients with extra protection
  • more frequent/detailed reporting

• Provides tools for communicating available data to CDRH
  • Device evaluation strategy based approach
EFS Program at a Glance

Significant FDA interaction from first Pre-Submission to EFS IDE review
Over 200 EFS approved

Based on FY18 data
Innovation Pathway 2.0
End Stage Renal Disease Innovation Challenge

- 32 Device applicants; 3 selected
- Collaboration Phase – Summer 2012

**HemoAccess Valve System**
- A mechanical valve system allowing blood flow into AV graft only during dialysis

**Wearable Artificial Kidney**
- A miniaturized wearable dialysis machine to provide hemodialysis

**Implantable Bio-Artificial Kidney**
- Filters toxins from blood, and provide other biological functions giving patients 24/7 dialysis
Breakthrough Devices Program

2015

FDAs EAP Final Guidance
April 13, 2015

2016

21st Century Cures Act
December 13, 2016

2017

2018

Breakthrough Devices Program Guidance
December 18, 2018

“(B) take steps to ensure the conduct of clinical trials is as efficient and practicable, when scientifically feasible.

“(C) facilitate, when scientifically appropriate, expedited and efficient development and review of the device through utilization of timely postmarket data collection with regard to application for approval under section 515(e); and
Breakthrough Program Purpose

- Help patients have more timely access to devices
- Expedite device development and review for certain medical devices
- Work with sponsors to define a roadmap to FDA marketing authorization
  - Breakdown perceived barriers
  - Collaboration & interaction in a positive feedback loop
- Devices subject to PMA, De Novo and 510(k) that:
Breakthrough Eligibility & Criteria

• 1: provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions;

and

• 2A: that represent breakthrough technologies; or
• 2B: for which no approved or cleared alternatives exist; or
• 2C: that offer significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients’ ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or
• 2D: the availability of which is in the best interest of patients.”
Program at a Glance – Granted Designations
as of May 1, 2019

- 2015 reflects data from publication of final EAP Guidance on 4/13/2015
- 2019 reflects data from first 4 months – 149 devices

* 2015 reflects data from publication of final EAP Guidance on 4/13/2015

2019 reflects data from first 4 months – 149 devices
Least Burdensome Provisions

The Least Burdensome Provisions: Concept and Principles

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE
This draft guidance document is being distributed for comment purposes only.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1065, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

2000 – FDAMA – suggested format for developing and responding to deficiencies

2002 – FDA guidance – focus on statutory and regulatory criteria (eg., need to know vs nice to know)

2017 – MDUFA 4 and 21st Century Cures – “the minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time”, decisions based on sound science, use of alternative approaches, use of real world evidence, and effective use of regulatory resources
Least Burdensome Provisions

Does not raise or lower the regulatory “bar”......

....and does not translate into “I don’t want to do it”
Device Patient Preference Initiative
Partnering with Patients

Patient Reported Outcomes

Patient Preference Information

Patient Engagement Advisory Committee

JAMA - Engaging Patients Across the Spectrum of Medical Product Development
Early engagement with patient community and FDA at Kidney Health Initiative (KHI) public workshop in 2015

Development of patient preference study consistent with FDA Patient Preference Information guidance through the presubmission process

Expanded indication allows patients trained to perform solo home hemodialysis to dialyze at home without a care partner during waking hours.
Submission Background: NxStage Solo dialysis

- Originally cleared for home hemodialysis (HHD) with a partner

- Care partner was originally considered necessary to mitigate rare, but serious adverse events

- Clinical trial to evaluate rare events was not feasible

- Patient preference (PPI) study measured patients’ maximum acceptable risk for HHD without a partner instead of in-center dialysis
Evidence in Regulatory Decisions

TRADITIONAL REGULATORY PATHWAY

Pre-Clinical Testing → Clinical Studies → Pre-Market Application → Post-Market

Real-World Device Use
Physician and Patient Experience

NON-TRADITIONAL CLINICAL DATA GENERATION

Hypothesis Generation
Device Innovation

Informed Clinical Decision Making

Healthcare Information

Claims Databases
Pharmacy Data
Laboratory Tests
Patient Experience
Social Media
Registries
Electronic Health Records
Hospital Visits

