KHI KIDNEY HEALTH INITIATIVE

Request for Information (RFI):

Defining Appropriate Verification and Validation Studies for Physiologic Closed Loop Control Systems in Hemodialysis

De-Identified Responses

Responses Collected:

Friday July 1, 2022 – Friday, September 2, 2022

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Response 1

Question: What level and type of preclinical verification and validation data could demonstrate safety of closed-loop hemodialysis devices in support of an application for an Investigational Device Exemption from the FDA?

- **Answer:** Depends on the PCLC level of control. All HD machines use safety sensors to monitor venous/atrial pressure, presence of air in blood, temperature of the blood, conductivity of dialysate, etc. These sensors will 'safe' the system if an out of range level is detected. Some sensors are redundant (Air in Blood) or continuously perform self-test to detect a mis-functioning sensor. A pressure sensor will control an actuator to raise or lower the measured pressure if required. All of the aforementioned sensors are usually verified as a sub-system and validated at system level. Known, proven, technology like ultrasonic Air-In-Blood (AIB) sensors are usually tested in vitro and not in vivo. A new, different, PCLC like a potassium sensor in the blood line which could be used to vary the treatment prescription would require extensive in vivo V&V in both animal and human. Preclinical would require performance testing over a wide environmental and system operation range. Also, extensive material compatibility testing if direct and less for indirect contact. This requires a complete system test of operational software. If transmitted outside of the device to remote data collection and Rx adjustment, then end-to-end cryptology would be expected and tested in the final system.

Question: What type of credibility criteria is needed for the use of computational physiological models in evaluating closed-loop hemodialysis devices?

- **Answer:** If the model is created before the system to determine performance specifications, then it would be expect that theoretical model outputs are compared to the same model but with live inputs from the PCLC sensors in system. The model output would be compared to actual device performance. Actual system level with simulated patient physiological inputs in both in vitro and in vivo (animal). Think - Digital Twin (https://www.mathworks.com/discovery/digital-twin.html)

Question: What types of sensors could be used to automatically and reliably adjust hemodialysis parameters over the course of treatment?

- Answer: Typical sensors internal in HD machines – conductivity, temperature, pressure. External sensors – BPC & weight scale. New sensors which could adjust the HD treatment parameters: HCT, K, Ca, Mg, Na, pH. HCT can be used to adjust Ultra Filtration removal Rate in conjunction with patient's BP. An HD device would have to be explicitly designed to automatically adjust for input from ionic sensors.

Question: What common clinical trial framework and endpoints could be used to evaluate the safety of closed loop systems in hemodialysis?

- **Answer:** Any new PCLC sensors for HD therapies should first be tested, via a CT, only as a monitor to determine if they can meet specifications over a range of patients and treatments. And the clinician must determine when & how a treatment can be modified

with this new physiological data. This could be performed with a separate device vis the blood line without involving the HD machine.

Question: What solutions exist that could broadly address the technical questions described earlier? This could include evaluation of PCLC in non-hemodialysis devices.

- **Answer:** For these remaining questions ASN might be better served to convene a group dialysis product developers and provide updates to the FDA's PCLC guidance in harmony with the IEC 60601-1-10 standard. To help drive this process (meaning to get us involved) is that the FDA should recognize the 60601-1-10 for renal devices (KDI)
    - What questions remain in applying FDA's existing guidance documents, such as those cited earlier in this document, to the evaluation of PCLC in hemodialysis devices?
    - What other questions remain on PCLC in hemodialysis devices to contextualize existing guidance?

Response 2

PCLC systems have the potential to improve patient outcomes and increase safety in dialysis and support creating additional guidance for their development and utilization. The development of sensors that are better able to accurately measure physiological properties lowers the technical difficulty of implementing PCLCs; however, the testing and regulatory burden remain high.

Areas where we think sensors and PCLC systems could contribute immediately are:

- Venous Needle Disconnect Detection
- Blood flow adjustment
- Ultrafiltration control
- Electrolyte balancing
- Clearance Optimization

General Topics Questions

We have the following questions about applying current FDA guidance to PCLC systems:

1. Sensors that could be used for closed-loop control may be contained in separate medical devices. These devices may be designed and manufactured by a separate company. What special requirements (regulatory, testing, or otherwise) exist for using a separate device, made by a separate company, as part of a closed loop system?
2. Given that PCLC systems are designed to remove some of the interactions between the device and the user, how do we focus on usability testing when some of the risks happen over long time frames or are risks of omission? For example, how do we test for things like Loss of Situational Awareness, Complacency and Skill Degradation?
3. Beyond standard risk-management requirements outlined in ISO 14971, are there additional ways to evaluate and mitigate risks we should consider, especially when we think about systems of devices working together?
4. For the purposes of modeling physiological properties, how should we set limits in relation to the distribution of the underlying patient physiologic conditions?
5. What models, simulations or in vitro testing are sufficient to demonstrate safety and efficacy? Standard in vitro testing today in dialysis machines focuses on clearance testing and ultrafiltration, as well as simulating standard potential hazardous situations. None of this testing requires simulating patient physiological conditions. For simulation or testing of PCLC systems, how narrowly, or broadly, do we try to simulate physiological conditions? What type of statistical significance is recommended?
6. How does the variation in patient physiologies impact the number of patients that might be needed in a clinical trial?