Draft Guidance for Industry and Food and Drug Administration Staff

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The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Low Glucose Suspend (LGS) Device Systems

DRAFT GUIDANCE

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

Preface

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The Content of Investigational Device Exemption (IDE) and Premarket Applications for Low Glucose Suspend Device (LGS) Systems

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This draft guidance is intended to provide recommendations to Sponsors or Applicants[1] planning to develop and to submit, an Investigational Devices Exemption (IDE) or marketing application for a Low Glucose Suspend (LGS) system for single patient use in the home environment. The guidance discusses critical elements regarding nonclinical testing and clinical studies needed to support such an application. Section VII of the guidance and Appendix A identify the necessary information for an IDE submission whereas the rest of this guidance describes the information necessary to support a premarket approval (PMA). FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] For purposes of this guidance, *Sponsor* refers to any person who takes the responsibility for and initiates a clinical investigation; *Applicant* refers to any person who submits an application, amendment, or supplement to obtain FDA approval of a new medical product or any other person who owns an approved application. *Sponsor* is used primarily in relation to investigational device exemption (IDE) applications and *Applicant* is used primarily in relation to premarket approval (PMA) submissions.

II. Background

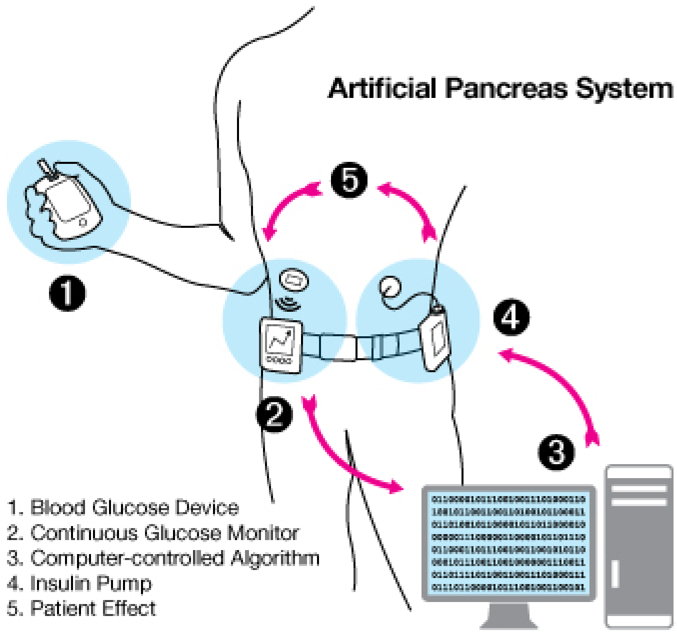
Diabetes mellitus has reached epidemic proportions in the United States (US) and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although there are many devices available that help patients manage the disease, FDA recognizes the need for new and improved devices for treatment of diabetes.

Today, patients with Type 1 Diabetes[2,3] (T1D) utilize a variety of devices to monitor and manage their blood glucose levels. Hand-held portable glucose meters which have been cleared by FDA for home-use, referred to as Self Monitoring Blood Glucose (SMBG) devices in this document, allow patients to determine what their blood glucose level is by performing a finger stick. Patients use SMBG devices multiple times a day to help make decisions regarding insulin administration. Some patients also use insulin pumps that allow for continuous subcutaneous insulin infusion (CSII). The most recent device available to patients is the continuous glucose monitoring system (CGM), which uses a sensor inserted into the subcutaneous tissue and continuously measures the concentration of glucose in the interstitial fluid. While not a substitute for testing glucose in the blood, the CGM device allows patients to monitor trends and patterns of glucose excursions. However, even with the aid of these devices, maintaining blood glucose levels within a suggested optimal range is a daily struggle for people living with T1D, and the risk of hypoglycemia associated with tight glycemic control remains an ever-present danger to patients with diabetes.

An LGS system links a CGM to an insulin pump and automatically suspends or reduces insulin infusion temporarily based upon specified thresholds of measured interstitial glucose levels. An LGS system is a type of autonomous system commonly known as an artificial pancreas. This type of system is designed to reduce the likelihood and/or severity of a hypoglycemic event.

The illustration below describes the parts of a type of artificial pancreas system such as an LGS system and depicts how they work together.

[2] ADA Clinical Guidelines (2011) Diabetes Care, 34 (Suppl 1):S62-69
[3] AACE Guidelines (2011) Endocrine Practice 17 (Suppl 2):1-53



(1) **Blood Glucose Device (BGD).** Patients use blood glucose devices, such as SMBGs, to measure blood glucose levels at home. To get the most accurate readings possible from a continuous glucose monitoring system (CGM), the patient needs to adjust the CGM at intervals throughout the day using readings from a blood glucose meter. For some artificial pancreas systems, like the LGS system, the patient will still need to use a blood glucose meter to manage his or her diabetes throughout the day.

(2) **Continuous Glucose Monitor (CGM).** A CGM provides a steady stream of information about the patient's blood glucose levels. A sensor placed under the patient's skin (subcutaneously) measures the glucose in the fluid around the cells (interstitial fluid). A small transmitter then sends information to a receiver, which continuously displays an estimate of blood glucose.

(3) **Control algorithm**. A control algorithm is software embedded in a computer that receives information from the CGM and performs a series of mathematical calculations. Based on these calculations, the controller sends insulin dosing instructions to the insulin infusion pump.

(4) **Insulin pump or Insulin infusion pump.** Based on the instructions sent by the controller, an insulin infusion pump adjusts the insulin delivery to the subcutaneous tissue to lower the reduce hypoglycemia.

(5) **The patient effect.** The patient is an important part of the LGS system. The amount of glucose circulating in the blood is constantly changing and affected by the patient's diet, level of activity, and how the body metabolizes insulin.

This kind of system serves as a potential back-up when a patient is unable to respond to a hypoglycemic event. Patients using this system will still need to be active partners in managing their blood glucose levels by periodically checking their blood glucose levels with a BGD and giving themselves insulin or eating, to maintain control of glucose levels. There are two types of LGS systems:

1) A **reactive low glucose suspend system** temporarily reduces or stops insulin infusion when the CGM value reaches a predetermined low glucose value.

2) A **predictive low glucose suspend system** predicts (or anticipates) a future hypoglycemic event based on the rate at which glucose levels are falling and temporarily stops or reduces insulin infusion before the patient becomes hypoglycemic.

This guidance will outline critical elements for the investigation of these devices and the regulatory path in the development of an LGS system. Sponsors and Applicants are encouraged to consult closely with FDA during the course of development of their LGS system.

III. Scope

The scope of this guidance is limited to the discussion of autonomous systems that temporarily reduce or suspend insulin infusion (i.e., LGS systems) in an effort to reduce or mitigate hypoglycemia. The guidance makes recommendations for LGS systems based upon current technology. However, this guidance can be applied similarly to LGS systems using new glucose sensing and/or infusion pump technology. The availability of various CGMs, BGDs, insulin pumps, and control algorithms allows for the development of a number of LGS systems; each of these systems would constitute a unique device system that will require individual study for device approval.

The primary product code for the LGS system is 'LHE' (controller closed-loop blood glucose), which is currently regulated as a class III device system. The scope of this document is limited to the devices that makeup the LGS system.

If particular disposable devices will be provided or recommended for use with the LGS system, such as infusion sets or cassettes or test strips, these accessories should also be identified. These disposable devices should be included in the PMA as they are part of the system.

For purposes of this document, FDA defines the LGS system to include the:

- Continuous Glucose Monitor (CGM)
- Blood Glucose Device (BGD) used for calibrating the CGM and making diabetes management decisions
  - BGD reagents or test strips
  - BGD quality control solutions

- Control algorithm
- Infusion pump
  - Fluid infusion set for the complete fluid pathway from, and including, the drug reservoir or fluid source container (e.g., bag, cassette, vial, syringe), infusion set, extension sets, filters and valves, clamps, up to and including the patient connection
- Components and accessories (e.g., power cord, wireless controller)
- Network (i.e., any device or system physically or wirelessly connected to the insulin pump)

The patient interface plays a critical role in the performance of the LGS system and should be considered an integral component related to the overall performance of the LGS system.

This guidance is based on the assumption that any insulin, used as part of the device has been approved by the FDA for delivery via an insulin infusion pump and is being used in accordance with the drug labeling. It does not discuss the data needed to support a drug labeling modification. Also, this guidance does not include LGS systems that may have synthetic or artificial cells, tissues or organs. It should be noted that the lead Center authority may change depending upon the inclusion of biologics. Consequently, this guidance does not address issues unique to combination products.[4] Although elements of this guidance may be applicable in those circumstances, additional considerations outside the scope of this guidance would also need to be addressed.

The use of this guidance can be applied to LGS systems for hospital use, but this guidance does not focus on the additional information needed to address the limitations of glucose measurement devices in hospitalized patients and multiple patient use.

IV. Device Description

The LGS system currently is a single device that consists of a number of device components communicating to one another to form a complete system. However, as technology advances and the potential for miniaturization of the various device components becomes possible, the LGS System could one day be a single unit containing the various functions of an LGS system. To unify the device description for all types of LGS systems, Applicants who seek to

[4] 21 CFR 3.2(e): Combination product includes: (1) a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that is physically, chemically, or otherwise combined or mixed and produced as a single entity: (2) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (4) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

market an LGS system should describe the device by the system and each of the functional components. FDA recommends Applicants provide the following information for an LGS device description.

A. LGS System

The Applicant should provide the following descriptive information regarding the device system.

- A clear statement of the intended use and indications for use as described in Section V.
- A picture or schematic of the entire system and how the components interface.
- A listing of all the device functional components and accessories that are part of the LGS system (including model numbers).
- Because the system is intended for ambulatory use, a description should be provided on how the system was designed for mobility, various environmental conditions (e.g., water exposure, altitude, electromagnetic interference), and ruggedness.
- Because the system is intended for lay use, a description should be provided on how the device has been designed to be safely and effectively used by the lay user population, which often have limited or no clinical background, and how hazards arising from lay use have been mitigated.
- Detailed description of the technological features of the system (e.g., alarms, etc.).

For each of the device functional components, the descriptive information identified in the following sections should be provided.

B. Blood Glucose Device (BGD) functional component

Applicants should provide the information listed below for the Blood Glucose Device (BGD) component of the LGS system, if applicable.

- Description of function(s) performed by the BGD.
- A list of all BGD functional components and accessories as appropriate. In addition to the instrument, reagents and quality control materials, accessories might include standards (calibrators), data transmitting equipment or software that processes data or quality control results.

- A summary description of the methodology (e.g., electrochemical, spectrophotometric measurement).

- A description of the test principle, i.e., all chemical reactions and concentration of all reagent components, as appropriate.

- Matrix of blood sample to be analyzed (e.g., fingerstick capillary blood).

- The specifications for the BGD including, for example:
    - Bias
    - Imprecision
    - Linearity
    - Measuring range
    - Traceability to reference materials or methods
    - Stability of device components, as appropriate
    - Expected values, as appropriate;
    - Detection limit (e.g., limit of blank, limit of detection, and limit of quantitation), as appropriate;
    - Analytical specificity, as appropriate, including:
        1. Cross-reactivity with compounds that have similar molecular structures; and
        2. Interference (from endogenous and exogenous compounds/conditions as well as both prescription and over-the-counter medications).
        3. Environmental interference (e.g., from temperature, humidity and altitude).

C. Continuous Glucose Monitor (CGM) functional component

Applicants should provide the following list of information presented below for the CGM functional component of the LGS System.

- Device description, including a list of all device components and accessories. As appropriate, this would include sensors, transmitters, receivers, display monitors, devices to aid in the insertion of the sensor, quality control materials, standards (calibrators), data transmitting equipment, and software that processes data.

- Description of the function(s) the CGM performs in the LGS system.

- Description of the methodology employed for glucose measurement (e.g., electrochemical measurement), chemical reactions, including concentrations of reaction substrates, as appropriate.

- Description of the sample matrix analyzed (e.g., interstitial fluid) and the anatomical site, as appropriate.