31
Consideration of Uncertainty In Making Benefit-Risk Determinations in PMA, De Novo, and HDE Approvals

• Some degree of uncertainty generally exists around benefits and risks for regulatory decisions
• The regulatory standard is reasonable assurance – not absolute assurance
• Flexible regulatory paradigm

Clarified Through Draft Guidance Issued on September 5, 2018
Circumstances Where FDA is More Likely to Accept More Uncertainty

• For example:
  – Breakthrough Devices
  – PMAs with small patient population
  – De Novos with minimal risk
  – Particularly if established postmarket data collection mechanism

• Provides opportunities for international harmonization, where appropriate, and supports the establishment of a Medical Device Single Review Program
Real-World Evidence

• **Real-World Data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

• **Real-World Evidence (RWE)** is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.

Under the right conditions, data derived from real world sources can be used to support regulatory decisions.
Real-World Evidence

• RWE recently used to expand Indications for a hemodialysis catheter cap device

• RWE supported a reduction in the incidence of central-line associated bloodstream infections (CLABSI)

FDA Broadens ClearGuard® HD Antimicrobial Barrier Cap Indications

ClearGuard HD Caps Have Been Shown to Reduce Central Line-Associated Bloodstream Infections in Hemodialysis Patients

Maple Grove, Minn., May 30, 2018 /PRNewswire/ – Pursuit Vascular, Inc., manufacturer of ClearGuard HD Antimicrobial Caps, the leading antimicrobial device for catheter-based dialysis patients, today announced that the U.S. Food and Drug Administration (FDA) granted clearance for a broader indication of the company’s ClearGuard HD caps to include reduction in the incidence of central-line associated bloodstream infection (CLABSI) in hemodialysis patients with central venous catheters (CVCs). The safety and efficacy of the ClearGuard technology is well established, and ClearGuard HD caps were first cleared for use with hemodialysis catheters in 2013. The expanded clearance was based on post-market clinical surveillance data.

http://www.pursuitvascular.com/includes/FDA_Broadens_ClearGuard_HD_Indications.pdf
National Evaluation System for health Technology

NEST

Patient Groups

Industry

Clinician Groups

Health Systems

Payers

FDA CDRH

NESTcc

NEST SHARED RESOURCES

<table>
<thead>
<tr>
<th>Data Partner Network</th>
<th>Clearinghouse of Expertise</th>
<th>Communications Platform</th>
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</table>

COORDINATING CENTER

NEST National Evaluation System for health Technology

Coordinating Center

MEDICAL DEVICE INNOVATION CONSORTIUM
Medical Device Development Tool Program (MDDT)

**MDDT**: *a method, material or measurement used to assess effectiveness, safety or performance of a medical device*

**Benefit of Qualifying Tools**
- Fosters innovation
- Encourages collaboration
- Reduces resource expenditure
- Qualified MDDT applied in multiple device submissions
- Promotes efficiency in CDRH regulatory review resources
- Minimizes uncertainty in regulatory review process
Communicating with FDA

- Covers informational meetings to explain device concepts to FDA
- To obtain guidance/advice prior to submitting a device application.
- Knowing as much as possible prior to a formal device submission benefits both FDA and the sponsor
Interactions: Keys to Success

- Informational Meeting
- Pre-Submission Meeting
- Interactive Review Process
- Post-Decision Conference Call
- Submission Issue Meeting
Other Innovative Programs at CDRH

• Benefit/Risk Guidance
• Balancing Premarket and Postmarket Data Collection
• Adaptive Design for Medical Device Clinical Studies
• NIH SBIR/SBTT Regulatory Assistance
• Incubator/Accelerator Visits (ELP)
• CMS Parallel Review
• Payer Communication Task Force
• Early Regulatory Assistance
• Increased Sponsor Interactions
Once fully implemented, the CDRH reorganization will:

**Establish the Office of Product Evaluation and Quality (OPEQ)** - Combines the Offices of Compliance, Office of Device Evaluation, Office of Surveillance and Biometrics and the Office of In Vitro Diagnostics and Radiological Health into one “super office” focused on a Total Product Lifecycle approach to medical device oversight.

