Closed-Loop Anesthesia: Invention or Innovation?

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About me
Advanced Thermal Engineering 2004-2006
R&D engineer / Device instrumentation and testing

FDA-CDRH 2006-2018
- Lead Reviewer - Surgical implants & Critical care medical devices
- Subject matter expert (Physiological Closed-Loop Systems)
- Team leader (Physiological Closed-Loop Systems)
- Digital health, in silico physiological models for decision support and closed-loop system

Education:
- BS, 2004 Biological Engineering UMCP
- MS, 2007-2009 Biomedical Engineering JHU (mathematical models of respiratory system)
- PhD, 2013-2019 Mechanical Engineering UMCP

“A framework for credibility assessment of mathematical models used for evaluation of critical care clinical decision support and automated systems”

Lighthouse Regulatory Consulting Group
Jan 2019-Present
- Founder & Principal Consultant

Society for Technology in Anesthesia
Annual Meeting – January 10, 2019
Disclaimer

I work for Lighthouse Regulatory Consulting Group

Outline

1. History of automation in medical devices
2. Define automated anesthesia and PCLC systems
3. Define invention & innovation
4. Automated anesthesia: Invention or Innovation?
5. Taking Automated anesthesia to the next level
6. Regulatory Opportunities and Challenges
History of Automation

- Aviation and auto industry have developed technology behind automation
- First wave of advancements: during WWII to improve accuracy of missiles
- Second wave of advancements: increasing computational power, amount of data

What’s new?
The evolution of automatic devices trying to take on more responsibility for diagnostic and therapeutic purposes

Closed-Loop Anesthesia: Invention or Innovation?
Closed-Loop anesthesia is a PCLC.[2]

Definition 1. A PCLC (Physiological Closed-Loop Control) system is a medical device that incorporates physiological sensor(s) for automatic manipulation of a physiological variable(s) through actuation of therapy that is conventionally made by a clinician. [3]
What is Physiological Closed-Loop Control?

**PCLC example Application:** Premature Neonates in need of oxygen therapy

- Detected \( \text{SpO}_2 \) too far from the target
- **Adjusted concentration of O\(_2\)**
- **Pulse Oximeter**
- **\( \text{SpO}_2 \) of 95%**
Definition 2

**invent**: to produce (something, such as a useful device or process) for the first time through the use of the imagination or of ingenious thinking and experiment[4].

**Definition 3**

"**Innovation** is production or adoption, assimilation, and exploitation of a value-added novelty in economic and social spheres; renewal and enlargement of products, services, and markets; development of new methods of production; and the establishment of new management systems. It is both a process and an outcome." [5]

OECD's manual's definition
Public Health Need

45%

Up to 45 percent of critical care physicians reported symptoms of severe burnout syndrome.

Burnout Syndrome in Critical Care Health-care Professionals: A Call for Action

Human Error and Patient-Controlled Analgesia Pumps
S. Lori Brown, PhD, MPH, Maureen Sue Begon, PhD, Christine M. Parmentier, RN, Jo Lynn R. Taylor, RN, MEd

Medication errors involving patient-controlled analgesia

Rodney W. Hug, Yasu Shimok, Winnie Nelson, Jeff R. Schein, and Diane D. Cousins

The fact that ventilators are such an established technology by no means guarantees that these issues are clearly understood … we continue to receive reports of hospital staff misusing ventilators because they’re unaware of the devices’ particular operational considerations.

Deaths from medical errors

An estimated 1 million people are injured during hospital treatment and 120,000 die from the result of these injuries.