- Description of the specific BGD intended for calibrating the CGM, if applicable.

- The specifications for the CGM including, for example:
    - Bias
    - Imprecision
    - Linearity
    - Reportable range
    - Traceability to reference materials or methods
    - Stability of device components, as appropriate
    - Detection limit, as appropriate
    - Analytical specificity, including:
        1. Cross-reactivity with similarly molecular compounds; and
        2. Interference (both endogenous and exogenous compounds/conditions, as well as both prescription and over-the-counter medications).
        3. Environmental interference (e.g., from water, humidity, etc.).

D. Control Algorithm functional component

The control algorithm functional component should include the entire signal processing from the generation of the raw CGM signal to the changes in the command for insulin delivery. The control algorithm should include the following information.

- Description of the signal processing starting from the raw CGM signal to the reported CGM value. This should describe the method (e.g., signal averaging) of calculating the reportable CGM value, the frequency of reporting the CGM value, and the devices used in the calibration method (identification of the BGD).

- Description of how the algorithm addresses signal dropout and if applicable a description of any analyses that occur to determine if the CGM value is real or physiological.

- Description of the control algorithm that adjusts insulin dosing. This description should be detailed sufficiently to allow the recreation of the control algorithm. This should include.
    - Defining the control algorithm equation(s) in symbolic form.
    - Defining each symbol with a parameter name for the control algorithm equation(s).
    - Defining all parameters that cannot be modified (fixed) by the user and/or healthcare provider and their corresponding parameter value.
    - Defining all parameters that are adjustable by the user and/or healthcare provider.
        - Define the parameter value range.
        - Identify the user that can adjust the parameter (i.e., patient or healthcare provider) and describe how the device secures these parameter values that are adjustable only by the specified user.

- Summary of the requirements necessary for the control algorithm to reduce or stop insulin infusion.

- Summary of the requirements necessary for the control algorithm to recommend restart of insulin infusion and identification of the returned infusion rate.

- If applicable, a description of any safety check that the control algorithm performs to ensure insulin infusion has been turned on or off.

- Summary of the verification activities to show the control algorithm has been properly coded into the software.

E. Infusion Pump functional component

The infusion pump functional component should include the following information.[5]

- If the infusion pump is labeled for use with a specific drug, the labeling should be consistent with the approved indications and route of administration. To facilitate FDA's review, the FDA approved labeling for that device or drug should be provided.

- A detailed description should be provided (including, where appropriate, assembly drawings, schematics, and/or specification control documents) of the pump and its functional components, and accessories including:
    - The infusion delivery mechanism

[5] Also see the draft *Guidance for Industry and FDA Staff - Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions*, issued April 23, 2010.
When final, this guidance will represent the Agency's opinion regarding elements for consideration for this component.

  - The bolus mechanism
  - The drug reservoir
  - Pump tubing and connectors (built-in or external to the pump)
  - A user-interface, consisting of the programming unit, display unit, audio and tactile notification units
  - Power supply or pump battery and circuitry to charge the battery
  - A communication interface, including network components and interfaces to other devices and systems
  - Refill frequency

- If the pump contains software, a detailed description of the software design should be provided, including key elements, such as:
  - A drug library or other dose error reduction mechanism
  - A real time clock (RTC)
  - On-board memory
  - Pump log
  - Alarm handler
  - Watchdog timer

- The principle of operation of the infusion pump (i.e., the scientific principles behind how the device achieves its intended use).

- The user interface components of the pump, including keypads, control menus, data entry screens, displays, indicator lights, alarms, auditory and tactile feedback, infusion sets, cassettes, free-flow prevention mechanisms, tubing, latches, doors or other components of the physical pump that may be manipulated.

- The specifications for the infusion device (e.g. flow rate accuracy specifications for bolus and basal deliveries, time to deliver bolus, etc.).

F. Communication Pathway functional component

The Communication Pathway functional component should describe the passage of information between the functional components. This functional component should include a description of the hardware and software that allows the passage of information. The description should include:

- Communication pathway. Applicants should describe all of the ways each functional component communicates to other functional components within the LGS system. The Applicant should identify the flow of communication (e.g., unidirectional or bidirectional) between the functional components and identify the information that is passed.

- Communication hardware. Applicants should describe how the information is passed between each functional component and describe the hardware necessary to communicate this information.

- If the system incorporates or is intended to incorporate radio-frequency (RF) wireless technology (e.g., IEEE 802.11, Bluetooth, Zigbee), the description should include information about the specific RF wireless technology and characteristics, its use and functions (e.g., remote monitoring or control, software updates), the data to be transmitted including any alarms transmitted wirelessly, quality of service (QoS) needed, wireless security protocols, and any limitations or restrictions relating to coexistence with other RF wireless technology or electromagnetic interference (EMI).

- If the device is capable of being remotely controlled or monitored from a distance, this capability should be identified with a description of the measures incorporated to assure safety.

- Any communication between the device and a hospital information management system or another device outside the LGS system.

V. Indications for Use

According to 21 CFR 814.20(b)(3)(i), an indications for use statement is "a general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended." As LGS systems are intended to mitigate or reduce hypoglycemic events, the indications should specify how the LGS system reduces the observed event and how events are defined. The Agency recommends the use of validated methods to determine if the hypoglycemic event has been mitigated and or reduced.

The Agency currently proposes the following indications for LGS systems.

For device systems that are evaluated using clinically validated endpoints of hypoglycemia (e.g., seizures or loss of consciousness due to severe hypoglycemia, need for third party assistance, plasma glucose < 70 mg/dL as determined by devices that have been approved/cleared for monitoring of such, etc.).

- The LGS device system is indicated for subcutaneous infusion of insulin, continuous measurement of interstitial glucose, the quantitative measurement of glucose in fresh capillary whole blood samples, and to reduce the (e.g., frequency, duration, or number) of hypoglycemic events during the (e.g., day, at night, both) in the home, for patients with type 1 diabetes who have recurrent hypoglycemia to aid in the management of their disease.

For device systems using a correlate marker for hypoglycemia, such as data derived from CGMs that are not FDA approved for monitoring of blood glucose levels, the Agency recommends the following indication.

- The LGS device system is indicated for subcutaneous infusion of insulin, continuous measurement of interstitial glucose, the quantitative measurement of glucose in fresh capillary whole blood samples, and to reduce the likelihood or severity of a possible hypoglycemic event (e.g., frequency or duration) from occurring in the home, as determined by CGM measurements during the night (or day, or both) for patients with type 1 diabetes who have recurrent hypoglycemia to aid in the management of their disease.

Alternative indications can be proposed based upon the functional components used in the LGS system, the clinical study design, and the validity of the correlate used.

VI. Evidence - Performance

The Agency recommends the following critical performance characteristics be provided in the PMA.

A. LGS System

1. Software

Software documentation is an important aspect of both the IDE (Appendix A-V-B) and PMA. FDA recognizes that software updates or modifications that do not affect the performance of the device system can change between the pivotal study and the PMA submission. The Applicant should provide complete software documentation in the PMA. Some useful guidance documents for software considerations are provided below.

- The Agency considers the LGS system and all of the components of the system to be a "Major" level of concern for the purposes of software review. The information to provide in a submission related to software has been delineated in the *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*.

- If the device includes off-the-shelf software, additional information should be provided as recommended in the *Guidance for Industry, FDA Reviewers and Compliance on Off-the-Shelf Software Use in Medical Devices*.

2. Animal or In-Silico Testing

A complete test report should be provided in the PMA submission describing the nonclinical testing used to support approval of the LGS system. Details of the non-clinical studies can be found in Appendix A-V-H.

3. Biocompatibility

Biocompatibility testing is a critical safety concern and should be provided prior to approval of an IDE (Appendix A-V-F). However, FDA notes that the biocompatibility testing provided in the IDE may be limited due to the short duration of contact of the LGS system in the proposed clinical study design. For a PMA, biocompatibility tests should be appropriate for the duration and level of contact with the device. For the purpose of assessing biocompatibility, the Agency recommends considering LGS systems to have prolonged (24h to 30 days) duration due to the potential for cumulative use of the device and its accessories. FDA recommends biocompatibility testing of the LGS system be performed on the final finished sterilized device for all device components and accessories. The Applicant should provide a complete test report of each biocompatibility test performed in the PMA. When addressing biocompatibility, we recommend following the FDA blue book memo entitled, Use of International Standard ISO 10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing' (Replaces #G87-1 #8294).

4. Sterility

Each of the different device components will require different types of processing or reprocessing, based on their intended use. The intended use will determine whether a device must be sterile, such as an implant that will be contacting normally sterile locations within the body, or whether it will require a lesser degree of microbicidal processing, such as a reusable component that is intended to contact only intact skin.

For sterile device components, use of FDA recognized consensus standards for conducting process development and validation testing is recommended. A searchable list of these standards is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. Products labeled "sterile" should be processed by methods that have been comprehensively validated by the Applicant to provide a sterility assurance level (SAL) of 10^{-6}.

For general guidance on reprocessing of reusable devices, we suggest referring to FDA's *Draft Guidance for Industry and FDA Staff - Processing/Reprocessing Medical Devices in Health Care Settings:*

Validation Methods and Labeling.[6] This document recommends that the labeling for reusable medical devices include at least one validated, technically feasible, comprehensive method for cleaning; and one validated, technically feasible, comprehensive and appropriate microbicidal method such as sterilization. Additionally, this provides a system to allow determination of the appropriate microbicidal process (based on intended use).

Regardless of whether the components are single use or reusable, the validated methods chosen need to be compatible with the device. The ability of the packaging materials to keep the product sterile and free from damage during transportation and shipping should be demonstrated and documented.

The product labeling should prominently indicate that the particular component is supplied sterile, or that it is supplied non-sterile. For device components that are not supplied sterile, the Agency recommends that a scientifically valid rationale be provided.

LGS systems and accessories intended for prolonged use should include instructions in the labeling for cleaning and disinfecting the device, as appropriate, between uses. Also, where appropriate, "use life" information should be provided in the labeling, with supporting information (see Section X1. d. Product Performance and Shelf Life, below). This may include information such as the number of times the device can be reused, or guidance as to how users can make that determination (e.g., inspecting for wear and tear).

LGS systems may be used in the home environment. The Applicant should indicate cleaning agents/products in the labeling that are readily available to the average home-based user along with validated instruction for cleaning the device, in a manner that is consistent with the FDA Labeling Reusable Devices guidance.

In addition to the FDA Labeling Reusable Devices guidance mentioned above, reference to relevant Technical Information Reports (TIR) developed by the Association for the Advancement of Medical Instrumentation (AAMI) when developing labeling instructions for reusable medical devices is recommended.[7,8]

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[6] Note that this guidance is in draft form, but when final, this guidance will represent the Agency's thinking on this topic.
[7] AAMI TIR 12:2010, Designing, testing and labeling reusable medical devices for reprocessing in health care facilities: A guide for medical device manufacturer
[8] AAMI TIR 30:2003, A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices

5. Shelf Life

The shelf life of the LGS system, including accessories, should be supported with appropriate data, including both performance-based testing and package integrity, when applicable.

Performance

If the particular system contains sterile components, materials or reagents that could degrade over time, a shelf life should be included on the packaging. Additionally, performance data should be generated after an appropriate number of complete "use cycles" which should include cleaning or disinfection per the labeling.

The Applicant should provide data to demonstrate that the performance specifications of the particular system are maintained throughout the time period specified by the shelf life. If accelerated test methods are utilized, information validating that the test methods accurately simulate real-time conditions for the device should be provided.

Package Integrity

The Applicant should ensure that device package design and construction are validated to protect the device components from alteration or damage during shipping and transportation studies, and should also be validated to support the labeled shelf life (e.g., 1 year, 3 years). The validation process should be designed to assure that packaging will maintain its integrity (no breaches of the sterile barrier system) after being subjected to the rigors of real world, worst case shipping and handling, as well as stability testing (i.e., aging). This typically requires two validation test pathways: simulated shipping of packaged product (or accurate surrogate of product) followed by package integrity testing, and simulated (accelerated) aging followed by seal strength testing. The Agency recommends that confirmatory, real-time package shelf life testing be submitted as part of the PMA.

