Regulatory Science in CDRH’s Office of Science and Engineering Laboratories

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Overview of CDRH’s Office of Science and Engineering Labs

Regulatory science questions and research to advance analytics and automation in electro-medical equipment

AI/ML Discussion Paper for SaMD
• Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.

• The U.S. is the world’s leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety.

• U.S. post-market surveillance quickly identifies poorly performing devices, accurately characterizes real-world performance, and facilitates device approval or clearance.

• Devices are legally marketed in the U.S. and remain safe, effective, and of high-quality.

• Consumers, patients, their caregivers, and providers have access to understandable science-based information about medical devices and use this information to make health care decisions.
CDRH in Perspective

1900
EMPLOYEES

18k
Medical Device Manufacturers

183k
Medical Devices On the U.S. Market

22k/year
Premarket Submissions includes supplements and amendments

570k
Proprietary Brands

1.4 MILLION/year
Reports on medical device adverse events and malfunctions

25k
Medical Device Facilities Worldwide
CDRH Structure After Reorg Implementation

- Office of the Center Director (OCD)
  - Office of Policy (OP)
  - Office of Strategic Partnerships and Technology Innovation (OST)
  - Office of Product Evaluation and Quality (OPEQ)
  - Office of Communication and Education (OCE)
  - Office of Management (OM)
  - Office of Science and Engineering Laboratories (OSEL)
CDRH Mission

...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.
What is Regulatory Science?

Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

A common use of rules, conditions, guidelines for products and production methods…
A definition of terms; classification, procedures, specification, materials, performance, design, or operations…
A measurement of quality and quantity in materials, processes, products, systems, services…
A description or test methods and sampling procedures; measurement of size or strength…

An MDDT is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. An MDDT is scientifically validated and can be qualified for use in device evaluation and to support regulatory decision-making. [https://www.fda.gov/media/87134/download](https://www.fda.gov/media/87134/download)

Guidance documents represent FDA’s current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. [https://www.fda.gov/industry/fda-basics-industry/guidances](https://www.fda.gov/industry/fda-basics-industry/guidances)
Office of Science and Engineering Laboratories

- OSEL is comprised of 155 engineers, physicists, biologists, material scientists, mathematicians...

- Our objective is to:
  - Ensure readiness for innovative technologies
  - Develop test methods and facilitate optimization of devices
  - Deliver timely and accurate decisions for medical devices
  - Create accessible and understandable public health information
  - Through a culture of “4Cs”: Customer first, Communication, Collaboration and Consultancy.
OSEL in Perspective

- **183** Federal Employees
  - Up to 180 visiting scientists

- **2,500k/year**
  - Premarket Regulatory consults

- **140 Projects**
  - In 27 Laboratories and Program Areas

- **400/year**
  - Peer reviewed presentations, articles, and other public disclosures

- **75** Standards and conformity assessment committees

- **55,000 ft²**
  - Lab facilities

- **70%**
  - Staff with post graduate degree
OSEL in Perspective

• Key role in Pre-regulatory phase technology

• AND in translational phase(s)
  – We are developing tools for a more efficient evaluation of new devices
Office of Science and Engineering Labs

Ed Margerrison, Director

Admin and Lab Support
   Angie Clingerman

Applied Mechanics
   Anton Dmitriev
   Fluid Mechanics
   Solid Mechanics
   Ultrasonics

Biology, Chemistry and Materials Science
   Jose Centeno
   Materials Performance
   Microbiology and Infection Control
   Toxicology and Biocompatibility

Imaging, Diagnosis and Software Reliability
   Kyle Myers
   Clinical Trial Design
   Image Analysis
   Medical Imaging
   Software Reliability

Biomedical Physics
   Zane Arp
   Biophysics
   Electromagnetics (EMC)
   Optics
   Cardiac Modelling
The Division of Biomedical Physics (DBP) participates in the Center's mission of protecting and promoting public health by identifying and investigating the biophysical interactions between medical devices and the human body.

Contact: Zane Arp (Zane.Arp@fda.hhs.gov)

- EMC/wireless/electrical safety
- Neuroscience
- Optical physics
- MRI
- Functional performance and device use
- Cardiac electrophysiology
- Advanced patient monitoring and control
- Biomechanics
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Regulatory science questions and research to advance analytics and automation in electro-medical equipment

AI/ML Discussion Paper for SaMD
Areas of interest: Advances in analytics, automation, and interoperability in safety critical electro-medical equipment

Objective: Investigate and develop novel solutions aimed to assure the safety and effectiveness of medical devices that include advanced patient monitoring, physiological closed-loop control, or interoperable technology

Example research topics:
- Developing performance assessment methods for advanced patient monitoring algorithms
- Evaluating computational models of physiological systems for testing physiological closed-loop controlled medical devices
- Investigating research platforms and engineering methods to explore the safety implications of increasing complexity in the design and use of medical devices

