

Technical Considerations for Medical Devices with Physiologic Closed-Loop Control Technology¹

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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

¹ This guidance has been prepared by the by the Center for Devices and Radiological Health in consultation with the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

Preface

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I. Introduction

A Physiological Closed-Loop Controlled (PCLC) device is a system consisting of physiologic-measuring sensors, actuators, and control algorithms that adjusts or maintains a physiologic variable through automatic adjustments to delivery or removal of energy or article (e.g., drugs, or liquid or gas regulated as a medical device) using feedback from a physiologic-measuring sensor(s). PCLC technology can enable automation in a variety of medical device types. Such devices have the potential to deliver timely, accurate and consistent therapy and can play an important role in reducing cognitive overload, minimizing human error, and enhancing medical care including, for example, during emergency response and medical surge situations. Ensuring patient safety is an important consideration while evaluating the potential benefits of PCLC devices.

This document highlights technical considerations for the development of medical devices employing PCLC technology to ensure safe and effective use and provides recommendations for the content of premarket submissions (i.e., premarket notifications (510(k)s), De Novo requests, premarket approval applications (PMAs), Humanitarian Device Exemptions (HDEs)) for such devices.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the [FDA Recognized Consensus Standards Database](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm).²

² Available at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>

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II. Background

Automation in PCLC devices is enabled by the control system technology in host medical devices such as infusion pumps, ventilators, extracorporeal systems (e.g., dialysis delivery systems and organ reperfusion devices), and stimulation systems. PCLC devices can benefit the patient by facilitating safe and effective, consistent, and timely delivery or removal of energy or article (e.g., drugs, or liquid or gas regulated as a medical device). However, introducing automation and minimizing clinician involvement can incur new types of hazardous situations that can render the medical device unsafe if not properly designed or evaluated. Algorithm flaws, lack of operational transparency, and automation bias are examples of potential automation-induced hazards.

The Center for Devices and Radiological Health (CDRH) held a public workshop entitled “Physiological Closed-Loop Controlled Devices” on October 13 and 14, 2015, with the aim of fostering an open discussion on design and evaluation considerations associated with PCLC devices used in critical care environments.³ Automated therapy delivery, such as automated fluid resuscitation, ventilation/oxygenation, and anesthesia delivery, are emerging applications for the critical and emergency care environments. This workshop provided a forum for medical device manufacturers, clinical users and academia to discuss technical considerations for automated medical devices with PCLC technology.⁴ The feedback received during this workshop and from numerous interactions with companies designing PCLC medical devices through the [Q-submission process](#)⁵ was taken into consideration while drafting this guidance.

³ Available at <http://wayback.archive-it.org/7993/20170112084803/http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm457581.htm>

⁴ A summary of the discussion topics of the workshop can be found in Parvinian B, Scully C, Wiyor H, Kumar A, and Weininger S. Regulatory Considerations for Physiological Closed-Loop Controlled Medical Devices Used for Automated Critical Care: Food and Drug Administration Workshop Discussion Topics. *Anesthesia and Analgesia*. 2018 Jun; 126(6): 1916-1925. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6233305/>

⁵ Information regarding the Q-submission process can be found in “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program - Guidance for Industry and Food and Drug Administration Staff” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>

III. Scope

This guidance provides technical considerations related to the PCLC technology when designing PCLC medical devices. PCLC medical devices can include functions or components⁶ that have risks separate from the PCLC functions that are not addressed in this guidance.⁷ Not all considerations in this guidance will be applicable to every PCLC device given the variety of device types that can incorporate PCLC technology. Manufacturers should determine and justify in premarket submissions, which considerations are appropriate for their device based on the technology being used and the intended use of the device. Example PCLC device areas include, but are not limited to, automated anesthesia delivery systems, mechanical ventilation, and hemodynamic stability systems. Manufacturers should consider applying certain principles in this guidance to medical devices with automatic technology that adjust delivered energy or article to control a non-physiologic variable (e.g., pressure in a ventilator breathing circuit).

Although elements of this guidance may be applicable to active implantable devices with PCLC technology, including neurostimulators and pacemakers, additional considerations outside the scope of this guidance may also need to be addressed (e.g., related to the long-term use of the PCLC function). In some cases, there may be device-specific guidances that should also be utilized, and this guidance is not intended to supersede other device-specific guidances.

The technical recommendations in this document should be applied as appropriate to the following premarket submissions:

- Premarket notifications (510(k));
- De Novo requests;
- Premarket Approval (PMA) Applications; and
- Humanitarian Device Exemptions (HDE).

Overall premarket submission requirements and recommended information to provide can differ depending on the submission type. Additional information on each submission type can be found on the FDA's [Premarket Submissions](#) webpage.⁸ The type of premarket submission that is required for your PCLC device is determined by the classification of your device, based on the risk of the device and the level of regulatory controls necessary to provide reasonable assurance of safety and effectiveness for the device. This guidance document does not include information about the classification of PCLC devices. Questions regarding the regulatory requirements for specific devices should be submitted through the Q-Submission process, see

⁶ In this guidance, the word component refers to the functional elements that make up a PCLC device. For example, the physiologic-measuring sensor(s), actuator(s), and software implementing the control algorithm are all components of a PCLC device.

⁷ In addition, this guidance does not address considerations with respect to the compatibility between a PCLC device and the article intended to be delivered, nor does it address the technical considerations with respect to evaluating whether the PCLC device is suitable for delivery of the article.

⁸ Available at <https://www.fda.gov/medical-devices/how-study-and-market-your-device/premarket-submissions>

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“[Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program - Guidance for Industry and Food and Drug Administration Staff](#).”⁹

Many of the recommendations here can also be useful for supporting the safety of a PCLC device in an Investigational Device Exemption (IDE).¹⁰ The design and testing of a device incorporating PCLC technology will depend on a variety of factors, including, but not limited to, the energy or article being delivered, environment of use, level of automation, training of the user population, patient population, validity of the sensor, method of control algorithm design, and properties of the delivery system. CDRH encourages sponsors to utilize the [Q-Submission process](#)¹¹ to obtain more detailed feedback on clinical study designs evaluating the risks of their automated medical devices with PCLC technology.

This guidance is not intended to provide specific recommendations as they relate to machine learning (ML) aspects of a PCLC device design. We recommend discussing with the Agency through the [Q-submission process](#)¹² the design and test plan of control algorithms designed with and/or incorporating ML.

IV. Definitions

The definitions listed here are for the purposes of this guidance and are intended for use in the context of the design and evaluation of PCLC devices.

Automation bias: the tendency for users to give greater belief to information from automation technology without verification

Complacency: a phenomenon that refers to the monitoring of technology less regularly or with less vigilance because of a lower degree of suspicion of error and a stronger belief in its accuracy

Entrance criteria: information about the patient and clinical state that the user enters into the PCLC device before beginning an automated mode

Exit criteria: information about the patient and delivered energy or article communicated by the PCLC device to the user when an automated mode is ending

⁹ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>

¹⁰ For additional information related to IDE submissions, see the FDA’s Investigational Device Exemption webpage (<https://www.fda.gov/medical-devices/how-study-and-market-your-device/investigational-device-exemption-ide>).