The Agency recommends the use of FDA recognized consensus standards for conducting various simulations and validation testing as described by the relevant standards.[9,10,11]

6. Electrical Safety

A complete test report should be provided in the PMA submission describing the electrical safety testing used to support approval of the LGS system. Details of the electrical safety can be found in Appendix A-V-G.

[9] AAMI / ANSI / ISO 11607-1:2006, Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems

[10] AAMI / ANSI / ISO 11607-2:2006, Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes

[11] ASTM D4169-09, Standard Practice for Performance Testing of Shipping Containers and Systems

7. Magnetic Resonance (MR) Imaging Safety

For information regarding Magnetic Resonance (MR) Imaging safety testing and labeling, please see FDA's guidance document, *Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment*. While the subject of the referenced guidance is passive implants, the information contained in it is also relevant for active devices like LGS systems.

8. Human Factors

FDA recommends a complete human factors evaluation of the entire system be conducted and provided within the PMA.

Reports of device-related incidents and recalls for diabetes devices have shown that patterns of use errors resulting from flaws in the design of the user interface have led to patient harm. The term *user interface* denotes all components of the device system with which the user interacts; for example:

- Control mechanisms (e.g., key pads, touch screens, sliders)
- Feedback mechanisms (e.g., auditory alarms, visual alarms, status indicators, and other messages to users)
- Graphical user interface, including presentations of responses to user actions (including auditory and visual feedback, and changes in device operation or programming)
- Labeling (including directions for use)

Use hazards associated with use of functional components of the LGS system are a unique form of hazard in that they can exist even when a device operates in perfect accordance with its specifications. These hazards may not involve failures due to faulty mechanical, electrical or software components that are previously known or reasonably anticipated but rather, arise specifically from interaction with a human operator.

The analysis should consider:

- Operator (user) interface component features and operation including overall logic of operation (interaction between the user and the device and user interface components)
- Adequacy and convenience of the arrangement of user interface components for users' physical interactions with the device
- Potential errors associated with atypical user actions or techniques
  Legibility of visual information, including device labels and displays
- Audibility and distinctiveness of aural information, including different alarm tones

- Potential difficulties associated with each possible setting or input available to operators
- Potential errors associated with input, selection or modification of critical treatment parameters
- Potential errors associated with non-standard or unusual parameter settings or default values
- Potential confusion due to non-standard, unfamiliar or ambiguous conventions or abbreviations
- Potential confusion due to non-standard, ambiguous, or inadequate alarm condition or informational messages
- Potential errors due to improper storage conditions (e.g., test strip/reagent storage temperature and humidity, etc.)
- Potential errors due to inappropriate use handling (e.g., glucose test strip handling)
- Potential errors due to failure to follow instructions including:
  - Improper fingerstick sampling technique (e.g., "milking" the finger)
  - Inadequate volume of blood sample, collected
  - Improperly performing quality control procedures
  - Improperly calibrating the CGM
  - Failure to discontinue CGM use at the end of the sensor wear period
  - Failure to take a blood glucose measurement when instructed

For more information about human factors evaluation procedures, see the FDA guidance document, *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*.

For the additional functional components composing the LGS system, the following additional performance testing is recommended.

B. Blood Glucose Device Function Component

Applicants should provide appropriate safety and effectiveness information for the Blood Glucose Device (BGD) functional component of the LGS system.

Applicants should provide detailed study protocols and test reports which support the following performance specifications:

- Bias
- Imprecision
- Linearity/reportable range
- Traceability to reference materials or methods
- Stability of device components, as appropriate
- Expected values, as appropriate
- Detection limit (e.g., limit of blank, limit of detection, and limit of quantitation), as appropriate
- Analytical specificity, as appropriate, including:

  - Cross-reactivity with compounds that have similar molecular structures; and
  - Interference (both endogenous and exogenous compounds/conditions, both prescription and over-the-counter medications).
  - Environmental interference (e.g., from temperature, humidity and altitude)
- Method comparison studies (with intended users collecting the sample (e.g., performing the fingerstick) and analyzing the sample, and where results from the BGD are compared to results obtained with an established reference method (e.g., Yellow Springs Instrument, YSI).
- Matrix comparison, if more than one sample type may be analyzed.
- Lot release criteria for the BGD reagent or test strips which are used in the method comparison studies and which are used in the LGS clinical study.

A description of the statistical analyses should also be provided. We recommend that Applicants use the most recent and applicable study guidelines published by the *Clinical and Laboratory Standards Institute* (CLSI) as guides to assist with the design and analysis of data.[12,13,14,15,16]

C. Continuous Glucose Monitor functional component

Applicants should provide appropriate information regarding the safety and effectiveness of their CGM functional component when used as part of an LGS system. Applicants may also find it helpful to review the FDA-recognized Clinical Laboratory Standards Institute guideline.[17]

Applicants should provide detailed protocols and test reports for the following performance specifications:

- Bias
- Imprecision
- Linearity/reportable range
- Traceability to reference materials or methods
- Stability of device components, as appropriate
- Sterility of device components, as appropriate
- Detection limit, as appropriate
- Analytical specificity including:

[12] CLSI EP5-A2 Protocol (Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition)
[13] CLSI EP17 document (Protocols for Determination of Limits of Detection and Limits of Quantitation)
[14] CLSI EP7-A2 Protocol (Interference Testing in Clinical Chemistry; Approved Guideline- Second Edition)
[15] CLSI EP6-A document (Evaluation of the Linearity of Quantitative Measurement Procedures, A Statistical Approach; Approved Guideline, 2003)
[16] CLSI EP9-A3 protocol (Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline- Third Edition)
[17] CLSI POCT 05-A, Performance Metrics for Continuous Interstitial Glucose Monitoring

- Cross-reactivity with similarly molecular compounds;
- Interference (both endogenous and exogenous compounds/conditions, both prescription and over-the-counter medications).
- Environmental interference (e.g., water, humidity)

- Study protocol and results of an in-clinic method comparison study (preferably to an established reference method, e.g., YSI)
- Validation of important user considerations such as the average length of sensor wear or missed CGM data points

A description of the statistical analysis should also be provided. Applicants should identify all applicable standards or guidance documents which they followed as they evaluated the device. Form 3654[18] should be completed for each referenced standard.

D. Control Algorithm functional component

The control algorithm should be fully described as discussed in Section IV-D. This description should be complete and allow the Agency to fully understand the algorithm in its entirety. In addition to the description, there are critical elements of the control algorithm that should be provided to support the safe use of the control algorithm. They are:

- Control Algorithm Verification - One of the more critical requirements of the LGS system is the testing to ensure that the algorithm has been properly programmed into software. This testing is needed prior to approval of an IDE. Details surrounding this verification testing can be found in Appendix A-V-C. FDA recommends the Applicant describe in the PMA how they have ensured the correct algorithm has been properly coded into their final finished device.

- Parameter Sensitivity Analysis - One of the requirements for a control algorithm is flexibility of the algorithm as each user may have different needs for the algorithm. As such, the control algorithm of an LGS system may contain parameters that are adjustable by the healthcare provider or patient. These adjustable parameters should be identified in the device description. Although a limited sensitivity analysis is expected prior to an IDE approval (Appendix A-V-A-5), FDA recommends a comprehensive parameter sensitivity analysis in the PMA. This analysis should evaluate the likelihood of an improper/unsafe shutoff for all combinations of the adjustable parameter values using representative CGM tracings. A summary of the complete test report should be provided, justification of how the CGM tracings used are representative of the intended patient population, and reference to the full test report in the software documentation set should be provided by Applicant.

[18] Available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM081667.pdf

E. Infusion Pump functional component

FDA recommends Applicants provide appropriate information regarding the safety of the infusion pump. We encourage Applicants to refer to the *Draft FDA Guidance for Industry and FDA Staff - Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions*

- **Drug Stability and Compatibility**
  The Applicant should demonstrate that the system does not adversely affect the drug product being delivered by the infusion pump and that these products do not adversely affect the infusion pump.

  If the infusion pump includes a reservoir or container, the Applicant should provide stability and compatibility data, which assesses the stability and compatibility for the recommended use period and conditions included in the product labeling. The assessment should include an assay to demonstrate that the drug retains its specifications. The Applicant should also provide a safety evaluation of any extractables, leachables, impurities and degradants.

  Some infusion pumps use syringes as the "drug reservoir" to contain the product that is being infused. If the infusion pump is set up in this configuration, the Applicant should adapt the stability and compatibility testing stated in the paragraph above to include combinations of drugs and syringes that are intended to be used with the pump functional component.

  The Applicant should verify that the mechanical structure and function of any drug contacting components are not degraded to the point that harm could occur to the patient or infusion pump user.

  As noted in the labeling recommendations of this document, the Applicant should identify the particular drugs that have been evaluated for use with the infusion pump functional component. For pumps that utilize a syringe as the "drug reservoir," the labeling should identify the specific syringes that are approved for use with the pump.

- **Catheter Occlusion Bench Testing**
  Applicants should provide a complete test report in the PMA submission describing the bench testing performed to show catheter occlusion does not occur when the pump is turned off. Details of the Catheter Occlusion Bench Testing can be found in Appendix A-V-K.

VII. Clinical Studies

LGS systems are considered significant risk device systems as defined in 21 CFR 812.3(m). As such, approved Investigational Device Exemption (IDE) submissions are required for clinical investigation of these systems in the US. Appendix A outlines the IDE content that the Agency recommends for LGS system IDEs and identifies critical information to be provided when submitting an IDE. The information described below identifies important information that should be considered in the development of your clinical study design for an LGS system.

The American Diabetes Association (ADA) Workgroup on Hypoglycemia defines three categories of hypoglycemic events: severe hypoglycemia, documented symptomatic hypoglycemia, and asymptomatic hypoglycemia.[19] The Agency recognizes that severe hypoglycemia is infrequent. Therefore, it is generally not feasible to power a trial to show a reduction in events of severe hypoglycemia. For this reason, we expect that trials for LGS systems will generally only be able to show a reduction in events of asymptomatic hypoglycemia and symptomatic, non-severe hypoglycemia (for example, episodes involving a corresponding plasma glucose concentration < 70 mg/dL (3.9 mmol/l) with or without symptoms of hypoglycemia). Because asymptomatic hypoglycemia by definition has no symptoms and because episodes of symptomatic hypoglycemia may not awaken patients from sleep, the Agency recognizes that these events of hypoglycemia cannot be reliably captured and reported by the patient. If it is anticipated that the severe or documented (plasma blood glucose < 70 mg/dL) hypoglycemic event rate will be low during a clinical trial, the Agency will consider the use of a CGM-based correlate for symptomatic or documented hypoglycemia.

The ADA Workgroup acknowledged the limitations for obtaining plasma glucose values: "although a precise laboratory-based plasma glucose measurement would be ideal, monitor-based estimates (or those with a validated glucose sensor) are the only practical method.[20]" However, the Workgroup did not speak to the manner in which these devices could be used to provide such estimates or recommend what value of glucose as determined by CGM could be used.

There are many challenges associated with the use of CGMs in the evaluation of LGS systems. Some of the major challenges include:

- Using the same CGM to measure success and to make decisions about if and when to turn the pump off will introduce bias. Although the size of the bias may or may not be large, determining the extent of the bias will be impossible without an independent measure.
- Although CGMs have been successful in improving diabetes management through their tracking and trending functions, these devices have not been shown to be accurate enough to support use for insulin dosing.

[19] American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes (2005) Diabetes Care, 28:1245-1249.
[20] American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes (2005) Diabetes Care, 28:1245-1249.