Lester L. Lave, Harvard School of Public Health

14,360 Deaths from falls
5300 Suicidal deaths
309 Commercial aviation deaths
230,000 Deaths from anesthesia

Medprogram a PCA pump! It’s easy!
Public Health Need

- Need timely, distraction-free, and accurate therapy delivery devices
- Need devices that can lower mental workload and allow clinician to focus on higher-level tasks

Closed-loop anesthesia devices do just that...
State of automated anesthesia

- Scientific literature on development and evaluation of PCLCs is abundant (dates back to 1950s- Significant increase in past 5-10 years)
- exploratory, focused on proof of concept, and feasibility of technology, and OUS
- focus on safety or tool-based claims (time to target, time within prescribed range) with limited sample size
- Outcome based studies are limited
  - Clinical outcomes
  - Workflow outcomes
  - Environmental outcomes (e.g. lowering inhalational drug use)
  - Financial outcomes
- Two automated anesthesia systems approved by FDA so far:
  - IVAC Titrator (closed loop SNP delivery)
  - Sedasys System (semi closed loop propofol delivery)
  - Attempts for commercialization were unsuccessful

"Innovation is production or adoption, assimilation, and exploitation of a value-added novelty in economic and social spheres; renewal and enlargement of products, services, and markets; development of new methods of production; and the establishment of new management systems. It is both a process and an outcome."

✓ Unmet need /Value added novelty
✓ New method of care delivery
✓ Innovation as a process
? Adoption/assimilation
? Innovation as an outcome

Invention or Innovation?
Closed-Loop Anesthesia devices are maturing into an innovative technology.
They have the potential to be innovative in outcome.
Definitive proof of “Innovation”

Kaffee “…..It doesn’t matter what I believe. It only matters what I can prove!”

Taking automated anesthesia one step ahead in the innovation process towards innovation outcome
Approach

1) Avoid singling out stakeholders as an isolated source of challenge.

- Insufficient predictability of what information is needed to allow for the initiation of clinical studies
  - Data requirements can be difficult to identify
  - Increasingly complex devices
  - No established guidance or standards for innovative devices
  - No generally accepted method for justifying data requirements
- Ineffective communication between CDER and industry
- Poor-quality submissions that do not include or coherently describe relevant information

“no outcome, no income”
David B. Nash, Dean, Jefferson College of Population Health

Risk Transfer & Accountability

- Manufacturers
- Payors
- Automated Anesthesia
- FDA

Community buy in, trust, and adoption

Episodic Care vs Population Health Models: Transitioning From Volume to Value

“no outcome, no income”
David B. Nash, Dean, Jefferson College of Population Health
Approach

2) Form a stakeholder team/ task force/ work group

- Did this as part of FDA workshop in 2015 initiated by FDA
- ASA, STA, FDA, NIH, ONR
- Need a broader team representing various stakeholders to present each perspective

3) Technology benchmarking

- Did this as part of FDA workshop in 2015 initiated by FDA
- ASA, STA, FDA, NIH, ONR
- Need a team representing various stakeholders to present each perspective
Note the differences and grid locks

“One day before breakfast, an orange rolled off the counter and escaped its fate, bounding happily through the kitchen door.

Filled with hope, the egg followed.”

Approach

4) Work towards consensus on key issues (where you can)
- Type and extent of clinical/engineering data to inform R/B estimation
- Sensor qualification
- Terminology Standards/Training & Usability
- Integration of technology in clinical workflow

End products: white paper consensus standards

“It is difficult to get a man to understand something, when his salary depends [or he thinks his salary depends] upon his not understanding it!” Upton Sinclair
Regulatory Challenges

Type and extent of testing at different stages of regulatory process (e.g. study initiation) is unclear:
- No standards on criteria for sensor validation
- No standards on validity of mathematical models

Submissions are extensive (not 500 pages, but 500 sections!)
- Often poorly organized

Regulatory Designation and classification:
- PCLCs can be Drug/Device combination products (may require multicenter review)
- PCLCs have new Intended Use as defined under (21 CFR 807.81(a)(3))

Unknown risks/benefit profile associated with complex and novel technology:
- PCLCs involve Risk Transfer

Regulatory Classification

New intended use/technological characteristics warrant different questions of Safety and Efficacy.
Challenge 1: PCLC Regulatory Designation & Classification