¹¹ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>

¹² Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>

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Fallback mode: mode of operation (or state) into which the PCLCS [physiological closed-loop control system] transitions when the PCLC stops operating due to detection of a fault¹³

Loss of situational awareness: reduction of the user's awareness of the patient or technology state due to the automation of clinical decisions and execution functions by a device

Physiological closed-loop controlled device: a medical device that automatically adjusts or maintains a physiologic variable(s) through delivery or removal of energy or article¹⁴ (e.g., drugs, or liquid or gas regulated as a medical device) using feedback from a physiologic-measuring sensor(s)

Physiologic variable: quantity or condition, from a patient, whose value is subject to change and can usually be measured¹⁵

Physiologic-measuring sensor: measurement component of a PCLC device that uses a combination of patient-contact or imaging materials, transducers, signal conditioning, and algorithms to estimate the value of a physiologic variable¹⁶ [Note: When the term sensor is used in this guidance document it is referring to a physiologic-measuring sensor.]

Skill degradation: reduction of decision-making and execution ability which can lead to *forgetting* and *skill decay* manifestation if the clinical decision-making choices are consistently executed by automation

V. Design Considerations for PCLC Devices

Consistent with 21 CFR part 820.30, a manufacturer must establish, document, and maintain throughout the medical device lifecycle an ongoing process for design control activities, which can include activities such as identifying hazards, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls. This process should include risk analysis, risk evaluation, risk control, and incorporation of production and post-production information. Recommendations below related to the design process address risk

¹³ Clause 3.11 of International Electrotechnical Commission (IEC) 60601-1-10 Edition 1.2 2020-07: *Medical electrical equipment - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers*

¹⁴ The term article in this guidance is used in the same way as substance in IEC 60601-1-10 Edition 1.2 2020-07: *Medical electrical equipment - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers*

¹⁵ Adapted from Clauses 3.21, 3.28, and 3.29 in IEC 60601-1-10 Edition 1.2 2020-07 : *Medical electrical equipment - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers*

¹⁶ The term physiologic measuring sensor in this guidance document is used in the same way as measuring transfer element in IEC 60601-1-10 Edition 1.2 2020-07: *Medical electrical equipment - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers*

management considerations, system and component level design considerations, and verification and validation considerations. Design inputs for a device with PCLC technology should consider the risks associated with the complete device and not only the PCLC functions. The design of a PCLC device should support safe use in the patient population, clinical environment, and clinical workflow in which the device will be used. We recommend that manufacturers follow development procedures as described in International Electrotechnical Commission (IEC) 60601-1-10: *Medical electrical equipment - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers* or an equivalent method when designing PCLC devices, as well as risk management process recommendations as described in International Organization for Standardization (ISO) 14971: *Medical devices - Application of risk management to medical devices*.

A. Risk Management Considerations

PCLC devices are complex systems that involve and have performance affected by measurement devices, therapy delivery devices, control algorithms, software, user interfaces, characteristics of the article being delivered, and the patient's physiology. Hazards can arise from failures of individual device components, loss of communication between components, software failures, inappropriate control algorithm design, use errors, or disturbances to the patient's physiology. This can result in harm to the patient due to too much or too little energy or article being delivered, either over a short time period or the length of time the PCLC device is being applied to the patient. We recommend manufacturers consider hazards identified in IEC 60601-1-10 (e.g., Clause 4 General Requirements of IEC 60601-1-10 Edition 1.2 2020-07) and follow all recommendations related to risk management in this consensus standard. Appropriate verification and validation techniques will depend on the risks of individual hazards as well as the type of hazard.

FDA recommends identifying the following causes of hazards as part of the risk analysis in a PCLC device submission. The submitted risk analysis should include hazards that were considered, possible hazardous situations, the risks that can result from each, and how the hazards and risks were addressed.

(1) Patient-related hazards

The response of the patient to the energy or article being delivered or removed (i.e., the patient transfer element as defined in IEC 60601-1-10) is a critical factor to consider in the design. This response can differ between patients (inter-patient variability) and within an individual patient (intra-patient variability). It can be affected by disturbances caused by, for example, other therapies being delivered to the patient. These scenarios can affect the patient's response and cause the system to not perform as anticipated, if the PCLC device is not designed and tested adequately, and result in the delivery of inappropriate therapy and harm to the patient. Safely managing such scenarios involves adequately characterizing the patient's response and using this

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information to design appropriate controllers, safe fallback modes, and communication to the user. Safe mitigations are not the same for all patient populations, environments of use, or clinical workflows. Design considerations including risk analysis, user interface designs, safety features, testing needs, and training can vary depending on the specific patient population a PCLC device is intended for and how the device is expected to impact patient care and clinical workflows. We recommend manufacturers identify the following related to the patient population:

- Intended patient population, including diseases, health status, and potential comorbidities;
- Contraindications for use of the PCLC technology;
- Clinical environment where the device is intended to be used (e.g., patient transport, intensive care unit, operating room);
- Current standard of care related to device objective, including the various therapies and physiologic variables and measurements that could be used to make therapy decisions related to the objective of the PCLC technology in the intended patient population; and
- Identification of differences between the standard of care and the method that will be employed by the PCLC device (e.g., if current standard of care relies on a comprehensive patient assessment to make decisions about changes, but the PCLC technology will only use a single measured physiologic variable).

When designing a PCLC device, manufacturers should characterize and consider disturbances related to the patient's response as relevant for their device and consider the following in their risk analysis:

- Expected response of the physiologic variable being controlled to the delivered energy or article in the intended patient population including delays in the response of the physiologic variable to the delivered energy or article and considering, as applicable, how changes to the article being delivered (e.g., formulation changes for a drug) may affect that response;
- Variability in the physiological response between patients (i.e., inter-patient variability);
- Variability/changes in the physiological response over time due to, for example, disease progression (i.e., intra-patient variability);
- Interactions between systems that can result in changes in the controlled physiologic variable (e.g., respiratory modulation of the arterial pressure waveforms);
- Physiological response to concurrent therapies expected for the intended patient population including other PCLC devices that can be applied to the patient (e.g., other drugs that might affect the patient's response);
- Disturbances to the patient's response that can occur, such as change in other therapies being provided, movement or change in positioning of the patient; and

- Other physiologic variables besides the physiologic variable intended to be controlled that can be affected by the delivered energy or article (e.g., respiratory effects during PCLC for pain management).

(2) Device-related hazards

Device-related hazards refer to those hazards resulting from the PCLC device and its components, rather than the patient. Manufacturers should identify and characterize uncertainties in their system design and foreseeable functional disturbances given the clinical environment and workflow. Examples of device-related hazards that manufacturers should consider in their risk management process include the following:

- Transient as well as persistent motion / noise artifacts in the measured feedback variable;
- Accuracy of sensor is not sufficient;
- Component (e.g., sensor or actuator) no longer meets system specifications;
- Communication failure between device components;
- Actual quantity of delivered energy or article not equal to that set by the control algorithm (e.g., due to physical saturation of the actuator);
- Latency and delay times within the system and individual components that can result in unsafe conditions;
- Other known risks associated with the individual PCLC device components and any single fault in the system; and
 - If a PCLC device uses a component that is a legally marketed device (e.g., a 510(k)-cleared blood pressure monitor that serves as the physiologic-measuring sensor in the PCLC device), we recommend you also evaluate postmarket information such as recalls and Medical Device Reporting. We recommend that manufacturers address any postmarket concerns identified for these PCLC device components that can impact the performance of the PCLC device, and provide information on mitigations in your device design and labeling that addresses this issue.
- Changes to third-party components of the PCLC device that can affect the safety or performance of the PCLC device or changes to the article (e.g., drug) that the PCLC device delivers so that the PCLC device and article are no longer compatible.
 - FDA recommends that manufacturers of PCLC devices establish processes, as part of their Quality System (see 21 CFR part 820), to identify when changes to third-party components used as part of their device, or changes to the articles that the PCLC device delivers, occur and evaluate whether the changes no longer meet the PCLC device specifications.