- The glucose meters used to calibrate the CGMs also have inaccuracies that can compound the errors in the glucose values reported by the CGM and are part of the device system.
- Use of retrospective signal calibration using reference blood glucose values or introducing a reference method to be performed by the patients may be possible solutions if the approach is appropriately validated.
- CGMs have periods of sensor irregularities and signal drop out. These sensor performance problems arise in addition to sensor accuracy challenges and would need to be resolved and/or mitigated.

Although a number of studies examining methods of diabetes management (such as treatment goals, method of insulin administration, CSII versus MDI, or addition of CGM) have provided descriptive information based on continuous glucose monitor values as secondary endpoints (for example, 'time under 70 mg/dL' or area under the curve), the clinical relevance of these metrics have not been validated. In addition, a continuous glucose monitor-reported value of 70 mg/dL has a low likelihood of being within 6 mg/dL of the expected value (the criteria for a reference method). Therefore, using CGMs for determining biochemical hypoglycemia may lead to inaccurate conclusions about the ability of the LGS system to prevent or mitigate actual hypoglycemia.

To assist in the challenges associated with appropriate endpoints for these innovative systems, FDA held a joint workshop in collaboration with the National Institutes of Health,[21] which discussed the clinical expectations of clinical studies for artificial pancreas device systems such as the LGS system. As a result of this workshop and continued collaboration between FDA and the investigators of these device systems, FDA proposes the use of a CGM-based correlate in evaluating the LGS system. This proposal is FDA's recommendation given the challenges described above. As more information is gathered from the conduct of these studies, FDA may change its guidelines over time.

A. Study Progression to Support a PMA

The Agency recommends the following study progression for evaluation of LGS systems.

1. Pilot Study

It is recommended that initial studies for LGS systems be performed in a hospital setting, such as a clinical research center (CRC), to demonstrate that the device system functions as expected and does not have any obvious unexpected safety concerns. Although more common than severe clinical hypoglycemia, biochemical hypoglycemia (plasma glucose < 70 mg/dL) is unpredictable and may not occur spontaneously during the relatively short

[21] November 10, 2010, Innovations in Technology for the Treatment of Diabetes: Clinical Development of the Artificial Pancreas (an Autonomous System). Morning Session available at: http://fda.yorkcast.com/webcast/Viewer/?peid=a030c9f9b45c4ddc99ef1887688e81f0. Afternoon Session available at: http://fda.yorkcast.com/webcast/Viewer/?peid=c99b98eac96d45dd90de77c6e359f139

period of a CRC study. Therefore, a reasonable approach would be to test the system with induction of hypoglycemia by increasing insulin administration, withholding food, and/or exercise. This portion of the study should be performed under the close supervision of a medical team that can intervene to prevent severe hypoglycemia or hyperglycemia occurrence during the trial. In addition to the induced hypoglycemia portion of the study, the pilot study should also allow the patient some freedom to use the system as intended. To provide safety monitoring and comparison to CGM values, reference blood glucose levels (i.e., laboratory measurements) should be checked frequently. When appropriate, additional capillary blood glucose levels can be obtained; the interval and method (reference vs. capillary) is determined by the safety issues at different times during the study. We recommend the clinical protocol be developed with an identifiable goal and pre-specification of success criteria for the pilot study.

Potential Pilot Study Exemption

In cases where the control algorithm is binary, such as a reactive LGS control algorithm, that is, turns off when a threshold is reached, a feasibility study may not be needed prior to an outpatient (pivotal) study if appropriate safety information can be provided to the Agency. Safety information that FDA believes is critical to assess prior to initiation of a pivotal study is outlined in Appendix B.

New or Modified Device Components of the LGS system

In all cases such as predictive control algorithms, new CGMs, or new insulin pumps, the Agency recommends a pilot and pivotal study progression for device development. Please note, in the case of a new CGM, additional clinical data will be needed to support the diagnostic intended use of the CGM (e.g., tracking and trending) when the LGS system is not active. Also, if modifications to the LGS system are made between the pilot and pivotal study, bridging studies may be appropriate; however, it will depend upon the specific change(s). We strongly recommend the Sponsor seek FDA input via the pre-IDE process when intending to make modifications to any of the device components included as part of the LGS system.

Note: Prior to approval of an unsupervised outpatient clinical study, the Agency recommends a human factors evaluation of the device system as described in Section VII-A-8.

2. Pivotal Study

A pivotal study should be performed in the actual use environment and by the intended use population. The pivotal study should be conducted with the finished LGS system for which approval will be sought. A description of the Agency recommendations regarding an example of a pivotal study design can be found in Section VII-B.

B. Pivotal Clinical Study Design

FDA recommends either a randomized cross-over design or a randomized parallel design for evaluating the safety and effectiveness of a LGS system in an outpatient pivotal trial. Patients should manage their diabetes by responding to alarms, performing finger stick blood glucoses, and acting according to these results. Patients should perform fingerstick blood glucose tests if they are experiencing symptoms of hypoglycemia even if a low glucose alarm has not sounded. The low glucose suspend would serve as a potential back-up when the patients are unable to respond to their alarm. To demonstrate the safety and effectiveness of the low glucose suspend system, the Agency recommends comparisons be made between patients using sensor-augmented pump control and patients using the low glucose suspend system.

FDA recommends the following information to guide the Sponsor/Applicant in designing their pivotal study.

1. Patient Population – Enriched Population

The overall goal of the pilot and pivotal studies is to determine the safety and effectiveness of the LGS system in preventing and/or mitigating hypoglycemia. Literature has indicated that the conversion from multiple daily injection (MDI) to continuous subcutaneous insulin infusion (CSII) and the addition of sensor guided therapy improves glycemic control.[22,23,24,25] Therefore, it is important that any study designed to examine the LGS should be limited to the effects of the suspend function and not the effects of sensor-augmented pump control.

Ideally, the patient population would consist of those patients who are already using sensor-augmented pump control for > 3-6 months, but who are known to continue to have relative frequent hypoglycemia. However, it has been suggested that although it will be easy to identify and enroll patients who are experienced with pump use there are far fewer patients using sensor-augmented pumps. Therefore, patients who have successfully used pumps but continue to have relatively frequent hypoglycemia can undergo a training period with sensors for 4-6 weeks. This learning period will screen out subjects who cannot optimally use the sensor feature of sensor-augmented

[22] Bergenstal RM, et al. (2010) Effectiveness of sensor-augmented insulin-pump therapy in Type 1 Diabetes, NEJM:363:311-320.
[23] Hermanides, J, et al. (2011) Sensor-augmented pump therapy lowers HbA1c in suboptimally controlled Type 1 Diabetes; a randomized controlled trial. Diabetic Medicine (*Accepted Article*)
[24] Junvenille Diabetes Research Foundation Continuing Glucose Monitoring Study Group (2009) The effect of continuous glucose monitoring in well-controlled Type 1 Diabetes. Diabetes Care 32:1378-1383
[25] Garg, SK et al. (2007) Continuous Home Monitoring of Glucose - Improved glycemic control with real-life use of continuous glucose sensors in adult subjects with Type 1 Diabetes. Diabetes Care 30:3023-3025

pumps. FDA recommends that final enrollment and randomization occur after this training period.

The purpose of enrolling an enriched population is to study a patient population that is likely to have hypoglycemia with an event frequency that is sufficient to detect treatment-related differences in occurrence. If the event frequency is low, it may not be possible to power a trial to support clinical effectiveness.

FDA recommends the following criteria be considered for enrolling patients into studies for the LGS systems:

Initial subject population:

- Age >18 years (younger subjects to be enrolled after sufficient number of adults have demonstrated reasonable safety and prospect of benefit (21 CFR 50 Subpart D)
- Disease onset < 40 years old
- T1DM minimum ≥ 2 years
- Stimulated C-peptide negative
- Experienced with pump > 6 months
  - willing to perform ≥ 4 finger stick blood glucose measurements daily
  - willing to perform required sensor calibrations
  - willing to wear the system ≥ 6 days per week
  - willing to keep a minimum log
    - sick days
    - days with exercise
    - symptoms of low blood glucose episodes

To enrich the trial with patients who are likely to have hypoglycemia and, therefore, ensure feasibility of the study, we recommend that patients have a significant history of hypoglycemia. One example is to enroll patients with at least **one of the following** indications of hypoglycemia:

- Finger stick confirmed blood glucose (BG) < 70 mg/dL ≥ 3 times per week for the past 3 months on average
- Requirement of assistance from other for the treatment of hypoglycemia at least once in the past six months
- Finger stick confirmed nocturnal hypoglycemia (BG<70 mg/dL) > 1 weekly for the past 3 months on average

To avoid masking treatment effect, it is recommended that patients be under the treatment of a well-trained diabetes team for six months minimum, yet continue to have hypoglycemia as described above.

Note that a comprehensive list of inclusion and exclusion criteria is not included in this guidance. The Agency will assess additional inclusion and exclusion criteria to ensure that the patient population is appropriate for the intended use of the LGS system.

Broadening Patient Population

Sponsors may want to widen the criteria for the enrollment of subjects with diabetes (e.g., younger patients). The Sponsor/Applicant should consider how the addition of different subject groups may affect the analysis of study outcomes. The Sponsor should also justify how enrollment of these subjects is necessary to support the development of the LGS system for its intended use.

When pediatric subjects[26] are to be enrolled in studies, a staged approach should be considered, starting with the oldest pediatric sub-population and phasing in the younger sub-populations. As risk versus benefit is assessed, the Sponsor should address any pediatric-specific issues. For example, the Sponsor should identify any inclusion and exclusion criteria that are unique to the pediatric population, any limitations such as exercise or the daily volume allowed for blood draws, etc.

2. Study Endpoints

Use of CGM Based Event as a Correlate Endpoint for Hypoglycemia

The purpose of this section is to describe the challenges in using a CGM for determining effectiveness and to propose rules for defining CGM-based events (CGM-BE) that may permit CGM-based data to serve as correlates for hypoglycemic events (as defined by the ADA). Using continuous glucose monitoring-based events (CGM-BE) will permit the evaluation of changes in CGM values after the LGS threshold has been reached and the pump has been suspended. The use of correlates will permit comparison of the rates of these events between treatment groups (LGS on and LGS off) and further describe the duration and severity of the CGM-BE. It is worth re-emphasizing that no CGM-based data patterns have been validated as correlates for true clinical hypoglycemia.

Definition of CGM-BE for Hypoglycemia

[26] The pediatric population is defined as birth to 21 years of age. For details surrounding this definition and recommended pediatric subpopulations, please refer to *Guidance for Industry and Staff: Pediatric Expertise for Advisory Panels*. For the purposes of the LGS system, FDA recommends the subpopulation of 18-21 be considered transitional adolescents enabling this pediatric subpopulation to be studied with adults.

The following is a proposed description of a CGM-BE for detection of Hypoglycemia:

- Alarm/suspend threshold is set.
  - Threshold for suspend can be set or vary throughout the study based upon documented individual patient needs. The alarm/suspend threshold should be set at least 10mg/dL above the hypoglycemic event definition (<60 mg/dL). Sponsors should consider the choice of threshold (single) or thresholds (variable) for suspension of insulin infusion for the study design and statistical analysis that will support the indications for use.

- A CGM-BE correlate for hypoglycemia may be defined as:
  - CGM value < 60 mg/dL.
  - A CGM value of at least 10 continuous minutes <60 mg/dL.
  - There is no patient intervention for 30 minutes after the activation of the alarm/suspend threshold. A period of 30 minutes, although arbitrary, is proposed because any changes in CGM values during this period of time are more likely to reflect the patient's actions such as eating or restarting the pump (due to false positive alarm/suspend). Additionally, 30 minutes is within the expected duration of action for insulin infused prior to pump suspension. Other times can be provided with a justification.
  - Events should be filtered to avoid erroneous signals. For example, events should not be immediately preceded by a decrease in glucose concentrations of ≥ 5 mg/dL/min as these rates are not physiological. In addition, there are periods when the sensor either fails to report values or has 'noise'. Because the analysis of CGM-BEs will depend on sensor data, it is important not to include erroneous sensor signals in the analysis. Therefore, as with assessments of Holter-monitor tracings, ECGs, and image analysis evaluation, filters should be applied in a consistent and pre-specified manner to exclude erroneous signal for the definition of a CGM-BE. Sponsors should use experience gained in the pilot study to develop the appropriate signal processing algorithms specific to their systems. Additional filtering can also be provided with a justification.