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False alarms

Alarm Fatigue

Non-actionable alarms

Poor interpretation of patient condition

Fixed settings

No clinical context

Limited use of information from multiple signals

Alarm Condition Detection
Measurement Algorithms
Filtering

Alarm Condition Detection
Measurement Algorithms
Filtering

Alarm Condition Detection
Measurement Algorithms
Filtering

Biopotentials

Pressure Transducer

Patient movement
Identify Critical Events Earlier

Blood Pressure
Heart Rate
Breathing Rate
Oxygen Saturation

Blood Loss

Time
Mean Arterial Pressure

0% 15% 30% 45%
Applications for Analytics in Patient Monitoring

<table>
<thead>
<tr>
<th>Disease Progression</th>
<th>At-risk population</th>
<th>Symptomatic</th>
<th>Diagnosed</th>
<th>Deteriorating</th>
<th>Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring Needs</td>
<td>Trauma</td>
<td>Infective agent</td>
<td>Systemic Inflammatory Response Syndrome</td>
<td>Infected</td>
<td>Septic</td>
</tr>
</tbody>
</table>

Continuous monitoring for patient improvement/deterioration

<table>
<thead>
<tr>
<th>Needs</th>
<th>Screening</th>
<th>Diagnostic</th>
<th>Monitoring organ function</th>
<th>Guiding supportive therapy</th>
</tr>
</thead>
</table>

Reducing false alarms and improving measurement performance

- Alarm management – determining optimal settings for patients
  - Automatic adjustment of alarm settings by analyzing past patient data
- Signal quality assessment:
  - Signal artifact detection
  - Use of information from multiple signals
  - Identifying false positive and false negative alarm conditions

Predictive analytics for earlier identification of events

- Aid in the assessment of patient current and future condition
  - Patient risk / status indices
  - Monitors of patient deterioration
- Computer-aided detection and diagnosis
  - Detect disease signatures in physiologic waveforms
  - Measure and predict future response to therapy
- Feedback variables for physiological closed-loop systems
- Many other possibilities
Filtering
Measurement Algorithms
Alarm Condition Detection
Alarm Condition Detection
Alarm Condition Detection

Multivariate Models
Fusion of Data
New Physiological Measurements
Signal Quality Assessment

Display
Heart Rate
Blood Pressure
Oxygen Saturation
Predictive Index
Alarm Signals

Pressure Transducer
Biopotentials

Other Data Sources:
Lab values
EHR
Other medical devices
Considerations for Predictive Analytics in Patient Monitoring

- Traditionally, physiological measurements evaluated on an individual basis against established reference methods (may be clinical or bench testing)
  - According to consensus standards for many (e.g., IEC 60601-2-47:2012 for ambulatory ECG)
  - Alarms, generally, use thresholds on measurements or detect ‘known’ patterns in signals

- Considerations for evaluating data-driven algorithms
  - How representative is the patient population that the data is collected from?
  - How to ensure data quality?
  - Does the specific measurement device used to create the database (or settings on the monitor) have a meaningful impact on the data for the algorithm being developed?
  - What are meaningful endpoints and adequate annotation procedures?
  - How to effectively use potentially limited number of critical events for training and testing?
AAMI TIR66:2017 Guidance for the creation of physiologic data and waveform databases to demonstrate reasonable assurance of the safety and effectiveness of alarm system algorithms

- Recognized by FDA
- Provides guidance for:
  - Validating novel & intelligent alarm system algorithms
  - Disclosing performance of those systems
- Database requirements
  - Alignment with intended application of the algorithm
  - Population and Study Design
  - Engineering requirements
  - Annotation requirements
  - Archive requirements
- Waveform acquisition and synthesis
  - Data quality
  - Annotation processes
- Application of waveform databases to testing
Medical Device Interoperability

• Designing systems with interoperability as an objective
• Conducting appropriate verification, validation and risk management activities
• Specifying the relevant functional, performance, and interface characteristics in a user available manner such as labeling
Simulating physiologic signals for efficient use of databases in algorithm design

Use of patient monitoring databases to evaluate predictive alarm algorithms and effects on alarm fatigue

Computational methods to investigate the effect of noise and motion artifacts on monitor algorithms

Non-clinical testing for interoperable monitoring systems to test performance with different physiologic signal acquisition systems
Characterizing Patterns of Indices Leading up to Critical Event

• Novel index with an alarm system may have a variety of patterns prior to a critical event
• How should performance be evaluated to provide meaningful and understandable information?
  – Performance within clinically relevant time period before event
  – Distribution of warning times
  – Whether the alarm condition is present until event
  – Number of false alarms / event
Extracting noise from electrocardiogram recordings for robust algorithm testing