(3) Use-related hazards

To ensure PCLC devices with automatic decision-making capabilities operate as intended, it is important to have an accurate understanding of fundamental human factors considerations such as human cognitive capabilities and limitations, and how these impact human-automation

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interactions for the PCLC device. When designing devices with varying levels of automation, we recommend that manufacturers consider the possibility that users can experience reduced interactions with the patient and device compared to current standard of care. As a result of reduced interaction, the user could not have a complete understanding of the patient or device status (reduced cognitive awareness) jeopardizing their ability to provide appropriate interventional responses.

Designers of PCLC devices should consider how a user's role can change from active to passive interaction with the automated features. Careful consideration is needed to address such reduced interactions. Users could have the tendency to over-trust or over-rely on the device automation which can affect the users' ability to recognize the need for interventions. Therefore, we recommend manufacturers consider that the human-automation interaction has the potential to introduce automation-related use errors relative to complacency, automation bias, loss of situational awareness, and skill degradation on behalf of the users. Determining the anticipated users will help in appropriately applying risk management strategies for activities such as designing the device user interface and developing appropriate labeling for use of the device. We recommend manufacturers consider the following related to the anticipated users when designing a PCLC device:

- Whether the device will be operated by physicians, nurses, other clinical staff, patients (for example, if patients will be able to modify the target level), or other caregivers;
- Expected training of users related to the objective of the PCLC technology in the intended patient population;
- Level of clinical supervision expected for the patient population; and
- Whether biomedical technicians or other individuals can service or configure the device.

A PCLC device can have the capability of sensing and processing patient physiological data and executing therapeutic decisions with varying levels of clinician involvement for a particular decision; this can be referred to as the level of automation of the device. Understanding the levels of automation and associated hazards is critical to safe operation of the subject device. Use-related risks and design considerations can depend on the level of automation that the PCLC device employs (for example, methodologies to classify the degree of autonomy see IEC/TR 60601-4-1: *Medical electrical equipment -- Part 4-1: Guidance and interpretation -- Medical electrical equipment and medical electrical systems employing a degree of autonomy*). These use-related risks are dependent on user's behavior, which is difficult to predict. An appropriate risk management technique should be used to identify these human-automation interaction hazards so that effective mitigation measures can be implemented. The manufacturer should consider human factors and user characteristics such as sensory ability, attention, memory, reasoning, decision-making, emotions, knowledge, experience, and skills associated with each automation level when deciding how to automate a device.

We recommend that manufacturers perform a use-related risk analysis assessing the potential harm that could arise during step-by-step use of the device. Any reasonable, foreseeable misuse

as well as known risks associated with the PCLC device components should be taken into account in this use-related risk analysis. However, automation-related use errors are not always predictable until a device is used in clinical situations. Therefore, we recommend that when clinical studies are performed, manufacturers collect data on device operation during clinical situations, including when fault conditions occur and fallback modes are entered, to examine user responses. This information can then be used as part of the process to identify use-related hazards.

Manufacturers should follow recommendations in the FDA guidance document, “[Applying Human Factors and Usability Engineering to Medical Devices](#),”¹⁷ when performing risk management for use-related hazards considering all device user-automation interfaces such as dynamic information displays, buttons, and logic of operations that can impact the device use.

B. PCLC Device Design

PCLC devices can have different design and engineering parameters. Some systems can combine PCLC device components into a single unit while others can include distributed components. The design of PCLC devices can include different approaches towards risk mitigation and system fault handling, including inclusion of various open-loop and manual modes in case of fault occurrence and the use of supervisory layers that determine how and when the transition from these modes should take place. Regardless of the design method, FDA recommends that the design of the PCLC device is such that device safety and performance can be assessed in a transparent and reliable fashion. Manufacturers should set design specifications such that handling of challenging clinical (e.g., patient variability) and functional (e.g., component malfunction) scenarios can be verified and to enable root cause analysis for corrective action where needed.

A PCLC device includes 1) a sensor(s) that measures a physiologic variable from the patient, 2) a controller/control algorithm, and 3) an actuator that delivers or removes energy or article to the patient (see Figure 1). We recommend manufacturers describe the technical components and specifications of a PCLC device as described in IEC 60601-1-10 (e.g., Clause 8.2.2 Equipment Specifications of IEC 60601-1-10 Edition 1.2 2020-07).

¹⁷ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices>

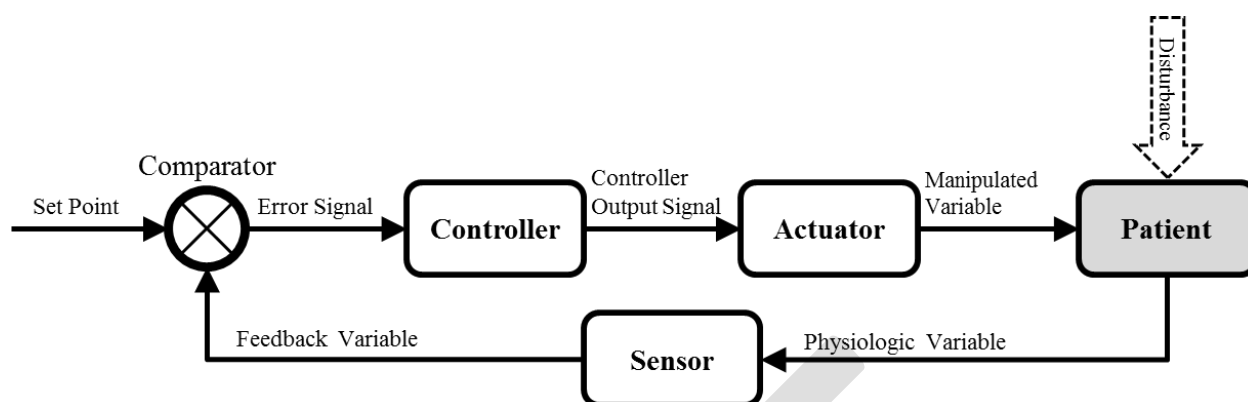


Figure 1. Basic block diagram of a PCLC system. The “Patient” block includes the patient’s physiologic processes that will be affected by the manipulated variable (i.e., the delivered energy or article). While a “Disturbance” arrow is shown here to act on the patient and the patient’s physiologic processes, disturbances could occur at various points in a PCLC system.