- Each event should be described for duration and severity (area under the curve).

As stated previously the purpose of these studies is to assess the safety and effectiveness of the low glucose suspend function added to existing sensor-augmented pump control. Therefore, patient interactions with the system after a low glucose alarm sounds are not assessed.

Primary Endpoints

Based on the hypoglycemic event defined above, two effectiveness endpoints can be operationally defined for each subject: Event Rate and Mean Area Under The Curve for the detected events.

- Event rate is defined as the total number of days when hypoglycemic events occur divided by the number of days in the follow-up period. Since the numerator of Event Rate is in the unit of day, only one event will be counted per day even if multiple events occur on the same day.
- Mean area under the curve (AUC) is defined as the sum of areas of the readings recorded by a CGM below 60 mg/dL (AUC) for each detected event divided by the number of events.

These two endpoints summarize two different, yet related, dimensions of hypoglycemic events: On the one hand, the event rate captures the frequency of the hypoglycemic events. On the other hand, the mean AUC describes the duration and the extent of the hypoglycemic events. Other effectiveness endpoints may also be considered if they are adequately justified.

It is recommended that the following co-primary endpoints be used for primary treatment comparisons between the pump with the LGS turned ON group and the pump with LGS turned OFF group.

- Primary Safety endpoint
  - HbA1c should be used to demonstrate that automatic pump suspension does not result in an unacceptable worsening of glycemic control.

and

- Primary Effectiveness endpoint
  - Reduction or mitigation of hypoglycemic events
    - Event Rate (reduction), and/or
    - Mean AUC (mitigation)

Alternative Endpoints

The Sponsor is encouraged to explore the above correlate for hypoglycemic events or develop an alternative correlate for CGM based hypoglycemic events. Other correlates can be considered which will be dependent upon the indication and an appropriate justification.

Research Endpoints

Other exploratory endpoints may also be considered provided the submission identifies those endpoints as exploratory, justifies the use of these exploratory endpoints, proposes a clinical study that would allow further validation of these endpoint(s), and provides the appropriate safety information to support the proposed clinical study.

Safety – HbA1c Measurement

Clinical studies may involve the measurement of Hemoglobin A1c (HbA1c). The differences in HbA1c levels between study and control groups or between individuals in a cross-over study design may be small. Additionally, there is significant variability in performance among HbA1c assays and point-of-care HbA1c test systems may not be as accurate as assays performed in central laboratories. Therefore, Sponsors/Applicants should minimize potential variables in the study by having all study subjects' HbA1c values determined at one central laboratory location using only a National Glycohemoglobin Standardization Program (NGSP) certified laboratory method. The Sponsor/Applicant should provide the name of the HbA1c test system that was used to obtain the HbA1c values.

Secondary Endpoints

Additional secondary safety and efficacy endpoints that may be considered include, but are not limited to:

- Incidence of severe (clinical) hypoglycemia within each group
- Incidence of Diabetic Ketoacidosis (DKA) or severe hyperglycemia within each group
- Incidence of catheter blockage within each group
- Incidence of pump restart before suspend completed
- Capillary blood glucose values < 70 mg/dL and > 240 mg/dL.
- Fasting whole blood ketone levels within each group, evaluating beta-hydroxybutyrate levels >3mmol/L.
- Time spent (hours/week) in hypoglycemic events <70 mg/dL, including both day and night
- Average duration for all hypoglycemic events <70 mg/dL within each group
- AUC and Time spent <50, <60, and <70 mg/dL using sensor glucose values within each group
- AUC and Time spent >240 mg/dL using sensor glucose values within each group
- Glycemic variability (such as coefficient of variation and standard of deviation within each group)
- Mean sensor glucose, mean SMBG glucose within each group
- For LGS ON period: incidence of LGS events, timing during the day and night, duration, time spent below each subject's individually-set LGS threshold, sensor glucose levels during and after LGS events of 120 minutes, paired sensor and SMBG glucose levels at time of LGS (for available data), threshold settings
- Safety and efficacy sub-group analysis, such as pediatric subjects

3. Statistical Analysis

<u>Study Populations</u>

The safety population should include all randomized subjects. For effectiveness endpoints, two widely used populations are the Intention to Treat (ITT) Population and the Per Protocol (PP) Population. The Intention to Treat (ITT) population should include all randomized subjects. The Per Protocol (PP) population should include all randomized subjects who finish both treatment periods successfully without major protocol deviations. The ITT population is preferred for the analysis of primary endpoints. FDA recommends the Sponsor/Applicant provide details on defining the major protocol deviation in the PP population.

<u>Primary Hypothesis</u>

The Sponsor/Applicant should clearly state the hypothesis for each primary endpoint and define the overall success criterion of the study.

<u>Safety - Non Inferiority</u>

For the HbA1c endpoint, it is recommended that the study will be considered successful if non-inferiority is demonstrated with a non-inferiority margin of 0.4% (absolute difference). The hypothesis is mathematically expressed as:

$$H_O: \mu_{ON} \geq \mu_{OFF} + 0.4\%$$

$$H_A: \mu_{ON} < \mu_{OFF} + 0.4\%$$

Where 0.4% is the pre-specified non-inferiority margin, μ_{ON} is the mean of HbA1c (%) of the treatment group with the LGS ON, and μ_{OFF} is the mean of HbA1c (%) of the treatment group with the LGS OFF. The Null hypothesis is rejected if the two-sided 95% upper boundary of the difference between the two treatments, $\mu_{ON} - \mu_{OFF}$, is less than 0.4%.

<u>Effectiveness - Superiority</u>

For the primary effectiveness endpoints in terms of reduction of severe hypoglycemia or CGM based hypoglycemic events, it is recommended that the study will be considered successful if superiority is demonstrated with a superiority margin of 10% (relative difference) for either severe hypoglycemia or CGM-based Event Rate (prevention), or Event AUC (mitigation). The hypothesis is mathematically expressed as:

$$H_O: \mu_{ON} \geq 90\% \times \mu_{OFF}$$

$$H_A: \mu_{ON} < 90\% \times \mu_{OFF}$$

Where μ_{ON} and μ_{OFF} are the endpoints of the treatment group with the LGS ON, and the treatment group with the LGS OFF, respectively. Specifically, for Event Rate, μ_{ON} and μ_{OFF} are the proportions of hypoglycemic event as previously defined. For AUC, μ_{ON} and μ_{OFF} are the means of AUC per event. If AUC is not normally distributed, an appropriate nonparametric test should be used to compare the distributions of AUC within patients and between groups. Please note that a minimum of 10% superiority margin is used to ensure that a clinically significant reduction is observed. A reduction of CGM based events or extent of events by 30% would be desirable whereas a reduction of rate of severe hypoglycemia by 10-20 % would be beneficial. A mere statistically significant difference is not sufficient. Other superiority margins can be considered if adequately justified.

Study Success Criterion

With the above primary endpoints used, FDA recommends that the overall study success criterion for the study meet the following three conditions:

a) Non-inferiority for HbA1c; **and**
b) Superiority for one of the effectiveness endpoints: either Event Rate or the mean AUC; **and**
c) Non-inferiority for either Event Rate or the mean AUC.

It might happen that the study shows superiority for one of the effectiveness endpoints but inferiority for the other. If this is the case, the study will not be deemed successful. Since this situation is unlikely to happen, it does not have to be taken into consideration in the sample size calculation.

Sample Size Considerations

For a cross-over or parallel study design, sample size estimates should be calculated. FDA recommends the overall significance level be two-sided 5% and the overall power be no less than 80%. The Applicant should make reasonable assumptions of important parameters, including the means and standard deviations of HbA1c and other primary endpoints, the correlation between groups and within subjects, the loss-to-follow-up (LTFU) rate, and provide justifications for these assumptions. An appropriate statistical method should be provided to calculate the overall sample size while controlling the overall type I error rate under 5% and maintaining the overall power above 80%. If necessary, simulation might be needed to obtain the sample size.

As an example to control the overall type I error rate and power, if the above three primary endpoints are used, the study is deemed successful if it meets HbA1c **and** one of the effectiveness endpoints (Event Rate **or** AUC), the sample size should be calculated as follows:

- Calculate sample size for HbA1c with a two-sided type I error rate of 5% and a power of 90%.
- Calculate sample size for Event Rate with a type I error rate of 2.5% and a power of 90%.
- Calculate sample size for AUC with a type I error rate of 2.5% and a power of 90%.
- Take the maximum of above three sample sizes as the overall sample size.
- Adjust for LTFU to obtain the final overall sample size.

If an interim analysis is planned, the sample size should be further adjusted using appropriate methods to control the overall false positive rate.

Handling of Missing Data

Starting at the study design stage and throughout the clinical trial, every effort should be made to minimize patient withdrawals and lost to follow-ups. Premature discontinuation should be summarized by reason for discontinuation and treatment group. For an ITT population, an appropriate imputation method should be specified to impute missing HbA1c and other primary endpoints in the primary analysis. It is recommended that the Sponsor/Applicant plan a sensitivity analysis in the protocol to evaluate the impact of missing data using different methods, which may include but is not limited to per protocol, Last Observation Carry Forward (LOCF), multiple imputation, all missing as failures or success, worst case scenario, best case scenario, tipping point, etc.

An important issue is how to handle cases of subjects with partial CGM data. For example, if a subject has 80% of the valid CGM data available and completes both HbA1c study visits, the Sponsor/Applicant should address how the missing data is imputed. The Sponsor/Applicant should describe if the patient can be included in the PP cohort. The Sponsor/Applicant should consider a study criterion for the minimum percentage of available CGM data for a subject to be included in the PP cohort.

General Considerations for Data Analysis

FDA recommends patient demographics, medical history, and other important baseline characteristics be summarized using descriptive statistics and frequency tables as appropriate. Patient accountability and withdrawals from the treatment phase of the study should be reported. Summaries (number and percent) of the reasons for withdrawals should be presented by treatment group.

Summaries of the crossover data should be presented for the LGS ON and LGS OFF categories. Sequence and period summaries will also be provided.

The effects of carryover, sequence, site, baseline variables and prognostic variables should be tested using appropriate models (usually, a linear model for a continuous variable and a logistic regression for a binomial variable).

Analysis of Primary Endpoints

The primary effectiveness analysis is the between-group comparison (LGS ON Period vs. LGS OFF Period) of all primary endpoints. A paired t-test can be used for a cross-over design and a t-test for a parallel design. Appropriate statistical models should be specified to evaluate the impact of covariates. If some covariates are found to confound with a primary endpoint, their effects should be adjusted through appropriate models.

Analysis of Secondary Endpoints

For all secondary endpoints, descriptive statistics is recommended. If the Sponsor/Applicant intends to make claims for any of the secondary endpoints in the labeling, the hypotheses, the analysis, the patient population of these endpoints should be clearly specified in the protocol. An appropriate multiplicity adjustment strategy to control the type I error rate is also needed. It should be noted that if the study fails the primary endpoints, no secondary endpoints can be used to support the approvability of the device.

Adaptive Study Design

The adaptive study design provides flexibility in modifying some aspects of the clinical study during the clinical trial. If an adaptive study design is desired, the Agency recommends that the Sponsor/Applicant prespecify details such as the number of interim analyses, the time at which these analyses will be performed, the stopping rules, and the criteria to control the type I error rate, etc. Due to the complexities of an adaptive study design, FDA recommends the Sponsor/Applicant submit their proposal through a pre-IDE submission to discuss their design.