Factors affecting PCLC Regulatory Classification

**Moderate Risk PCLC**
- Single input single output
- Direct sensor
- Sensor with consensus
- Valid Models of underlying physiology available to stress test
- Simple to use and train on
- Intended for an “easy” phase of therapy (e.g. maintenance)

Will likely result in more identifiable risk and risk mitigation strategies → FDA special controls can be drafted → De Novo*

**High Risk PCLC**
- Multiple input multiple output (e.g. BP, DOA)
- Regulation of anesthesia is inherently MIMO
- Surrogate sensor
- Novel sensor
- Extensive training required to operate safely and effectively
- May be intended for entire phase of therapy (e.g. induction, maintenance, emergence, weaning etc)
- Underlying physiology is complex

Will likely have unknown risks → special controls are inadequate → PMA*

*Other factors such as patient population and level of supervision may affect the regulatory pathway
Challenge 2: Evaluating PCLCs Benefit & Risk

Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions

<table>
<thead>
<tr>
<th>Factors</th>
<th>Assessment Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usability</td>
<td>What is the quality of the information FDA is using (for example, MDRs, Incomplete, minority or clinical trial data, limited case studies, inspectional data, etc.)? Is the quality of information a reliable source for making an objective and unbiased benefit or risk assessment?</td>
</tr>
<tr>
<td>Mitigation</td>
<td>Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, etc.? What is the type of mitigation proposed? Is the intervention related to design, labeling, or training?</td>
</tr>
<tr>
<td>Detectability</td>
<td>Has the manufacturer corrected the cause of the nonconformity? Can the user easily recognize the hazard to avoid the harm? Can the problem with the medical device be corrected before use by the user?</td>
</tr>
<tr>
<td>Failure Mode</td>
<td>Has the manufacturer identified the underlying cause? Has the firm submitted changes to the FDA?</td>
</tr>
<tr>
<td>Scope of the device issue</td>
<td>Are the risks identified potentially inherent to similar medical devices of this type (i.e., industry risk)?</td>
</tr>
<tr>
<td>Patient impact</td>
<td>What are the risks to patients if the device is not available? What is the potential impact on patients related to the inspectional observation or regulatory non-compliance? Does the observation or violation directly relate to product quality? Does the observed regulatory non-compliance raise concerns regarding the firm’s ability to produce safe and effective medical devices?</td>
</tr>
<tr>
<td>Preferece for availability</td>
<td>Would patients and caregivers prefer to have access to the device? Are the benefits and risks adequately understood?</td>
</tr>
</tbody>
</table>


Benefits: Increased time in target

Challenge 3: Complex System of devices

- Closed loop systems combine, Interacting, interoperable electrical, mechanical, and chemical systems
- Require knowledge of control theory
- Computer science, cybersecurity

- Mathematical modeling
- Drug Device interaction
- Human Factors/Cognition /Psychology
- Training
Opportunity #1 Early Feasibility Studies

EFS is intended to facilitate the clinical evaluation of medical devices in US under IDE regulation using risk mitigation strategies that protect study subjects.

To be considered:

- Small sample size (fewer than 10 subjects)
- Device in early development and need clinical evaluation to mature in design
- Does not need to be FIH to qualify for EFS
Opportunity #2

Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act

Draft Guidance for Industry and Food and Drug Administration Staff

**Criteria**

<table>
<thead>
<tr>
<th>Description</th>
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<tbody>
<tr>
<td><strong>First Criterion</strong></td>
</tr>
<tr>
<td>The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions</td>
</tr>
<tr>
<td><strong>Second Criterion</strong></td>
</tr>
<tr>
<td>The device also meets at least one of the following:</td>
</tr>
<tr>
<td>a. Represents Breakthrough Technology</td>
</tr>
<tr>
<td>b. No Approved or Cleared Alternatives Exist</td>
</tr>
<tr>
<td>c. Offers Significant Advantages over Existing Approved or Cleared Alternatives</td>
</tr>
<tr>
<td>d. Device Availability is in the Best Interest of Patients</td>
</tr>
</tbody>
</table>