As part of the device description for a PCLC device in a premarket submission, manufacturers should identify and describe the elements in C(1-5) below. This should include information on the individual components that are part of the PCLC device design and how these components are integrated so that the PCLC device can function as intended. FDA recommends that, where possible, the manufacturer provide a schematic of the system configuration in the form of a functional block diagram with the physiologic variable, sensor, control algorithm, actuator, delivered energy or article, and patient clearly identified within the context of the device description (see Figure 1). The input/output relationship of each element (e.g., sensor, actuator, patient) in the system should be identified to allow for a description of the complete system over its intended range and under various pathological conditions. FDA recommends manufacturers identify and describe all automated modes and features related to the PCLC technology, describe all fallback modes, and provide information on how the user interacts with and sets device parameters including ranges of configurable parameters that can be set by the user in the device description. This should include information on all phases of therapy that will be controlled including the length of time the device is expected to be applied to the patient (e.g., inductance of anesthesia, maintenance of anesthesia, and/or emergence of anesthesia) and whether automated PCLC technology will make determinations, for example, about the therapeutic objectives (e.g., by determining the appropriate target level for a physiologic variable). For PCLC devices that deliver drugs or other regulated medical products, the PCLC device manufacturer should describe how the design, including the control algorithm, delivers the article consistent with the labeling of the product that is being delivered (e.g., maximum rate and cumulative amount over time of drug the PCLC device can deliver). The PCLC device labeling should also include information regarding compatibility with the article (e.g., drugs, or liquid or gas regulated as a medical device) it is intended to deliver.

Components of a PCLC device (e.g., sensors and actuators) can be specifically designed for the PCLC device or selected from existing off-the-shelf parts (i.e., a component that by itself is not a medical device) or can be existing, cleared or approved, stand-alone medical devices (e.g., infusion pumps, patient monitor). PCLC device component specifications should support the

component's function as part of the PCLC device considering the risks related to inadequate component performance. The performance specifications needed for a medical device used as a component in a PCLC device can be different from the performance specifications of the stand-alone medical device. For example, a sensor device with a certain accuracy level could be appropriate for stand-alone applications, but that same accuracy level would not be adequate for the PCLC device to meet performance specifications. Manufacturers should also consider relevant FDA guidances or special controls for PCLC device components that are previously cleared or approved devices. For example, an infusion pump developed to serve as an actuator in a PCLC device should follow recommendations in the FDA guidance document, "[Infusion Pumps Total Product Life Cycle](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/infusion-pumps-total-product-life-cycle),"¹⁸ as applicable for the PCLC device. For PCLC devices that include interoperable medical devices as part of the PCLC device, manufacturers should refer to the "[FDA Guidance Document: Design Considerations and Premarket Submission Recommendations for Interoperable Medical Devices](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-and-premarket-submission-recommendations-interoperable-medical-devices)."¹⁹

(1) Control Algorithms

The control algorithm determines the automated actions of the PCLC device. The main function of the control algorithm is to determine adjustments to the delivered energy or article so that the PCLC device meets clinically relevant performance specifications as defined in IEC 60601-1-10, such as response time, settling time, relative overshoot, steady state-deviation, tracking error, and switching between therapy modes over the range of expected uncertainty. We recommend manufacturers specify the system response characteristics such as those listed in Clause 8.2.2.6 (Responses of the PCLCS) of IEC 60601-1-10 Edition 1.2 2020-07, or define equivalent system response specifications as applicable for their device.

The design of control algorithms used in a PCLC device should be based on a characterization of the response of the physiologic variable to the energy or article provided by the PCLC system as well as the interplay of any factors that can affect such dynamics. For example, in an automated anesthesia system, the pharmacokinetics/pharmacodynamics and therapeutic index of the drug as well as time-varying patient sensitivity to the drug should be considered by the controller to safely induce and maintain anesthesia. Any element that affects these dynamics (e.g., concomitant drugs that can affect the patient's response to the drug provided by the device with PCLC technology) should be considered in the controller design as it can affect the controller performance, stability and safety.

A control algorithm should be designed to perform in the presence of inter-patient/intra-patient variability, disturbances, environmental interference, and other related hazards discussed in Section V.B. Risk Management Considerations of this guidance. We recommend manufacturers follow IEC 60601-1-10 (e.g., Clause 8.2.3.2 Disturbance Analysis of IEC 60601-1-10 Edition 1.2 2020-07) to identify and characterize disturbance variables, as applicable to their automated

¹⁸ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/infusion-pumps-total-product-life-cycle>

¹⁹ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-and-pre-market-submission-recommendations-interoperable-medical-devices>

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medical device with PCLC technology and address how the control algorithm enables the PCLC device to meet specifications during these conditions.

In many cases, a PCLC system with one control algorithm may not be sufficient to function as intended in the use scenario. As a result, PCLC technology within a medical device can consist of multiple control algorithms functioning simultaneously or within different modes that the system switches between. For example, for the purpose of automatic oxygen delivery, different control algorithms can be designed and activated depending on whether the patient is in a state of normoxemia, hypoxemia or hyperoxemia. In another example, for closed-loop anesthesia, individual control algorithms can be designed for induction, maintenance and emergence of anesthesia. FDA recommends manufacturers consider the following when using multiple control algorithms:

- In cases where different control algorithms are responsible for different phases of therapy, the system should be designed such that switching between control algorithms does not adversely impact the therapy provided.
- User interfaces should be designed so that the user is able to identify the current operating mode and when the control algorithm switches modes.
- The entrance/exit criteria for mode switching should be defined and implemented for each therapeutic mode. These criteria should be communicated to the user through the device user interface.
- Control algorithms for all modes should be designed to meet their performance specifications during reasonably foreseeable disturbances.

Figure 1 shows a PCLC device operating as a single ‘loop’ (i.e., the control algorithm is automatically adjusting therapy to control a single physiologic variable). Multiple PCLC ‘loops’ can be applied to the same patient simultaneously. This can occur as a manufacturer introduces a PCLC device with multiple objectives, a new PCLC feature is added to an existing PCLC device, or two or more PCLC devices are intended to function together. The interaction between control loops that can be used together should be characterized to identify potential hazards arising from the system. For example, if the objective of a PCLC device is to control mean arterial pressure through vasoactive drug delivery and depth of anesthesia through hypnotic drug delivery, the influence of each loop on the other should be considered in the design.

Control algorithms can be designed using a variety of techniques that could result in varying levels of transparency and understanding of the control algorithm. This will have an impact on the methods that can be applied for verification and validation. We recommend manufacturers consider the following scenarios for designing a controller:

- The design can follow a mathematical model-based approach. In this case, a mathematical model of the underlying physiological dynamics and potential variabilities and disturbances that might be encountered in clinical settings is obtained or developed and used to design a control algorithm. This can facilitate evaluation by providing physiological insight, transparency, and a framework for the design of the controller. See

Section VII.B(1) below for technical recommendations to establish the credibility of computational models used in the development of PCLC devices.

- The control algorithm can be designed based on, for example, a decision table developed from clinical guidelines or best practices (i.e., rule-based controller). In these scenarios, FDA recommends manufacturers examine the clinical evidence supporting the rules that the control algorithm will implement. Any differences between the implementation of the rules in the control algorithm and the way studies were implemented to determine and/or evaluate the rules should be identified. For example, a clinical study could be performed so that an infusion rate is adjusted once per hour according to a fixed decision table while a control algorithm could be designed to implement those updates more frequently. In this example, any clinical or physiological differences due to the faster update rate and how they could impact the safety and performance of the device should be considered.
- Control algorithms can be designed using machine learning (ML) approaches and/or include ML as part of the design. When preparing a premarket submission for control algorithms using ML approaches/designs, we recommend manufacturers describe the model (e.g., model architecture, implementation parameters) and training process for the ML control algorithm design. This should include information about the study design (e.g., patient population, any annotation process, data collection processes, how the data were partitioned and used to collect data for training and testing purposes). Manufacturers should describe how the patient population and methods used to develop and test the ML algorithms are representative of the intended patient population and use of the device.