- ANSI/AAMI EC57 includes testing ECG analysis algorithms across range of SNRs by applying 3 recorded noise records
- Same noise records used for all devices – unclear if these are adequate and representative for novel portable devices

**Approach**
- Developed method to enable noise component to be extracted from ECG signal
  - Representative noise records can then be added to annotated databases
Hazardous Situations for a Physiologic Closed-Loop Controlled Device

Controller:
- May leads to unstable system
- Not robust to different patient responses
- May not recognize change in patient response

- Drug empty
- Component failure
- Within patient changes
- Patients respond differently

Usability errors:
- Wrong patient information
- Wrong drug concentration
- Over-reliance on device

Measurement does not represent patient condition

Communication failure

Component failure

Sensor drop-out

Sensor errors

Purdon, FDA PCLC Workshop 2015.
Medical Device Evaluation

• Comprehensive evaluation of a marketing application for a therapeutic medical device typically includes valid scientific evidence from some combination of four possible types of models: animal, bench, computational, and human.

• Each model has its strengths and limitations for predicting clinical outcomes.

• Computational evidence has many potential uses for physiologic closed-loop controlled devices
## Uses of Modeling for Physiologic Closed-loop Controlled Devices

<table>
<thead>
<tr>
<th>Model-Based Design</th>
<th>Complete In Silico Testing</th>
<th>Hardware-in-the-Loop Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established field of engineering</td>
<td>Ability to produce a variety of physiological conditions (in silico patients)</td>
<td>Enables real time testing with device hardware</td>
</tr>
<tr>
<td>Enables quantitative assessment of system</td>
<td>Modularity</td>
<td>Allow for evaluation of worst-case scenarios</td>
</tr>
<tr>
<td>Analytical stability</td>
<td></td>
<td>Stress testing</td>
</tr>
<tr>
<td>Transparency</td>
<td></td>
<td>Scenarios not easy to replicate in clinical setting</td>
</tr>
<tr>
<td>Lends itself well to model-based evaluation</td>
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### Simulation Environment

- **Control Settings**
  - **Control Algorithm**
  - **Computational Patient Model**
  - **Computational Sensor Model**
- **Disturbances**
  - **Computational Therapy Delivery Model**

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### Evaluation of Fluid Resuscitation Control Algorithms via a Hardware-in-the-Loop Test Bed

- Hovora Minierjo, Boheme Perlmutter, Marga Ricks, Yi Zheng, Sandy Weininger, AoEh Hahn, and Christopher O. Anadu
Challenges for computational testing of physiologic closed-loop controlled devices

• Need physiological models that lend themselves to control system design
  – Need to be simple enough for design of controller but accurate enough to capture the physiology of interest
  – Physiological systems have many mechanisms that are unknown and difficult to model
• Variability in physiological systems from one patient to another, and within patient
  – 747s are manufactured to be similar with similar properties/response
• High degree of cross-coupling between physiological systems
  – cardiovascular-respiratory-renal
• High degree of versatility for a single physiological system
  – Function of respiratory system is for oxygenation and ventilation, but it also helps to cool the body

• How to demonstrate credibility of computational modeling and simulation results in the evaluation of physiologic closed-loop controlled devices?
The ASME V&V 40 standard outlines a framework for making risk-informed determinations as to whether a CM&S is credible for decision-making for a specified context of use.
Box 1: Define Use of Computational Patient Model in PCLC Development

- Characterize nominal performance
  - Response time
  - Stability
  - Disturbance rejection
- Assess performance across range of conditions
  - Determine worst case performance
  - Identify unsafe patient conditions

Box 2: Design Computational Test Strategy

- Box 4: Gather Evidence to Support Computational Patient Model

- Box 3: Establish Computational Patient Model Credibility Goals

Questions to Consider
- What other evidence will be used to address the use of the PCLC question? (animal study, clinical study, analytical assessment)
- What is the consequence of incorrect simulation evidence?
- What phenomena/physiological systems need to be modeled?
- What are the sources of uncertainties in the model?
- What is the range of input conditions and disturbance profiles that will be used for testing?
- How could the model error influence the device testing?

Device design evaluation
- Compare control algorithm designs
- Characterize influence of therapy and sensor inaccuracies and delays

Box 4: Gather Evidence to Support Computational Patient Model

- Verification of numerical model
- Sensitivity of model output to input parameters
- Comparison of simulation to experimental results
  - Animal / clinical model
  - Initial conditions and disturbance profiles
  - Numbers of test samples
  - Quantification of uncertainties
  - Error between comparator and model output
  - Applicability of initial patient conditions and disturbance profiles used for model assessment to device testing
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“Today, we’re announcing steps to consider a new regulatory framework specifically tailored to promote the development of safe and effective medical devices that use advanced artificial intelligence algorithms.”

Dr. Scott Gottlieb, FDA Commissioner
April 2, 2019
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