**Establish the Office of Policy (OP)** - Establishes two teams, the Guidance, Legislation and Special Projects Team and the Regulatory Documents and Special Projects Team. There are no changes in the functions for CDRH Policy.

**Establish the Office of Strategic Partnerships and Technology Innovation (OSPTI)** - Combines the Science & Strategic Partnerships, Digital Health, Health Informatics and Innovation teams. There are no changes in functions within the different teams.
Thank you!

Questions – carolyn.neuland@fda.hhs.gov
Extra Slides
Educational Resources: CDRH

1. **CDRH Learn: Multi-Media Industry Education**
   - over 125 modules
   - videos, audio recordings, power point presentations, software-based “how to” modules
   - mobile-friendly: access CDRH Learn on your portable devices
     www.fda.gov/Training/CDRHLearn

2. **Device Advice: Text-Based Education**
   - comprehensive regulatory information on premarket and postmarket topics
     www.fda.gov/MedicalDevices/DeviceAdvice

3. **Division of Industry and Consumer Education (DICE)**
   - Contact DICE if you have a question
   - Email: DICE@fda.hhs.gov
   - Phone: 1(800) 638-2041 or (301) 796-7100 (Hours: 9 am-12:30 pm; 1 pm-4:30pm EST)
   - Web: www.fda.gov/DICE

www.fda.gov
Better Tailored, More Consistent Benefit-Risk Determinations Supporting Our Decision-Making

- Premarket Guidance (Final) and De Novo Classifications
- Premarket Approval (PMA) and Investigational Device Exemptions
- Postmarket Guidance (Final) Medical Device Product Availability, Compliance and Enforcement Decisions
- Premarket Guidance (Final) 510(k)s

Years:
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
Balancing Premarket and Postmarket Data Collection

- Draft Guidance: April 23, 2014

- Outlines how FDA considers the role of post-market information in determining the extent of data that should be collected in the premarket setting to support premarket approval, while still meeting the statutory standard of reasonable assurance of safety and effectiveness.

- The right balance of premarket and postmarket data collection facilitates timely patient access to important new technology without undermining patient safety.

- Clarifies when post-approval studies at the time of approval are appropriate.
SBIR / SBTT Assistance

- Pilot program in partnership with The NIH
- CDRH will work collaboratively (via presubmission process) with Small Business Innovation Research (SBIR) and Small Business Technology Transfer (SBTT) awardees. Goal is for awardees to better understand the regulatory pathway and data requirements for their medical device.
FDA-CMS Parallel Review

**Exact Sciences**
Cologuard – Colon cancer screening

**Foundation Medicine**
FoundationOne – genomic profiling companion diagnostic

FDA approval & CMS proposed NCD on Same Day
Parallel Review with CMS

• FDA and CMS simultaneously review clinical data to help decrease the time between FDA's PMA approval and the subsequent CMS national coverage determination.

• Parallel Review has two stages:
  – FDA and CMS meet with the manufacturer to provide feedback on the proposed pivotal clinical trial within the CDRH Pre-Submission Program.
  – FDA and CMS concurrently review (“in parallel”) the clinical trial results submitted in the PMA or De Novo request.
Opportunities To Obtain Payer and Health Technology Assessment Input

Current Participants:

- BlueCross BlueShield Association
- CareFirst BlueCross BlueShield
- CMS
- Cigna
- Duke Evidence Synthesis Group/DCRI
- ECRI Institute
- Humana
- Kaiser Permanente
- National Institute for Health and Care Excellence
- United Health Group

Public Payer Pre-submission Participation

Opportunity to Obtain Private Payer Input

- Voluntary Program
- Obtain input on clinical trial design or other plans for gathering clinical evidence

For more information: Google Search “CDRH Payer Program”
Adaptive Designs for Medical Device Clinical Studies

Guidance for Industry and Food and Drug Administration Staff

The draft of this document was issued on May 13, 2015.

For questions regarding this document that relate to devices regulated by CDRH, contact Dr. Gerry Gray (CDRH) at 301-796-5750 or by e-mail at Gerry.Gray@fda.hhs.gov.