Safety Analyses

Descriptive statistics of all adverse events should be presented for the safety population. The descriptive statistics of the following subgroups should also be summarized. This includes, but is not limited to, the following information:

- All adverse events
- Serious Adverse Events (SAE)
- Adverse events and other reasons leading to patient withdrawal from the trial
- Unanticipated Adverse Device Effect (UADE)
- Severe Hypoglycemia (prospectively defined in the protocol)
- Severe Hyperglycemia (prospectively defined in the protocol)
- Diabetic Ketoacidosis (prospectively defined in the protocol)
- Ketone testing
  Urine ketones should be measured every morning to screen for preceding nocturnal ketosis. Capillary blood ketone levels (betahydroxybutyrate) should be evaluated any time the blood glucose is above 300 or if the subject is experiencing nausea, abdominal pain, or vomiting. First morning urine ketones may be positive even if the fasting blood is negative for betahydroxybutyrate if transient nocturnal ketonemia occurred earlier during the night as a result of insulin suspension, but subsequently resolved with resumption of insulin infusion.
- Skin infection

- Device performance

VIII. Labeling

The premarket application must include labeling in sufficient detail to satisfy the requirement of 21 CFR 814.20(b)(10), which states that copies of all proposed labeling for a device must be submitted in a PMA. Labeling must also satisfy the requirements of 21 CFR Parts 801 & 809.

In general, labeling for the LGS system should include:

- a user manual for the patient, written at an 8th grade reading level;
- professional labeling for the prescribing physician;
- Package inserts for the LGS system and all accessories (e.g., reagents or test strips, quality control materials, catheters, inserters, reservoirs, etc.);
- Box and container labels for the LGS system and each component that is packaged separately from the system.

Applicants may refer to the following documents for information on important principles for developing clear and complete labeling for the LGS system.

- *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA* (2001)
- *Write it Right – Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care* (1993)
- Labeling of Home-Use In Vitro Testing Products; Approved Guideline, CLSI GP-14 (1996)
- Device Advice website titled *Labeling Requirements - In Vitro Diagnostic Devices*
- *Total Product Life Cycle: Infusion Pump – Premarket Notification [510(k)] Submissions* (2010, Draft)
- IEC 60601-1-11 General Requirements for the basic safety and essential performance - Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

The patient instructions for use should be as simple and concise as possible and be easy to understand. Labeling for lay users should be written at an 8th grade reading level. Applicants should consider the use of graphics such as line drawings, illustrations, photographs, tables and graphs. Applicants should ensure that terms are used consistently throughout the labeling and should avoid using synonyms or alternate phrases. Comprehensive directions for preparation and use of all functions of the LGS system and the accessories should be provided. The Applicant should provide labeling that contains examples of expected performance and addresses issues that may occur in the home environment.[27]

The professional labeling for the prescribing physician should describe in sufficient detail the clinical testing performed for LGS system approval. The purpose of this information is to allow the physician to make an informed decision on whether to prescribe the LGS system to a particular patient. Information such as indications, warnings, precautions, contraindications should be provided. In addition, critical bench testing for the infusion pump (e.g., MR testing and drug stability testing), BGD (e.g., analytical specificity), and CGM (e.g., analytical specificity, indication, etc.) should be described.

IX. Postmarket Study

As a condition of PMA approval, LGS systems may require a post-approval study (PAS) to better assess long-term performance. The Applicant should develop a PAS protocol and submit the protocol with the original PMA. Depending on the type of system and its capabilities, several types of PAS may be appropriate. We recommend the Applicant develop a PAS and submit this study for review as a pre-IDE submission.

[27] CDRH Home Use Website is available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/HomeUseDevices/default.htm

Appendix A: IDE Content for LGS systems

This Appendix is to guide Sponsors who intend to submit IDE submissions for evaluation of a Low Glucose Suspend System. This Appendix is structured as an outline of the IDE submission and identifies the elements of an IDE review. FDA recommends that Sponsors follow this outline and address each section heading as part of their IDE submission. When different information is needed between pilot or pivotal or an unsupervised outpatient setting, the section is divided.

IDE Contents

I. Background

The Sponsor should provide background information as it relates to the development of the Low Glucose Suspend Device system that is intended to be studied. The Sponsor should identify whether there has been previous communication with the Agency regarding this device within a pre-IDE submission (the Sponsor should identify the pre-IDE #) or previous clinical studies performed using this device system.

II. Device Description

This section should include a device description of the LGS system.

If the Sponsor is using previously approved/cleared devices, please include following information for each device:

- the name of the device
- model number
- PMA or 510k number for the referenced devices
- Identify if the functional component has been modified from its approved/cleared form. If so, the Sponsor should describe how the device has been modified.

If the Sponsor is not using previously approved/cleared devices, FDA recommends the Sponsor include a complete description of all functional components of the LGS system (i.e., BGD, CGM, control algorithm, communication, and pump) as described in Section IV of the guidance.

The Sponsor should also identify the insulins and/or other drugs that are intended to be used with the LGS system in the clinical study.

III. Letters of Authorization

Letters of Authorization (LOA) are needed if the Sponsor intends to reference safety/effectiveness information from another manufacturer that has been included with a device Master File[28] or another regulatory submission. Some examples are identified below.

- If the Sponsor intends to use a medical device from a different manufacturer that has been modified and there is a document such as a device master file describing the changes and additional testing for this modification.
- If the Sponsor intends to use a device from a different manufacturer contained within a document such as a device master file that allows the interconnection of various device components into one system.

IV. Indication for Use

Describe the indication for use. Please refer to Section V of the guidance.

V. Nonclinical studies/Prior Investigations

Per 812.27, a report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation. The Agency recommends the Sponsor provide the following information as part of the IDE.

A. Algorithm

1. Definition of Algorithm(s)

FDA recommends the Sponsor define the algorithm in symbolic form and briefly define the purpose for each equation in the control algorithm.

2. Definition of Algorithm Symbols/Parameters

FDA recommends the Sponsor define each symbol (i.e., parameter) in the algorithm. This can be in table format.

3. Identification of Fixed Parameters

FDA recommends the Sponsor identify each fixed parameter and the value of this parameter. FDA defines a fixed parameter as a parameter value that will not be changed during the course of the clinical study. This can be provided in a table format.

[28] Master files are described on Device Advice. See link: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

✓ *Please note, that once approval for the investigational study is obtained, any modification to these fixed values will require a supplement to the IDE as such a change is viewed as a major device modification requiring Agency approval.*

Symbol/Parameter	Value

4. Identification of Adjustable Parameters that May be Modified During the Study

The Sponsor should identify each parameter and parameter value range that may be adjusted during the course of the study. This can be provided in table format.

Adjustable parameters				
Parameter	Symbol	Typical Starting Value	Minimum Value	Maximum Value

✓ *Please note, that once approval of the IDE is obtained, if the Sponsor modifies the adjustable parameter within the predefined ranged, the Sponsor can continue the study without Agency notification. However, for modifications of parameter values outside the predefined range, Agency approval is needed prior to modification as this is viewed as a major device modification.*

5. Parameter Sensitivity Analysis

For each parameter that is defined as adjustable, the Sponsor should provide a parameter sensitivity analysis to show the equation does not result in unsafe dosing adjustments such as stoppage/reduction of insulin infusion or the return of insulin infusion. For a PMA, FDA recommends the Sponsor evaluate all possible combinations of parameter values and the effects on the system as described in Section VI-D of the guidance. However, for pilot studies (Section VII-A-1 of the guidance) where the patient safety has been significantly mitigated due to the physician monitoring, a limited sensitivity analysis is acceptable. Such an analysis should evaluate all combinations of all adjustable parameters using the minimum, maximum and typical starting value for each adjustable parameter. The analysis should identify if any unsafe dosing adjustments have occurred. This type of analysis can be evaluated using CGM glucose tracings that would approximate the expected tracings observed in the study. The Sponsor should justify how the CGM tracings represent the tracings that may be observed in the clinical study.

B. Software Documentation

FDA recommends software documentation be provided for the LGS system. For assistance in developing the appropriate documentation set, Sponsors should refer to the FDA 2005 software guidance document regarding software.[29] All LGS systems are identified as a MAJOR level of concern. The software documentation set can be included as an Appendix to the IDE.

Unresolved Anomalies
Please note that if the Sponsor is using device components from different manufacturers as part of the LGS system, the Sponsor will need to obtain a list of all the unresolved anomalies from each manufacturer and describe how each unresolved anomaly will or will not affect the LGS system and the safe use of the device in the clinical study.

C. Summary of the Verification Activities for the Control Algorithm

The Sponsor should provide a summary of the testing (i.e., verification activities) they have performed to show that the algorithm has been properly programmed into the software to support the safe and effective use of the device. This summary should identify the test method used to verify the algorithm and reference where the detailed test reports can be found in the software documentation set.

D. Summary of System Communication

If the LGS system connects a CGM to a control algorithm and/or a control algorithm to a pump in which information is passed automatically (without user acceptance) and this is not a previously approved device system, a summary of the system level testing is needed. This summary should address how the Sponsor has ensured the correct passage of information such as CGM values and or insulin dosing recommendations. This summary should identify the test method used to verify the algorithm and reference where the detailed test reports can be found in the software documentation set.

E. Safety Measures for Reduction in Dosing

In addition, the Sponsor should identify if there are any hard-limits coded into the software of the LGS system that would restrict the maximum time the algorithm would shutoff infusion. The Sponsor should identify the minimum and maximum time that is allowed for pump shutoff for a single event and the maximum time allowed for pump shutoff over an extended period of time (e.g., 24 hours).

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[29] *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*

F. Biocompatibility Testing

FDA recommends biocompatibility testing of the device in accordance with FDA blue book memo, Use of International Standard ISO 10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing' (Replaces #G87-1 #8294). The Sponsor should provide appropriate biocompatibility testing for duration and level of contact. FDA recognizes that early studies may use device components previously approved/cleared. If this is the case, the Sponsor should provide the appropriate cross-reference or an LOA to reference the appropriate PMA or 510(k) documents. However, if the Sponsor has modified the approved device, it may be possible to use biocompatibility of the approved/cleared devices if the Sponsor can justify how the modifications do not affect the biocompatibility. If the Sponsor uses a new device, then complete biocompatibility is needed as described in Section VI-3 of the guidance.

G. Electrical Safety

If applicable, FDA recommends the following electrical safety information be addressed in the IDE submission.

- **Electromagnetic Compatibility**
  The IDE submission should include a complete description of the Electromagnetic Compatibility (EMC) characteristics of the device, and the information to verify those characteristics. Electromagnetic compatibility is the ability of a device to operate properly in its intended environment of use without introducing harmful electromagnetic disturbances into that environment.

  The Agency recommends that the LGS system meet the EMC requirements of IEC 60601-1-2. IEC 60601-1-2 describes EMC testing and includes both tests for immunity of the device to outside noise and emissions from the device to the outside. In addition to evidence of compliance with this standard, complete testing information describing what was done, how the device functions, modes that were tested, pass/fail criteria, reference standards, any deviations or allowances that were taken, and any device modifications needed to pass the testing should be provided with appropriate labeling.

- **Applicable Standards**
  The Sponsor should identify if the device meets the electrical safety requirements of *IEC 60601-1*. Complete test reports demonstrating that the device meets the electrical safety requirements should be provided.

- **Radio Frequency**
  If the submission includes radio frequency (RF) technologies, the IDE submission should include a complete description of the RF use. While applications of RF wireless technologies might comply with applicable technology standards and Federal Communications Commission rules, medical device safety and effectiveness concerns may remain. For detailed information about possible hazards and ways these

hazards should be addressed, reference should be made to the draft guidance, *Radio-Frequency Wireless Technology in Medical Devices*.[30]

Particular points that should be addressed in the IDE include: quality of service needed, data integrity, coexistence, security, and EMC. Due to the increased use of RF wireless technology that operates in the same frequency range, RF wireless coexistence via testing with other common applications of RF wireless technology that can be expected to be in the environment of use should be carefully addressed. The testing should also address the ability of two or more of the systems to co-operate wirelessly in proximity.

If the Sponsor is using previously approved or cleared products, the electrical safety may have been addressed in another regulatory submission. However, the Sponsor should evaluate any differences in the test environment from the proposed clinical study and the approved/cleared devices. Differences in test environments (e.g., home vs. hospital use) may require additional electrical safety testing. The Sponsor should justify these differences are minimal or provide additional testing.