(2) Sensors

The physiologic-measuring sensor in a PCLC device provides a patient-measured feedback variable to the control algorithm. In many scenarios, direct sensing of the physiologic variable of interest is not possible, and a sensor can provide a feedback variable (see Figure 1) to the control algorithm based on a representation of a physiologic variable. For example, when automatically delivering oxygen to neonates, it might not be possible to run continuous blood gas measurement to determine arterial oxygen saturation (SaO_2), the physiologic variable intended to be controlled, and the manufacturer would need to rely on measurement of functional peripheral oxygen saturation (SpO_2), the feedback variable, as sensed by a pulse oximeter. In this example, the objective of the PCLC technology is to control SaO_2 , and thus, the accuracy of SpO_2 as a measure of SaO_2 should be characterized across the intended patient population and considered in the design. The relationship between the feedback variable measured by the sensor and the physiologic variable of interest will affect the safety and performance of the PCLC device, and the performance of the feedback variable should be established and limitations of the relationship quantified for the intended application, user, patient population, and environment of use considering appropriate physiological and environmental variability. For example, in the case of an automated anesthesia delivery system based on EEG sensors, the effect of concomitant drugs (e.g., neuromuscular blockers, vasopressors), motion artifact, and surgical disturbances (e.g., electrocautery artifact) on the sensed depth of hypnosis should be considered across the expected patient population.

Manufacturers should consider the risks related to inadequate sensor performance within the PCLC device and determine design specifications related to the sensor to ensure that the PCLC device performs as intended. FDA recommends manufacturers consider the following when designing or selecting physiologic-measuring sensors to be used as part of a PCLC device:

- Sensor performance including measurement accuracy in relation to the physiologic variable of interest.
- Linearity of the sensor in relation to the physiologic variable of interest across the expected measurement range.
- Response time (i.e., latency) and bandwidth of the sensor to a change in the physiologic variable of interest. Sensors inherently exhibit some delay when measuring a change in the physiologic variable of interest. This delay could be negligible in the overall performance of the PCLC device or it could have detrimental impact on the performance. Manufacturers should account for and mitigate this response delay.
- Any changes in sensor performance as a function of measurement range (e.g., pulse oximeters can have degraded accuracy at low saturations) within the relevant range for the PCLC device.
- Any changes in sensor performance due to confounding factors in the intended patient population (e.g., interference from concomitant therapies).
- Any change in sensor performance due to environmental factors.
- Sensor update rate (i.e., the frequency that a sensor is designed to provide readings to the control algorithm).
- Sources of signal artifacts that can affect sensor performance. Measurement devices can include signal quality detection mechanisms that identify when the sensed data is insufficient to report accurate measurements. Manufacturers of PCLC devices should consider if such systems are present, how the information is communicated to the control algorithm, and the response of the control algorithm to poor signal quality or missing data.

Additional sensors can be included as part of an automated medical device with PCLC technology to provide redundancy or additional information about the patient's condition. For each sensor used as part of the PCLC device, the above items should be considered for the individual sensors.

(3) Actuators

The actuator (e.g., infusion pump, gas blender) component of a PCLC device receives a signal from the control algorithm and converts it to the physical delivery or removal of energy or article (e.g., therapy) to the patient. Failure of the actuator can cause therapy delivery to stop or result in delivery of therapy falling outside acceptable limits.

FDA recommends manufacturers consider the following when designing or selecting an actuator to be used as part of a PCLC device:

- Accuracy of energy or article delivery across the range that can be applied by the PCLC technology.
- Response time of the actuator to the signal from the control algorithm.
- Physical limitations of the actuator (e.g., maximum flow rate) and compatibility with the control algorithm (e.g., errors resulting from saturation of the actuator).
- Communication delay times associated with the output of the control algorithm.
- For some PCLC devices, it would be necessary to monitor the actuator performance so that the system can detect faults related to the actuator and revert to fallback modes as appropriate.

(4) System Safety Features

In addition to the primary control loop, there are a number of design elements for PCLC technology that can enhance safety and ensure the system meets its design requirements. We recommend manufacturers consider safety features such as:

- **Fallback modes** – During the presence of some patient-related disturbances or device failure conditions, the PCLC technology would not be able maintain delivery of therapy as intended. Manufacturers should design their PCLC technology to detect unsafe conditions and have procedures in place for fault tolerance to ensure patient safety. We recommend manufacturers follow IEC 60601-1-10 (e.g., Clause 8.2.2.3 Fallback Mode of IEC 60601-1-10 Edition 1.2 2020-07) related to fallback modes.
- **Transparent entrance and exit criteria** – The initiation of automated therapy delivery can depend on the patient state, how well the control algorithm is informed of that state, and the system response. FDA recommends manufacturers incorporate entrance criteria for the PCLC device so that the control algorithm has sufficient information about the patient state in order to initiate therapy as intended. Similarly, when a PCLC mode is ending the device should communicate relevant information to the user about the patient and device states for the user to safely manage the patient.
- **Constraints on delivered energy or article** – FDA recommends manufacturers consider designing PCLC devices to constrain the energy or article delivered to minimize unsafe conditions. For example, where the controller is designed to administer the drug in a manner that is consistent with the drug labeling, such as the rate of infusion of a particular drug, this design would, among other things, minimize unsafe conditions. Another example of a clinical constraint is a closed-loop oxygenation and anesthesia gas delivery device in which the controller should not deliver oxygen below 21% to avoid hypoxic mixtures. The following provide examples of constraints to consider, noting that they would not be applicable to all device types:
 - Upper/lower limits of delivered energy or article;
 - Total delivered energy or article over time;

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- Rate of change of energy or article delivered; and
- Allowable overshoot/undershoot.

- **Data logging** – FDA recommends that PCLC devices follow IEC 60601-1-10 (e.g., Clause 6.3 PCLCS Variable Logging of IEC 60601-1-10 Edition 1.2 2020-07) related to data logging of variables for a PCLC device. As part of data and time recording capabilities, manufacturers should consider maintaining a log of system variables and parameters, any mode switches including entering a fallback mode, number of adjustments to the physiologic variable, number of clinician interventions, any inputs to the user interface, and any other information essential to conduct root cause analysis in the event of system failure, malfunction, and/or patient harm. Information from data logging can be used in reporting Medical Device Reports,²⁰ including those related to automation use-related faults.
- **Alarms** – When manufacturers include an alarm system, as described in IEC 60601-1-10 (e.g., Clause 6.2 Alarm Systems of IEC 60601-1-10 Edition 1.2 2020-07), to notify users when hazardous situations exist, FDA recommends manufacturers follow IEC 60601-1-8: *General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems* or an equivalent method to evaluate the alarm system.