For questions regarding this document that relate to devices regulated by CBER, contact the Office of Communication, Outreach and Development (CBER) at 1-800-835-4709 or 240-402-4010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Clinical Trial Design Innovation:
Adaptive Designs Pathway
July 27, 2016
KHI Patient Preference Workshop

• August 12-13, 2015 in Baltimore, MD
  – “Understanding Patients’ Preferences: Stimulating Medical Device Development in Kidney Disease”

• 110 members of the kidney community

• Patients (in center HD, home HD, PD, transplant), living donors, care partners, physicians, researchers, device manufacturers, nonprofit/foundation members, and government representatives (FDA and NIH).

• KHI provided a forum for patients to voice their concerns and preferences about their treatments

• Discussed how to incorporate this patient feedback in the various phases of medical device development.
Q Submissions (Pre-Sub)

• Final Guidance: February 18, 2014
  [Link to Final Guidance]

• Expansion of former Pre-IDE program

• Program expanded to many types of pre-submissions and types of feedback

• More structured approach to improve predictability & consistency

• Voluntary program

• Considered a key part of the MDUFA III program by industry
  – Industry desire to understand FDA’s expectations before formal submission to ensure better quality submissions
CDRH (After Reorganization)
2018-2020 Strategic Priorities
Collaborative Communities

• Forum where public and private sector members work together on an ongoing basis to achieve shared outcomes and solve both shared problems and problems unique to other members
• In an environment of trust and openness, where participants feel safe and respected to communicate their concerns
• Where members share a collective responsibility to help each other obtain what they need to be successful
• And government has a seat at the table but does not run the forum
Device Development to Clinical Studies

Feasibility
Pivotal
(FIH
EFS
(much more known about device, procedure, indication)
Development Milestones & FDA Programs

- Device Design and Pre-Clinical Testing
  - Feasibility study
  - Pivotal Study
  - Pre-/Post-Market Balance
  - Real World Evidence
  - Marketing Application
  - Next Generation

- Expanded Access
- Early Feasibility Studies
- Patient Engagement
- Medical Device Safety Action Plan

Breakthrough Devices Program
Breakthrough Devices Pathway (Formerly Expedited Access Pathway)

149 devices accepted into the program since April 2015
1st breakthrough device approved December 2017
11 breakthrough devices granted marketing authorization

• Interactive & Timely Communication
• Pre-Postmarket Balance
• Flexible Clinical Study Design
• Senior Management Engagement
• Priority Review

Breakthrough Devices Program
Guidance for Industry and Food and Drug Administration Staff

Document issued on December 18, 2018.
What Is A Qualified MDDT?

• Medical Device Development Tool (MDDT) is a method, material, or measurement used to assess effectiveness, safety, or performance of a medical device
  - MDDT Categories: Clinical Outcome Assessment (COA), Biomarker Test (BT), Nonclinical Assessment Model (NAM)
  - A MDDT is scientifically validated and qualified for a specific Context Of Use (COU) on the way the MDDT should be used
  - Qualification is a FDA conclusion that within the COU a MDDT has a specific interpretation and application in medical device development and regulatory review

Website:
http://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/default.htm

Questions? email: MDDT@fda.hhs.gov
DEVELOP NESTcc’S ROLE: BUILDING A DATA NETWORK

NESTcc surveyed its Data Network to determine current capabilities, gaps, and priority areas

Duke University Health System • HealthCore • Lahey Clinic • Mayo Clinic • MDEpiNet • Mercy • OneFlorida • PEDSnet • Vanderbilt University • Weill-Cornell Medical Center • Yale New Haven Health System

Survey respondents represent:

- 195 Hospitals
- 3,942+ Outpatient Clinics

Patient data represents:

- 495M+ Patient Records

Common data models:

- I2b2
- OMOP
- PCORnet
- Sentinel

Respondents report regular data refreshes:

- 4 Quarterly
- 3 Mixed Rates
- 2 Monthly
- 2 Daily

Most cited expertise:

- Cardiovascular and Cardiac Surgery
- Women’s Health
- Neurosurgery
- Gastroenterology
- Orthopedic
Guidance with Stakeholder Input

- Time to re-evaluate how “we conduct business”
- Take into consideration the 3R’s
- Solicit and incorporate stakeholder input