Public Roundtable Meeting

Verification and Validation for Physiologic Closed Loop Systems

Tuesday, September 20, 2022

12:00 p.m. – 1:00 p.m. ET

Meeting Notes

Attendees:

Acacia Welsford *Nephria Bio*	Daniel Bloomberg *Medtronic*	Gema Gonzalez *CDRH*
Barry Fulkerson *Kuleana Technology*	Daniel Call *Fresenius*	Glenn Bell *CDRH*
Charu Gupta *CDRH*	Daniel Rubery *Fresenius*	Jerry James *Fresenius*
Chistopher Scully *CDRH*	Douglas Silverstein *CDRH*	Michael Aragon *Outset Medical*
Chris Hobot *Medtronic*	Victor Gura *WAK*	Nicholas Clay *CDRH*
Clayton Poppe *Diality*	Eric Svendsen *Fresenius*	Perry Law *Fresenius*
Courtney Lias *CDRH*	Frank Hurst *CDRH*	Timothy Park *Outset* Medical

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I. Introduction (Zachary Cahill)
   a. The purpose of the meeting is to present KHI's work and discuss the Request for Information (RFI)
      i. Attendees were reminded that everything done at KHI is pre-competitive and this meeting will be recorded and posted on KHI's website.
   b. Mr. Cahill reiterated that the intent of the Roundtable is to convene the kidney community and identify and tackle common barriers to innovation
      i. KHI has process for considering and review new projects
         1. The RFI was a scoping exercise intended to help KHI hear from the community prior to devoting resources to the problem.

II. Review questions posed in the Request for Information (RFI) *Defining Appropriate Verification and Validation Studies for Physiologic Closed Loop Control Systems in Hemodialysis* (Cahill)

a. Questions asked in the RFI: Looking at two sets of issues around verification and validation testing for physiologic closed loop control systems in hemodialysis
    i. General
        1. Broadly applicable solutions to technical questions from outside dialysis
        2. Clarifying questions about existing FDA guidance
        3. Contextualizing existing guidance to kidney space
    ii. Technical
        1. Level and type of V&V safety data for IDE applications
        2. Credibility criteria for computational physiological models
        3. Types of automatic and reliable sensors
        4. Clinical trial frameworks and endpoints

III. Summarize key learnings from responses (Cahill)
a. General question responses
    i. V&V will vary depending on the type of sensor used in a HD machine. Factors influencing the type of V&V testing include:
    ii. Whether the sensor is new or old
    iii. The safety range of the physiological data being monitored.
    iv. An example of computational model could be a “digital twin” where the credibility criteria would be a comparison between the model and the system with live inputs.
    v. V&V testing for new sensors is costly and time consuming.
    vi. New sensors should be tested as monitors in clinical trials.
    vii. It may be useful for the community to recommend updates to FDA’s PCLC guidance to align with IEC 60601-1-10.
b. Technical question responses
    i. What are the V&V testing expectations of integrating sensors that are on the market into a new PCLCs?
    ii. How should usability testing be approached when risks are long term or are risks of omission?
    iii. Are there additional ways (beyond ISO requirements) to mitigate risks in systems of devices?
    iv. How should computational models or CTs set limits on the distribution of a patient's physiologic conditions?
    v. What statistical significance is recommended?

IV. Describe the Kidney Health Initiative (KHI) process for considering new projects (Cahill)
a. The KHI Board of Directors will consider devoting resources to an official project based on the outcomes of this Roundtable Meeting.