(5) User Interface

We recommend that manufacturers consider the user interface as an important safety element of the PCLC device and follow IEC 60601-1-10 (e.g., Clause 6.1 Usability of IEC 60601-1-10 Edition 1.2 2020-07) when developing their user interface. The user interface of a PCLC device directly influences aspects of a user's understanding of the control algorithm and energy or article that it is delivering. We recommend manufacturers consider user interface designs for their PCLC device that:

- Communicate relevant patient health status and device states considering a user's understanding of the device's operation and previous knowledge (e.g., with relevant devices) to allow appropriate responses.
- Ensure users have operational transparency, and can understand, supervise, monitor, and program the PCLC device operating at different modes.
- Provide sufficient information to avoid confusion about the current and past operating states of the device.
- Identify and communicate situations when the PCLC system is approaching safe operating limits or cannot safely control the intended physiologic variable (e.g., delivery rate saturated at the maximum value for longer than expected without the control objective being met).

²⁰ For more information on Medical Device Reporting see the “[FDA Guidance Document: Medical Device Reporting: Guidance for Industry and Food and Drug Administration Staff](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-reporting-manufacturers)” (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-reporting-manufacturers>).

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- Notify the user when the device enters a fallback mode due to occurrence of a fault in the system or switches to a different mode due to a change in the patient state including presenting clear information of why the change occurred, current mode of the device, and information for the user to successfully intervene if necessary.
 - For example, if the PCLC device delivers a drug in closed-loop mode and encounters a non-resolvable issue (e.g., sensor disconnected), the PCLC device, while notifying the user, can convert to an open-loop mode where therapy continues to be delivered at a pre-determined level. For the user to successfully intervene, information about the state of the patient such as the amount of drug delivered during the automatic mode, history of vital signs, reason for switching the mode, and how the issue can be resolved, should be communicated to the user through the device user interface. Likewise, if the automatic mode is to be resumed, the device should prompt for the user to input relevant information about therapy that was delivered by the user in order to ensure any safety constraints are met.
- Communicate current and past quantity of energy or article delivered or removed, including with alarms as necessary, for providing transparency on device operation and preventing delayed detection of physiological deterioration. A PCLC device can stabilize a physiologic variable that has associated physiologic monitoring alarm conditions with automatic changes in therapy that could go unnoticed by the user. This could result in patient deterioration that goes unnoticed, where, without the PCLC device applied, it could be recognized by the user from an alarm on the patient monitor due to a change in the physiologic variable or due to the need to change the dose of therapy.

C. Verification and Validation Considerations

The verification (demonstrating that the device meets specifications) and validation (specified design meets user needs and intended uses) activities warranted will depend on the level of risks associated with the device, the purpose of the PCLC technology, and the intended use of the device. The medical device manufacturer must verify and validate the PCLC device design consistent with 21 CFR 820.30. For example, a manufacturer should:

- Verify that sensor(s) meet all specifications for the PCLC device.
- Verify that actuator(s) meet all specifications for the PCLC device.
- Verify and validate the performance of all safety features including fallback modes and alarm systems.
- Verify that the PCLC system response related to safely controlling a physiologic variable meets specifications during normal and foreseeable worst-case conditions considering the range of device configurable parameters, modes of operation, clinical conditions, and patient conditions (i.e., inter-patient and intra-patient variabilities) that can affect the system performance. This can include a parameter sensitivity analysis to demonstrate that the device meets specifications across all combinations

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of adjustable parameter values. When applicable, we recommend providing graphical presentation(s) of time-domain responses such that any over- and under-shoot of desired delivery rates or physiologic set points can be determined at settings that will be commonly used.

- Verify the PCLC system response meets specifications during foreseeable functional disturbances (e.g., sensor noise and/or drop out, actuator failure, worst-case delivery rates) and clinical disturbances (e.g., change in the patient's response caused by a change in concomitant therapy), and demonstrate that the system responds as intended under these conditions.
- Validate the user interface(s) such as evaluating that user(s) are capable of correctly using the interface(s) including interpreting the therapy being provided by the PCLC system.
- Validate that use-related risks are mitigated to an acceptable level.
- Validate that the users understand how the system enters and exits different modes including device-human exchanges in operation and what the user needs to do during those periods.
- Validate risk control measures for the user to respond when fault conditions and automation-related use errors occur.
- Validate that the PCLC response specifications (e.g., Clause 8.2.2.6 of IEC 60601-1-10 Edition 1.2 2020-07) support safe and effective operation during normal and foreseeable worst-case conditions.
- Validate that the system will perform as intended.

As part of the device performance testing typically submitted in a premarket submission, a manufacturer should include documentation on the results of verification and validation for the PCLC device that addresses the elements listed above. This can include bench, computational, animal, and/or clinical testing as discussed below in Section VII. When reporting non-clinical bench testing, manufacturers should consider the recommendations in the FDA guidance document, "[Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submission](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket)."²¹

VI. Non-Clinical Testing Considerations

Evaluation of medical devices with PCLC technology necessitates a broad range of assessments common to medical devices such as biocompatibility, electromagnetic compatibility (EMC), electrical safety, sterility, cybersecurity, and software verification and validation. Manufacturers should refer to specific guidance documents related to these topics to determine when and what type of testing should be considered for their PCLC device. Additional testing not related to the PCLC technology could be warranted depending on the risks of the device.

²¹ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket>

When developing and evaluating a PCLC device, a combination of bench, computational, animal, and/or clinical test methods could be needed. Regardless of the specific test methods, FDA recommends that manufacturers consider following a structured method of designing disturbance and uncertainty scenarios to stress-test the PCLC device and ensure that the PCLC device is tested in clinically relevant worst-case conditions. The information in this section is intended to provide manufacturers with considerations for designing non-clinical testing for medical devices with PCLC technology. Clinical study designs for PCLC devices are expected to vary because of the variety of intended uses, risk profiles, and device designs. Therefore, this guidance document does not provide specific recommendations for performing clinical studies. Manufacturers are encouraged to refer to the FDA guidance document, “[Design Considerations for Pivotal Clinical Investigations for Medical Devices](#)”²² and to interact with the Agency through the [Q-submission process](#)²³ when designing clinical studies for PCLC devices.

A. Animal Testing²⁴

Animal testing of PCLC devices should address factors that cannot be evaluated through bench tests or in a clinical study. When *in vivo* animal studies are used to evaluate a PCLC device, we recommend manufacturers consider the following in their study design and include this information in premarket submissions as applicable:

- The clinical relevance of the animal model. The animal model should provide a test system that reasonably simulates use in humans. Manufacturers should provide scientific evidence to support the animal model chosen.
- Identification of the relevant physiological and anatomical differences between the animal model and intended human use. Manufacturers should justify why the animal model is appropriate given the physiological and anatomical differences between the animal model and human use.
- Differences in the expected intra- and inter-subject variability in the response of the physiologic variable to the delivered energy or article in the selected animal model compared to human use.
- If the PCLC device used in the testing differs from the final finished device, an assessment of why any differences between the device used and final finished device do not affect the study results.
- Use of a risk-based approach in developing animal study protocols. The animal study should address known risks of the PCLC device, which can be identified through

²² Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-and-pre-market-submission-recommendations-interoperable-medical-devices>

²³ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>

²⁴ FDA supports the principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

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literature review, device design, bench testing and basic exploratory studies. The risks inherent to the indications for use should be considered as well.