H. Animal/In-silico Testing

The Sponsor should provide evidence of safety for the LGS system intended to be studied. The Agency has accepted different types of nonclinical studies to support IDE approval. These types are briefly described below.

- **Animal testing**
  Animal testing should employ a device system similar to that intended for use in the clinical study and if possible, evaluated using a similar study design timeline. If there are any differences in the system or study timeline of the animal study versus clinical study, these differences should be identified. The Sponsor should justify that the differences would not affect the safe use of the device in humans. The animal model should best represent the intended patient population, and a justification should be provided. Prior to performing animal studies, the Agency recommends that the Sponsor seek FDA input on the animal study protocol via pre-IDE. FDA recommends the nonclinical laboratory studies be conducted in accordance with 21 CFR 58, Good Laboratory Practice for Nonclinical Laboratory Studies. Please note that all real-time traces of the animal study should be provided in an appendix.

- **In-Silico testing**
  As part of the Artificial Pancreas Critical Path Initiative, the Agency has accepted in-silico (i.e., software-based theoretical models) modeling as a reasonable nonclinical assessment tool. An in-silico model is a method to test the control algorithm in a theoretical human model of insulin and glucose metabolism using a sophisticated computer model rather than expensive animal experiments. This tool

[30] Note that this guidance is in draft form, but when final, this guidance will represent the Agency's thinking on this topic.

can be used to support the safe use in humans for a hospital-based/CRC clinical study. Prior to using an in-silico model, the Agency recommends submission of the model for FDA review under a pre-IDE. This model should minimally include the variability in human glucose metabolism, performance characteristics of the CGM and insulin pump, the pharmacokinetics of insulin, and diffusion of glucose between the blood and interstitial fluid. A complete test report for the in-silico testing of the control algorithm should be included in the IDE submission. Due to the flexibility of a theoretical model, the Sponsor should design the in-silico model identically to the proposed clinical study. All real-time traces should be provided in an appendix in the IDE.

I. Human Studies

FDA recommends the Sponsor provide all reasonably known clinical data applicable to the safe use of the LGS system in humans. This may be clinical data to support device components of the LGS system (e.g., CGM clinical studies) or studies conducted previously in another IDE or studies conducted outside the US. FDA recommends a complete test report be provided. Please note that all real-time traces should be provided as an appendix.

J. Human Factors (Use Error Testing)

- **Pilot Study**

As LGS systems in the pilot study phase may undergo significant modification between the pilot and pivotal study, a complete human factors study may be unnecessary. However, the risk of use error is present for any investigator (operator) of the system. FDA recommends the Sponsor mitigate this risk by describing the training procedure that all of the investigators (operators) of the LGS system will undertake prior to participating in the clinical study to ensure each investigator (operator) can safely and effectively use the LGS system. In addition, FDA recommends the recording of any user problems in the Case Report Forms.

- **Pivotal or unsupervised outpatient study**

For LGS systems, a human factors evaluation should be provided prior to approval of an unsupervised outpatient clinical study. As some of these device systems may have components that have been previously approved and or cleared, a focused human factors evaluation based upon the modified components could be provided to support the safe use of the device system in an outpatient study. For systems using novel (not previously approved or cleared devices) a more comprehensive human factors evaluation may be needed. A description of the comprehensive human factors testing is described in Section VII-A-8 of the guidance. FDA recommends the Sponsor provide the testing and justify the extent of their testing to support the safe use in human in the outpatient setting.

K. Catheter Occlusion Bench Testing

- **Pivotal or unsupervised outpatient study**

Current LGS systems are intended to mitigate or reduce the likelihood of hypoglycemia by turning off or reducing insulin infusion for a finite period of time. Insulin crystallization is a chemical process that occurs with or without flow, but the likelihood of crystallization is increased in the absence of flow. Such crystallization raises the risk of catheter blockage and the inability of the pump to deliver the appropriate insulin dosage when the LGS system returns insulin delivery. Although the incidence of catheter blockage due to insulin crystallization can be further evaluated in a clinical study, FDA recommends this risk be assessed via appropriate bench testing prior to an unsupervised clinical study. The testing of this system should mimic the conditions of the clinical study as closely as possible. Temperature should reflect the use environment and to ensure safety, the duration of time evaluated should be double the maximum time allowable for pump shutoff in the LGS system. FDA recommends the Sponsor report the incidence of crystallization and the incidence of catheter blockage due to crystallization.

L. Diagnostic Device Information for All Diagnostic Devices Used in Clinical Study

In addition to the diagnostic devices used in the LGS system, other diagnostic devices which are not part of the LGS system are often used during clinical studies (e.g., those that measure glucose or ketones). To assess the quality of the information supporting the IDE, Sponsors should provide the following information for each diagnostic device used in the clinical study:

- Name of the device, including model numbers, as applicable.
- Description of the purpose of the device during the study (e.g., assure patient safety, calibrate CGM, verification of other glucose measuring devices, assess the results of the study).
- Regulatory status of the device (including the FDA document number, if known).
- List of all device components and accessories. In addition to the instrument, reagents and quality control materials, accessories might include standards (calibrators), data transmitting equipment or software that processes or stores data.
- If the device was previously cleared or approved, Sponsors should:
    - Provide a copy of the device labeling
        - ✓ *Note 1: There may be multiple components of labeling, e.g., for the instrument and the reagent. Applicants should provide the labeling for each component of the device, as necessary.*
    - Describe any physical or mechanical modifications that were made to the device for purposes of conducting the study. If modifications were made, Sponsors should provide the details and an explanation of how the modification might affect its performance.
    - Indicate whether or not the device is intended to be operated according to the instructions for use which appear in the device labeling. This includes how the

device is operated, the sample type analyzed, performing recommended maintenance, evaluating quality control samples and calibration procedures. If there are deviations, the Sponsor should describe them and explain the rationale for the modified use.

- Sponsors should describe how the device was monitored to ensure accurate results. This information should include:
  - Quality Control (QC) solutions analyzed.
  - Number and glucose concentration levels in QC solutions.
  - Frequency of analysis of the QC solutions.
  - Criteria for determining acceptability of QC results.
- Sponsors should describe how individuals using the device during the study were trained to operate it.

M. Drugs Used in LGS System

Please identify the name of the drugs (e.g., insulin, glucagon, etc.) intended to be used in the LGS system and provide the drug labeling.

VI. Bibliography

The Sponsor should provide a bibliography of all publications. Copies of critical publications needed to support the proposed study should be included as an appendix.

VII. Clinical Study

A. Purpose/Objective(s)

The Sponsor should briefly describe the purpose/objective of the study.

B. Study Design

The Sponsor should briefly describe the study design. For example:

A nonrandomized double center study with X subjects who have Type I Diabetes will participate in one X hour inpatient experiment. The study will compare the treatment arm to a control arm. The arms are defined as:

- *Treatment Arm*
- *Control Arm*

C. Sample Size and Investigational Sites

The Sponsor should define the number of subjects that are intended to participate in the study, the proportion of male to female, age range, Type of diabetes, etc.

> *Please note the sample size should include all subjects enrolled. A subject is considered enrolled once the subject has signed the informed consent. Therefore, this may include subjects that do not participate in the study because they do not meet the inclusion/exclusion criteria. Please consider this issue when recommending a sample size.*

The Sponsor should define the investigational site(s) and include the address for each site.

D. Study Duration

The Sponsor should define the study duration for each subject (e.g., subject will participate in two 24-hour experiments).

The Sponsor should also define how long they believe the entire study will take to complete.

E. Inclusion Criteria

The Sponsor should provide a listing of the inclusion criteria. For recommendations of criteria for a pivotal study design, see Section VII-B-1 of the guidance.

F. Exclusion Criteria

The Sponsor should provide a listing of the exclusion criteria. For recommendations of criteria for a pivotal study design, see Section VII-B-1 of the guidance.

G. Study Timeline

The Sponsor should provide a detailed description of how the study will be performed. For example:

Enrollment Visit:

- *Informed Consent is obtained from eligible subjects, etc.*

Activities performed prior to CRC or Study Admission:

- *Sensor placement, etc.*

CRC Admission:

- *Detailed description of the CRC timeline*

Follow-Up

- *Describe the criteria used to determine when a subject can safely be discharged from the CRC.*
- *Describe when and how often a health care provider will follow-up with the subject after discharge.*

H. Safety Monitoring/Risk Analysis

Describe the Safety Monitoring that will be performed during the study. For example:

- Glucose Monitoring Risk - FDA recommends that performance of the LGS be assessed, in part, by evaluating blood glucose measurements taken from the subject while they are enrolled in the clinical study. It is therefore important to collect the most accurate glucose information possible.
    - *Pilot Study (In-hospital):* For studies taking place in CRC settings, Sponsors should use the most accurate method available for measuring subject glucose levels, i.e., established reference methods. Instruments such as the Yellow Springs Instrument (YSI) or other reliable laboratory tests such as a hexokinase method are most appropriate.
    - *Pivotal Study (Outpatient):* The need for accurate glucose information also exists for studies taking place in the home setting. Sponsor should carefully consider the BGD that they intend to use and assess the risk for measurement error.

- Hypoglycemic/Hyperglycemic Risk - To decrease the risk of severe hypoglycemia and hyperglycemia, the Sponsor should construct a schedule for monitoring blood glucose levels. The Sponsor should address how the interval of sampling and method of determination may be affected by the subject's current blood glucose value or period of the trial, such as during hypoglycemia induction. This information can be provided in tabular format.

Blood Glucose (mg/dL)	Frequency of BG measurement
0-XX	X min
XX-YY	Y min

Please Note: The Sponsor should describe how they will intervene for hypoglycemic and hyperglycemic episodes. This description should include time and glucose level. The Sponsor should describe how each defined episode will be treated.

- Calibration of CGM risk - When an erroneous glucose value is used to calibrate a CGM, the bias is carried through until the next opportunity to re-calibrate the CGM. This can result in an incorrect bias that lasts for 12 hours. Sponsors are encouraged to mitigate the risks posed by BGDs as much as possible when designing studies because they are used to calibrate the CGMs and could result in inappropriate suspension of insulin infusion.

- Sterilization Risk – The Sponsor should identify and describe if all of the devices are sterilized. If not, the Sponsor should assess this risk.

- Reuse Risk –The Sponsor should describe if components of the LGS system can be reused for other patients within the study. If applicable, the Sponsor should describe if the reusable devices are patient contacting. If they are patient contacting, the Sponsor should describe the reprocessing (cleaning, disinfection, re-sterilization) of the reusable devices. Please note, validation may be needed to ensure reusable devices have been adequately cleaned, disinfected and re-sterilized.

- Hb1Ac risk - Please refer to Section VII-B-2 of the guidance regarding the risk of variability in HbA1c measurements.

- Misuse Risk - Sponsors should provide a detailed description of how training will take place regarding the operation of the LGS system and all of the functional components during the study. As applicable, this should include training for clinical staff and/or the study subject.

  Please Note: If the study is being conducted for the purposes of supporting a marketing application, all training of staff and users should mimic that which will take place when the system is marketed. This includes written materials, videos and or checklists.

- Risks of blood sample collection, contamination from sampling techniques.

  Please Note: Sample collection procedures in hospitals are responsible for a significant number of errors when patients are in hospitals. This is particularly true when samples are taken from an intravenous (IV) line, irrespective of the fluids being administered. Ideally, the technique used to obtain the sample should limit the amount of blood taken so as not to harm the patient. The technique should ensure mitigation of the risk of contamination.

I. Stopping Rules

FDA recommends the Sponsor describe stopping rules for the subject and study.

- The Sponsor should describe under what subject conditions the patient study would be halted.
- The Sponsor should describe under what study conditions the entire study would be halted. For example, if 3 subjects were consecutively stopped.

J. Endpoints

The Sponsor should define the primary and secondary endpoints for safety and effectiveness.