V. Solicit additional responses to questions raised in the RFI
a. Has KHI looked at the artificial pancreas as a basis for how to approach PCLC systems in hemodialysis? In diabetes these PCLCs are already out there. What were the requirements? What were the basics to structure this? Coming from the pancreas point of view. (Michael Aragon)

i. Yes, that was the genesis of the RFI. What we could learn from ventilators from the artificial pancreas who have already thought through some of these issues. That is an area worth spending more time on in the formal project. (Cahill)
    1. Any direction that KHI should go? Or areas we should emphasize? (Cahill)

b. Looking at the technical questions, what comes to mind are what are the mitigations and safety parameters that should be in place? We can have credibility, computation, what types, redundancy, mitigation etc. (Aragon)

c. Is KHI's intent to reach out to people who are a part of these projects (in different applications) to learn from them and get insight on their methodology? (Glenn Bell)
    i. Yes, that is something we can do in the context of a formal project. We have these connections with people in those spaces. If we decide to go on, we have to explore more specifically analogous devices. (Cahill)

d. If you go that way (looking at the artificial pancreas as an analogous device), it may be more valuable to work with academics because a lot of these companies purchase work from the academics that host these studies. We can help you connect with them. Another question we could think about are the interface between devices… how the fidelity of information crosses across devices. If the devices are actually distinct and come from distinct entities such as separate companies, that can be a practical challenge to translating the technology to the marketplace. It might be worthwhile to make sure that those type of things are thought about early enough to prevent people developing these products being stuck in the competitive space and unable to translate it to these patients. That device communication, device interface, and ensuring fidelity between the two is important. (Courtney Lias)

e. Seems like spending time pursuing looking into analogous devices would be the most useful way to go… I'm wondering if anyone has some other things we should also consider? Or if we can kind of tackle everything? (Cahill)
    i. Couple thoughts… from the user perspective, it'll be important to know what processes within the treatment themselves do users have trouble with, what areas are errors most likely happen, what problem are we trying to solve for different groups of patients (non-professional user versus professional user)? It is important to consider where we could resolve errors. (Aragon)
    ii. Might take one or two items or issues to take examples from. For example, hemodialysis and blood pressure dropping. If you want to put the care and process into a machine to make these decisions instead of a nurse, you have to validate that the decision is correct. If it is not, what happens, then what are the risks? Also, are the patients going to accept these decisions by machines or not. Are the decisions going to be made by the nurse, the resident, or by the machine? Should choose two or three critical parameters within dialysis. (Victor Gura)
    iii. Outline dialysis specific decisions and consider the patient perspective on acceptance of these devices. Good way to contextualize these machines. (Cahill)
        1. Is there a different level of evidence or validation if the device is more identifying a problem and alerting the user vs a fully automated loop.

Monitor, pause, and wait for user interaction vs. monitor, pause, and react. (Aragon)

2. Should monitor, pause, and wait for interaction be considered a PCLCs? Is it in scope as a physiological closed loop control? Are we redefining the scope and definition of what counts? What's the difference between a PCLCs and the standard HD alarm system? There are standards already in place for technical alarm systems. (Daniel Bloomberg)
    a. Guidance we are referring to is draft, not implementation at this point. There is a standard for close loop systems that the FDA does recognize. Maybe there is a need to consider other automated functions that are not necessarily part of closed loop control in our definition. Something to consider is to think about what these functions are actually doing. (Christopher Scully)
3. To keep a risk-based approach when considering parameters for PCLC, where is our comfort level? What are things we are not comfortable with being handled by a PCLC based on risk vs other considerations? It needs to be incorporated into the scope and parameters of the project especially considering patient safety. (Gema Gonzalez)
    a. The way that the artificial pancreas tackled risk was fail safes. Instead of thinking that some things are too risky to do, thinking about the limits of algorithms when thinking of safety for high risk parameters? These are typically delt with via the algorithms themselves. Fail safes. What are the limits of algorithms. (Lias)

f. Another source of information and focusing problems to be addressed could be military medicine. In military medicine, things happen where there is a medic with instruments in a field hospital where they need to automate many functions. They are trying to automate some processes so that, in the future battlefield. The decisions about what to automate in a HD context pale to the automation decisions being made in the battlefield. (Dr. Gupta)

VI. Discuss potential next steps to be recommended to the KHI Board of Directors
    a. We will write this up and present it to the Board level to discuss prioritization. (Cahill)