- Study conduct should be guided by a protocol with objectives that assess each identified risk, and acceptance criteria should be developed with a scientific rationale. Objectives to evaluate potential adverse effects on the structure and function of tissue locally and systemically should be included.
- Best practices for the development, conduct and presentation of these animal studies while incorporating modern animal care and use strategies.
- Any differences in the timeline (i.e., amount of time the PCLC device is applied to the animal) of the animal study versus the clinical study.

Animal studies intended to evaluate safety must be performed in compliance with 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies (GLP). Prior to performing animal studies, FDA recommends that manufacturers seek FDA input on the animal study protocol using the [Q-Submission Program](#).²⁵ In addition, if you are proposing to use a non-animal testing method that you believe is suitable, adequate, validated, and feasible, we also recommend that you discuss the proposal using the Q-Submission Program. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

B. PCLC Device Testing Using Mathematical and Computational Models

PCLC systems are complex and there are many types of disturbances that could lead to unsafe conditions or to the device not functioning as intended. Evaluating a PCLC device in all possible clinically relevant scenarios using animal and/or clinical studies would not be feasible. Closed-loop systems across engineering domains are traditionally designed using computational and mathematical modeling approaches to increase efficiency (e.g., by effective iterative design), reduce costs, and prevent errors during system development. Therefore, evaluation of a PCLC device using a computational and/or mathematical model of the patient response can provide an alternative to or supplement animal and/or clinical studies. FDA recommends that manufacturers refer to the “[FDA Guidance Document: Reporting of Computational Modeling Studies in Medical Device Submissions](#)”²⁶ for FDA’s current thinking on information on computational modeling studies that should be collected and included in a premarket submission.

The validity of a model-based evaluation of a PCLC device will depend on, among other study design aspects, the computational model used and the evidence supporting that model. Generally, the patient model(s) used to design the control algorithm for a PCLC device will be different than the model(s) used for evaluation to validate device performance. The model used for design could be a simple model that captures basic physiological responses directly related to the inputs

²⁵ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>

²⁶ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions>

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and outputs of the PCLC device, while models used for evaluation could include, for example, a broader range of physiological responses, clinical inputs, and interactions with other physiological systems in order to simulate clinically relevant scenarios. We recommend each computational model used in PCLC device development, whether used for design or evaluation, be evaluated for predictive capability within its context of use.

When developing a computational patient model (or selecting a previously developed computational patient model) for testing a PCLC device, we recommend the following considerations:

- Characterization of the input and output response of interest;
- Identification and characterization of other physiologic system responses known to be impacted by the input or that interact with the physiological system of interest (e.g., cardiovascular and pulmonary system interactions can result in therapy to one system affecting the other);
- Identification and characterization of inter-patient variabilities (e.g., range of responses expected from different patients);
- Identification and characterization of intra-patient variabilities (e.g., degree to which an individual response can change over the course of a procedure);
- Identification and characterization of physiological and clinical disturbance scenarios expected (e.g., changes in other therapies provided to the patient);
- Assumptions of the model and how they can impact the testing and interpretation of the results; and
- Parameter selection including how parameters were identified and values selected, and why the values are applicable to the intended patient population.

Model evaluation should be focused around the proposed model context of use, that is the role of the model in performance testing of the PCLC device. We recommend credibility assessment of the computational patient model include consideration of:

- Model verification,²⁷ by addressing the credibility factors in ASME V&V 40 (i.e., Clause 5.1 Verification in ASME V&V 40-2018). We recommend manufacturers:
 - Identify sources of numerical error to include in calculation verification for the testing and computational patient model. Numerical Solver Error in ASME V&V 40 would not be relevant for patient models that are systems of ordinary differential equations only.
 - Include justification of the selections of numerical error sources in the study report.
- Model validation, that is, comparison of model predictions against independent experimental or clinical data that were not used for model development, by addressing the credibility factors in ASME V&V 40 (i.e., Clause 5.2 Validation in ASME V&V 40-2018). We recommend that manufacturers consider the following:

²⁷ Verification and validation in this section refer to the evaluation of computational models and are used as defined in the [“FDA Guidance Document: Reporting of Computational Modeling Studies in Medical Device Submissions”](#)

- An assessment of the assumptions in the model to demonstrate that physiological processes that have not been included in the model are not likely to impact results.
- Uncertainty quantification and sensitivity analyses to evaluate the impact of inter-patient and intra-patient variability on key parameters relevant to the input, output, and physiologic response of interest being evaluated.
- Information on the subjects and conditions in the experimental or clinical studies that provide the comparative data in the context of computational patient models to enable an assessment of the validation results.
- Assessment of the relevance of the validation activities to the context of use (for example, if a physiological model is validated against data derived from animal studies, the validity of this extrapolation to predict human physiological response should be assessed).

Information to support the use of a computational patient model can come from, validation results for sub-models of the overall patient model, historical validation results from previous versions of the patient model or related patient models, historical evidence of the model's predictive ability for other contexts of use, or calibration results demonstrating good fits to experimental or clinical data. We recommend manufacturers provide a description of how the information used supports the model for its context of use.

(1) Analytical Assessments

Analytical methods can sometimes be applied to evaluate the stability and robustness of a PCLC system. These methods generally use a mathematical model of the response of the physiologic variable to the delivered energy or article. The choice of analytical approach and its role in PCLC device evaluation will depend on the particular PCLC device, control algorithm design method (e.g., model-based), and the physiologic response. If analytical methods with mathematical models are used as part of a PCLC device evaluation, FDA recommends manufacturers consider the following, along with the information above in Section VII.B.(1) for each model used, in the testing:

- Description of the analytical method and why it is applicable for the application given the processes to which it is applied (e.g., phase and gain margin for linear processes);
- Description of how the analytical method is applicable to the particular PCLC application; and
- Limitations of the analysis methods (e.g., how simplifying assumptions impact the results).

(2) Entirely Virtual Testing

In the context of this guidance, entirely virtual testing refers to testing that is performed completely in a simulated computer environment so that all parts of the system including the patient's physiology and PCLC device components (e.g., physiologic-measuring sensor, control algorithm, actuator) are modeled. The advantage of this type of testing is that conditions can be simulated across a wide range of scenarios including inter-patient and intra-patient variability

and uncertainty, device variability and uncertainty, and device failure modes. Data from such simulations can potentially identify situations that can result in unsafe conditions, as well as potentially demonstrate expected performance of the system across the intended patient population, prior to a clinical and/or animal study.

When performing virtual testing, information demonstrating the validity of the individual models as well as the modeled system is important to support the virtual testing within its context of use. FDA recommends manufacturers consider the credibility assessment as discussed above in Section VII.B.(1) for each model (e.g., patient's physiology, physiologic-measuring sensor, actuator), as well as their interaction and the overall system implementation. This can include activities such as uncertainty quantification to evaluate how uncertainties associated with the individual models propagate through the simulations and affect the overall result.

(3) Hardware-in-the-Loop Testing

Hardware-in-the-loop testing can be performed using computational models of the patient's physiology interfaced with the PCLC device hardware. This can enable testing of the PCLC device in real time and with the device hardware. In some situations, this can provide a more realistic type of testing that can be used to identify system failure modes and hardware limitations. In addition, both physiologic and non-physiologic disturbances expected during clinical use can be simulated on the bench, thereby identifying unsafe conditions early in the device development lifecycle.