K. Success Criteria/Goal

The Sponsor should define how the study will be determined a success.

Pilot Study

In Pilot studies, the success criteria can be general. FDA recommends the Sponsor identify criteria that would allow the Sponsor to progress to the next study.

Pivotal Study
FDA recommends the Sponsor provide success criteria in accordance with the statistical plan. Please refer to Section VII-B-3 of the guidance regarding success.

L. Statistical Analysis Plan

Pilot Study
Pilot studies typically do not have sufficient sample size to allow for a statistical analysis. The Sponsor should describe the analysis that will be used to determine progression to the next phase of the study.

Pivotal Study
FDA recommends a complete statistical analysis plan to support the study objective(s). Please refer to Section VII-B-3 of the guidance.

VIII. Informed Consent

The Sponsor should provide a statement that all forms and informational materials to be presented to the subject were submitted and included in the IDE application. A copy of the informed consent and any informational or recruiting materials should be provided. This can be provided in an Appendix. All Informed Consent documents must contain the information described in 21 CFR 50.25(a).

FDA recommends the consent process not to only include a "short form" written consent (see section 50.27(b)(2)).

IX. Patient Case Report Form(s)

The Sponsor should provide a draft copy of the case report forms. This can be included as an appendix.

X. Investigator Agreement Forms

If the investigators are determined prior to the IDE submission, the Sponsor should identify the name and address of each investigator that will participate in the study. The Sponsor should provide an Investigator Agreement Form and this form should minimally have the information contained within 21CFR 812.43(c)(4). In addition to this form, the Sponsor should certify that no investigator will participate in this study prior to signing the investigator agreement form.

XI. Monitoring Information

The following information is recommended for adequate monitoring information.

- Written procedures for monitoring and the name and address of any monitor (21 CFR 812.25(e)).
- Monitor will report to the Sponsor any noncompliance with the signed Investigator's Agreement, conditions imposed by the IRB or FDA, and the requirements of the IDE. Sponsor shall then either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation (21 CFR 812.46(a)).
- A Sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with FDA regulations (21 CFR 812.43(d)).
- Monitor will conduct a pre-investigational visit. Monitor will ensure that the study protocol is thoroughly understood.
- A Sponsor shall immediately conduct an evaluation of any unanticipated adverse device affects (21 CFR 812.46(b)(1)) and report the findings to the FDA.
- A Sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect (21 CFR 812.46(b)(2)).
- A Sponsor may not resume a terminated investigation without IRB and FDA approval (21 CFR 812.46(c)).

XII. Institutional Review Board (IRB) Information

The Sponsor should provide the following IRB information.

- Identification of the IRB or IRBs.
- Name, address and chairperson of each IRB.
- Action taken by IRB,(i.e., approval).
- Identification of how many IRBs have approved the investigation.
- Identification of how many IRBs are currently reviewing the investigation or will review it in the future.

XIII. Labeling

FDA recommends the Sponsor provide the following product labeling information.

Pilot Study

The purpose of the product labeling for the pilot study is to ensure the clinical investigator (operator) has adequate instructions to safely operate the investigational device. The Sponsor should provide a copy of the draft product labeling which includes:

- Adequate instructions for the investigator to safely use this device.
- A caution statement, "*Caution – Investigational Device. Limited by Federal (or*

United States) law to investigational use" on the LGS labeling.

- If the LGS system uses device components that have been previously cleared and/or approved, the Sponsor should also provide a certification stating all product labeling for the cleared/approved devices will be available upon request for any patient and/or investigator that is participating in the study.

Pivotal Study (unsupervised outpatient study)
The purpose of the product labeling should allow the subject to safely operate the LGS system. FDA recommends the Sponsor provide a complete set of product labeling (Section VIII of the guidance). In addition, the product labeling should contain the following statement, "*Caution – Investigational Device. Limited by Federal (or United States) law to investigational use*".

XIV. Anticipated Changes

The Sponsor should describe any changes that are anticipated during the clinical study. For example, if the Sponsor intends to modify their adjustable parameters during their study within the predefined value range.

XV. Manufacturing

Pilot Study
This information may not be needed for feasibility studies that use devices that have already been approved or cleared. The Sponsor should describe the devices used in the study and provide the appropriate PMA and/or 510(k) number for completion of this section.

Pivotal Study
The following information should be provided to support a pivotal study design.

- Certification that device will be manufactured in accordance with Good Manufacturing Practices (21 CFR 812.20).
- A description of the methods, facilities, and controls used for the manufacture, processing, packing, and storage as required by 21 CFR 812.20(b)(3).
- The QA program should be described. The Sponsor can provide quantitative tests along with pass/fail criterion. QA/QC tests monitor processing methods and can be used in lieu of more detailed descriptions.
- Procedures for specification control measures are established to assure that the design basis for the device is correctly translated into approved specifications (21 CFR 820.100(a)(1).
- A description of the processes in accordance with 21 CFR 820.100(b)

Appendix B: Safety Information Needed in lieu of a Pilot Study

It is recommended that initial studies for LGS systems be performed in a hospital setting, such as a clinical research center (CRC), to demonstrate that the device system functions as expected and does not have any obvious unexpected safety concerns. Although more common than severe clinical hypoglycemia, biochemical hypoglycemia (plasma glucose < 70 mg/dL) is unpredictable and may not occur spontaneously during the relatively short period of a CRC study. Therefore, it is recommended this study test the system with induction of hypoglycemia by increasing insulin administration, withholding food, and/or exercise. This portion of the study should be performed under the close supervision of a medical team that can intervene to prevent severe hypoglycemia or hyperglycemia occurrence during the trial. To provide safety monitoring and comparison to CGM values, reference (laboratory) blood glucose levels should be checked frequently. When appropriate, additional capillary blood glucose levels can be obtained; the interval and method (reference vs. capillary) is determined by the safety issues at different times during the study.

In lieu of CRC studies, Sponsors may be able to provide supporting safety data from previous studies of approved sensor-augmented pump (SAP) systems. Although the data on CGM performance may be used in support of the outpatient study, the analysis of this data may vary from the analysis done to support an indication for 'tracking and trending'. In addition to the information needed for a pivotal study described in Appendix A, the following information should also be provided:

1. A complete device description of all device components used in the study that supported the approval of the SAP system as described Section IV.
2. The complete protocol of the study used to generate data on sensor performance. This should include a description of:
   - The study population with inclusion and exclusion criteria.
   - Any interventions performed, such as 'clamps' to accrue data pairs (CGM to reference) in the hypoglycemic and hyperglycemic ranges and how these ranges were defined for this study.
   - A reference blood glucose measurement. As this is a reference value there should not be adjustments in the reported value (such as altering the comparison to reflect the error in the reference method).
   - An analysis of data pairs in the lower glucose range should be provided in intervals of 10 mg/dL. For example, 50-60 mg/dL, 60-70 mg/dL, 70-80 mg/dL, and 80-90 mg/dL.
   - An analysis of alarm performance, reactive or predictive, as it relates to the proposed outpatient study. Alarms should be assessed by individual subject experience and not by individual data pairs. Comparisons between CGM and reference BG should be made based on the time it took to detect the threshold of interest (such as 70 mg/dL). For example, the CGM detected 70 mg/dL 10

minutes after (or before) the reference method. False positives and false negatives should also be captured.

- Individual plots of CGM tracings with reference blood glucose values of the periods analyzed should be provided.

Note: If the sensor was the subject of a CGM premarket application to FDA, this information may already be available. If this is the case, Sponsors should provide the reference for the date of the document, the FDA document number, volume and page number.

The Sponsor should provide a discussion of how the above information provides sufficient evidence (such as accuracy in the lower glucose range and or alarm performance) that the LGS system is likely to demonstrate safety and efficacy in the outpatient.

Appendix C: Glossary

Alarm handler - software that processes and handles the alarm functioning of the pump

Analytical specificity - How well an assay detects only a specific analyte (e.g, glucose) and does not detect closely related substances.

Bias - The difference between the expectation of test results and an accepted reference value. (CLSI EP21-A)

Blood Glucose Device (BGD) - A device to measure blood glucose levels.

Continuous Glucose Monitor (CGM) - A sensor placed under the patient's skin (subcutaneously), which measures the glucose in the fluid around the cells (interstitial fluid). A small transmitter then sends information to a receiver, which continuously displays an estimate of blood glucose.

Control algorithm - A control algorithm is software embedded in a computer that receives information from the CGM and performs a series of mathematical calculations. Based on these calculations, the controller sends instructions to alter the insulin infusion of the pump.

Correlate marker - a phenomenon that accompanies another phenomenon, is usually parallel to it, and is related in some way to it. In the LGS guidance, the correlate marker is using the CGM-based event definition for evaluation of hypoglycemic events.

Dose error reduction mechanism - Software based component, which primarily functions to reduce pump programming errors.

Enriched population - For the LGS guidance, an enriched population is to study a patient population that is likely to have hypoglycemia with an event frequency that is sufficient to detect treatment-related differences in occurrence.

Event Rate - The total number of days when hypoglycemic events occur divided by the number of days in the follow-up period. Since the numerator of Event Rate is in the unit of day, only one event will be counted per day even if multiple events occur on the same day.

Imprecision - An uncertainty of measurement parameter, associated with the result of measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand (the quantity intended to be measured). It is expressed numerically as standard deviation (SD) or coefficient of variation (CV). (POCT05)

Insulin infusion pump - A pump for delivering insulin into the subcutaneous tissue to achieve glycemic control. The pump is composed of a pump reservoir similar to that of an insulin cartridge, a battery-operated pump, and a computer chip that allows the user to control the amount of insulin being delivered.

Interference - The act of hindering, obstructing, or impeding the performance of the glucose sensing device.

In-silico model - a method to test the control algorithm in a theoretical human model of insulin and glucose metabolism using a sophisticated computer model rather than expensive animal experiments.

Linearity - The ability (within a given range) to provide results that are directly proportional to the concentration (amount) of analyte in the test sample.(CLSI EP6-A)

Low Glucose Suspend (LGS) system - A medical device autonomous system linking both a BGD and CGM to an insulin pump, which automatically suspends or reduces insulin infusion temporarily based upon specified thresholds of measured interstitial glucose levels. An LGS system is a type of autonomous system commonly known as an artificial pancreas. This type of system is designed to reduce the likelihood and/or severity of a hypoglycemic event.

Mean area under the curve (AUC) - The sum of areas of the readings recorded by a CGM below 60 mg/dL (AUC) for each detected event divided by the number of events.

Measuring Range - The range of values (in units appropriate for the analyte) over which the acceptability criteria for the method have been met; that is where errors due to nonlinearity, imprecision or other sources are within defined limits. (CLSI EP6-A)

On-board memory - internal memory for infusion pump.

Pediatric - Of or relating to the medical care of children. CDRH defines the pediatric age range from birth to 21 years of age.

Predictive LGS system - a medical device autonomous system consisting of a CGM, BGD, control algorithm, and insulin pump that predicts (or anticipates) a future hypoglycemic event based on the rate at which glucose levels are falling and temporarily stops or reduces insulin infusion before the patient becomes hypoglycemic.

Pump log - digital record of the bolus and basal deliveries from the infusion pump.

Reactive LGS system - a medical device autonomous system consisting of a CGM, BGD, control algorithm, and insulin pump that temporarily reduces or stops insulin infusion when the CGM value reaches a predetermined low glucose value.

Real time clock (RTC) - a battery-powered clock that is included in a microchip in a computer motherboard. This clock keeps track of the time even when the device is turned off. Real-time clocks run on a special battery that is not connected to the normal power supply.

Stability - The capacity of a drug substance and reservoir to remain within established specifications of identity, strength, quality, and purity in a specified period of time. Stability is officially defined as the time lapse during which the drug product retains the same properties and characteristics that it possessed at the time of manufacture.

Watchdog timer - A computer hardware or software timer that triggers a system reset or other corrective action if the main program, due to some fault condition, neglects to regularly service the watchdog. The intention is to bring the system back from the unresponsive state into normal operation.