Leverage Digital health initiatives

- PCLCs are Advanced Digital Health (ADH) medical devices
- Highly interoperable: building blocks are the digital health products that are currently being discussed at various levels (IMDRF, FDA, FTC)
- AI and automation
Opportunity #4
New Assessment methods tailored to PCLC Technology

“FDA is increasingly evaluating the possibility of relying on mathematical modeling and computational evidence to evaluate novel medical devices”


Conclusion & Future work

• Automated Anesthesia is maturing into an innovative technology
• Multifaceted challenges exist (Regulatory, community, manufacturers, payors). FDA has made its move (workshop in 2015 and guidance document). The ball is in manufacturer’s and users communities’ courts to work on developing consensus on key issues.
• Regulatory challenges
  • Regulatory pathway
  • Lack of predictability and clarity in extent and type of testing at various stages of regulatory process (lack of standardization)
  • Lack of consensus standards clouds R/B determination
  • Overall complexity
• Regulatory Opportunities
  • Leverage new programs such as EFS and Breakthrough designation programs
  • Leverage Digital Health Initiatives
  • Leverage new assessment methodologies
Questions

References

- IEC 60101-1-10
- FDA workshop paper
- Merriam-Webster Dictionary
- Organisation for Economic Co-operation and Development (OECD) manual's definition (source: wikipedia)
- https://www.fda.gov/medicaldevices/deviceregulationandguidance/howto marketyourdevice/investigationaldeviceexemptionide/ucm572934.htm
- https://www.fda.gov/medicaldevices/deviceregulationandguidance/howto marketyourdevice/ucm441467.htm
Back ups

Technology benchmarking

“The self-driving car raises more possibilities and more questions than perhaps any other transportation innovation”

“First, 35,092 people died on U.S. roadways in 2015 alone. Second, 94 percent human choice or error.”

“Automated driving innovations could dramatically decrease the number of crashes tied to human choices and behavior”

www.nhtsa.gov
Technology benchmarking  Aviation

Lessons from Transportation Industry

- It is well-documented that while it eliminates/reduces human intervention in certain tasks, it may require more attention and involvement from human for safe use
- Automation creates new needs and skills
- Risks are the same but sources of risks transfer
- Importance of consensus standards
Community consensus and adoption as the main activator: Lessons from another automated medical device

Cautious benchmarking and integration of automation: Grid locks

- Self Driving vs Autonomous vs Automated
  - Terminology nightmare
- over automation and not involving user
  - “Automation is not a panacea”

*Lane Desborough, Chief Engineer, Bigfoot medical*
Cautious benchmarking and integration of automation: Differences

<table>
<thead>
<tr>
<th>AUTOMATION IN CRITICAL CARE</th>
<th>AUTOMATION IN TRANSPORTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variability in patients (source inter and intra)</td>
<td>Variability in conditions (source environmental)</td>
</tr>
<tr>
<td>Variability not well characterized</td>
<td>Variability extensively studied and characterized</td>
</tr>
<tr>
<td>Few Physiological sensors have been proven to be robust for closed-loop applications</td>
<td>Mechanical (pressure, flow, accelerometer) and imaging sensors have much better robustness profile</td>
</tr>
<tr>
<td>Human-Automation interface evaluation in critical care setting is nascent</td>
<td>Human Automation interaction is extensively studied</td>
</tr>
</tbody>
</table>

Outcomes are clear but the path to outcome are highly variable

Outcomes and the way to realize them are clear
EFS benefits

- Work with FDA to develop a DES (Device Evaluation Strategy)
- Justify appropriate testing
- Justify risk mitigation strategy and level of testing
- Provide rationale behind the device development and implementation of iterations

Complex Devices & Regulatory Process

Example: Last closed-loop system as lead reviewer

- IDE (Less than 30 days to make a decision to initiate FIH study)
- Involved a team of 20 scientists, clinicians, statisticians, engineers
- Involved three FDA centers and 5 review divisions
- 4 review meetings
- Conclusion: There was not sufficient and accurate description of device features, capabilities, and risks to evaluate safety.