The patient model should be integrated with the device components in hardware-in-the-loop testing in a manner that would minimally affect the functionality of the system and not alter the realistic nature of the test (e.g., by introducing additional delays to the system). This will generally involve actuator transfer mechanisms to relay the actual output from the actuator to the computational patient model, and signal simulation and generation tools to communicate the output of the computational patient model to the sensor. The characteristics of these testing tools can impact the relationship between the bench testing results and device performance in a clinical environment. We recommend that manufacturers characterize the performance of the actuator transfer mechanisms and signal generators, including accuracy and time delays, and account for these properties in their test plans and analyses.

VII. Human Factors Testing

We recommend that manufacturers performing human factors testing of the PCLC device consider recommendations in the FDA guidance document, "[Applying Human Factors and Usability Engineering to Medical Devices](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices),"²⁸ which identifies different types of human factors validation testing including simulated use testing and actual use testing. Simulated use testing in the context of PCLC devices can include hardware-in-the-loop configurations as described above in Section VII.B.(4) that use computational models of patient physiology. While human factors validation testing is typically conducted under simulated use conditions in order to ensure the testing of all risk management measures related to critical tasks, testing in a clinical setting might

²⁸ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices>

be needed to enable realistic and meaningful evaluation because automation-related use errors might not be predictable. In these cases, it would be appropriate to perform human factors validation testing during actual use of the device. We recommend manufacturers consider if simulated environments are sufficient to evaluate each use scenario related to device automation or if actual use testing may be warranted. When performing human factors testing in either simulated or actual use environments, we recommend that use scenarios and post-test surveys be designed to capture information on automation-related hazards such as complacency and automation bias. When labeling includes instructions for the user to recognize an emergent unsafe condition and intervene to prevent harm, results of human factors testing should be provided to show that reliance on user intervention constitutes an adequate risk control measure. Whether simulated or actual use testing is used, test participants should receive training that is representative of the training provided during actual use of the device. We encourage manufacturers to seek feedback on the human factors testing protocol for the PCLC device via the [Q-Submission Program](#)²⁹ prior to conducting the test.

A. Training

We recommend appropriate training be developed for users of the PCLC device in accordance with the “[FDA Guidance Document: Applying Human Factors and Usability Engineering to Medical Devices](#).”³⁰ The training plan should be provided in your premarket submission. When designing training materials for intended users of PCLC devices, we recommend manufacturers consider how the training ensures the user’s understanding of the following:

- The role the device plays in the management of the patient;
- Factors and conditions that can affect the PCLC device performance;
- Configuring and operating the device through the user interface;
- The different automated and non-automated modes including:
 - Which modes the device can automatically switch to and when it will switch to those modes (e.g., fallback modes);
 - Which modes the user can select and when each mode should be used in the clinical management of the patient;
- How to detect when the control strategy is nearing its limitations and could fail (for example, if the therapeutic agent is being delivered at the maximum rate and the patient is not responding) and what the response of the user should be; and
- Responding to automation-related use errors that would be unanticipated by the user.

The training should include information about limitations of automation technology, as well as the potential use errors anticipated during the use of the device. Training plans for PCLC devices could include simulation-based training in appropriate clinical settings in addition to a standard training program. For example, simulation-based training could be dedicated to device

²⁹ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>

³⁰ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices>

automation interaction functions and related hazards, while a standard training program could be dedicated to non-automated device interaction considerations and hazards.

It is important for trainees to experience complacency, automation bias, and loss of situational awareness (see Section V.B.3) related to use-related hazards, automation failures, alert or warning failures, infrequent critical events, and inappropriate responses. Experiencing automation failures during practice sessions can help reduce automation-related use errors by encouraging critical thinking when using automated systems. Experiencing automation failures will also facilitate training in automation-related use error management and development of the skills needed to appropriately respond to use errors.

VIII. Labeling

The following recommendations are intended to help prepare labeling that satisfies the applicable requirements of 21 CFR parts 801 and 809, and applicable labeling requirements for premarket submissions (e.g., 21 CFR 807.87(e) and 21 CFR 814.20(b)(10)).

FDA recommends that devices with PCLC technology include in the labeling, all information identified in IEC 60601-1-10 Edition 1.2 2020-07 Instructions for Use and Technical Description clauses, as summarized in Annex C of that document, or equivalent information. In addition, FDA recommends that the following information be included in the device labeling as appropriate:

- Description of the PCLC device including the following components:
 - Physiologic measuring sensor including performance specifications, identification of specific models, software versions, and configuration (e.g., bandwidth) that the system can be used with, and any limitations on how or where the sensor can be applied to the patient compared to the cleared or approved standalone device (e.g., a standalone patient monitoring medical device might have sensors that could be applied to different anatomical locations, but the PCLC device could be validated to only place the sensor at a specific anatomical location);
 - Actuator including performance specifications, energy or articles that the system can deliver, identification of specific models, software versions, and configuration that the system can be used with and, as applicable, maximum and minimum delivery rates of the article or maximum amount of article that the system can deliver;
 - Description of control algorithm for all modes where the device can operate and performance specifications related to the PCLC system response for each mode including, for example, the time it takes to reach a target level and steady-state error and any constraints on the delivery of energy or article (e.g., so that the delivery is consistent with the drug label, see Section V.B.(4)); and
 - Alarm information including descriptions of the alarm conditions, related hazardous situations, and how the user is expected to respond.

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- Descriptions of the conditions under which the device has been tested to operate including patient conditions, disturbances (e.g., other therapies provided to the patient, sensor noise), and device configurations (e.g., range of parameters). This can include summaries of clinical and/or non-clinical testing to provide the user information on how the device should be configured.
- Description of how the PCLC device operates (i.e., mental model as discussed in IEC 60601-1-10) sufficient to allow the user to understand when the device is reaching its limitations, potentially creating a hazardous situation, and the appropriate actions to mitigate the risk of the hazardous situation.
- Descriptions of what the PCLC device does and does not do related to managing or treating the patient and what the user should do to ensure appropriate patient monitoring and management.
- Identification of entrance criteria related to the patient's condition and what information should be provided by the user for each PCLC mode to operate.
- Descriptions of fallback modes including scenarios that can result in the device entering a fallback mode and the expected response of the user (e.g., instructions for the user to switch to a different mode).
- Information on the system data logging features, including who has access to them.
- Information on how to program and operate the system, including how to change the set point and operational mode of the device.
- Information on how the user interface communicates the patient's condition, delivered energy or article, and operating mode of the device.
- Accessories that have been tested to function as intended with the PCLC device (for interoperable medical devices, see the "[FDA Guidance Document: Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-and-pre-market-submission-recommendations-interoperable-medical-devices)"³¹ for additional labeling recommendations);
- Instructions for device users on how device functionality should be confirmed before use including testing that all components (e.g., sensors and actuators), device modes, and safety features are functioning as intended.
- Identification of any PCLC components that should not be replaced, for example, during maintenance or if only representatives from the manufacturer should replace

³¹ Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-and-pre-market-submission-recommendations-interoperable-medical-devices>

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- 1131 certain components or perform maintenance including, where appropriate,
1132 information on the device of who to contact for servicing.
1133
1134 • For reusable (e.g., medical facility) PCLC components, we recommend affixing a
1135 label that identifies who to contact in the event servicing is needed and the use life of
1136 the PCLC component.
1137
1138 • Procedures to verify operation of all device modes and safety features following
1139 software updates.

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